

**INFLUENCE OF EXERCISE MODALITY ON BODY COMPOSITION,  
INSULIN RESISTANCE AND FUNCTIONAL FITNESS IN AGING:  
A RANDOMIZED CONTROLLED TRIAL**

by

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A thesis submitted to the School of Kinesiology and Health Studies  
in conformity with the requirements for  
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## Abstract

Excessive abdominal obesity, coupled with a decline in muscle mass and physical function that is exacerbated by sedentary living, contributes substantively to the disease and disability common to our aging population. The Senior Study, a randomized controlled trial designed to investigate the health benefits associated with performing resistance exercise (RE), aerobic exercise (AE), or a combination of both exercise modalities (RAE) for six months in the absence of caloric restriction, was conducted on otherwise healthy but abdominally obese, sedentary men ( $n=57$ ) and women ( $n=79$ ) between the ages of 60 and 80.

The purpose of the first manuscript (Chapter 3) was to compare the effects of exercise modality on visceral obesity and insulin resistance in the Senior Study. All exercise groups significantly reduced total abdominal and visceral fat ( $P<0.05$ ) and waist circumference ( $P<0.001$ ), which measure explained 30% of the variance in total abdominal fat changes ( $P<0.001$ ). AE and RAE improved insulin sensitivity ( $P<0.05$ ), but the RE group did not ( $P>0.1$ ). The greatest insulin sensitivity increase was observed within the RAE group (48% increase,  $P<0.001$ ).

The purpose of the second manuscript (Chapter 4) was to evaluate the effects of exercise modality on cardiorespiratory and functional fitness in the Senior Study. AE and RAE increased cardiorespiratory fitness ( $P<0.001$ ), whereas RE did not ( $P>0.1$ ). All exercise groups improved functional fitness performance ( $P<0.001$ ), but age- and sex-specific percentile ranking improvement within RAE was greater than AE ( $P<0.01$ ). RE and RAE significantly increased skeletal muscle ( $P<0.01$ ), predominantly in the upper body, while AE did not ( $P=1.0$ ). AE and RAE reduced total fat ( $P<0.001$ ). Both fat loss and muscle gain were independent predictors of improvements in functional fitness ( $P<0.05$ ).

The findings from these studies demonstrate conclusively that a combined resistance and aerobic exercise program without caloric restriction is an optimal strategy for the therapeutic reduction of health risk in abdominally obese men and women. While each exercise modality offers distinct benefits and remains a viable option for needs-based exercise prescription, the

combination was associated with the greater simultaneous improvements to body composition, insulin resistance, and cardiorespiratory and functional fitness than either resistance or aerobic exercise alone.

**Key words:** Exercise modality, obesity, visceral fat, skeletal muscle, disability, elderly

## **Co-Authorship**

Writing of the manuscripts contained within this dissertation (Chapters 3 and 4) and all statistical analyses were performed by Lance E. Davidson. Critical revisions for important intellectual content were provided by Dr. Robert Ross.

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## List of Abbreviations

ACSM	American College of Sports Medicine
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASAT	Abdominal subcutaneous adipose tissue
ADP	Air displacement plethysmography
BIA	Bioelectrical impedance
BMI	Body mass index
CIHR	Canadian Institutes of Health Research
CRP	C-reactive protein
CT	Computed tomography
DEXA	Dual energy x-ray absorptiometry
FFA	Free fatty acids
FFT	Functional Fitness Tests
HDH	Hotel Dieu Hospital
HDL	High density lipoproteins
Health ABC	Health, aging, and body composition study
HOMA	Homeostasis model assessment
HRmax	Maximal heart rate
HRR	Heart rate reserve
HU	Hounsfield units
Hydro	Hydrostatic weighing
IL-6	Interleukin-6
IMCL	Intramyocellular triglyceride
IR	Insulin resistance
IVNA	<i>In vivo</i> neutron activation
KGH	Kingston General Hospital

L4-L5	Intervertebral space between the 4 <sup>th</sup> and 5 <sup>th</sup> lumbar vertebrae
LDL	low-density lipoproteins
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NHANESIII	Third national health and nutrition survey
OGTT	Oral glucose tolerance test
PPAR- $\gamma$	Peroxisome proliferator-activator receptor- $\gamma$
RSMI	Relative skeletal muscle index
SI	Sensitivity index
SMI	Skeletal muscle index
TC	Total cholesterol
TNF- $\alpha$	Tumor necrosis factor- $\alpha$
T12-L1	Intervertebral space between 12 <sup>th</sup> thoracic and 1 <sup>st</sup> lumbar vertebrae
VAT	Visceral adipose tissue
VCO <sub>2</sub>	Rate of carbon dioxide expired
VO <sub>2</sub> max	Rate of oxygen consumed during maximal exercise
VO <sub>2</sub> peak	Peak rate of oxygen consumed during exercise
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio

## Chapter 1. General Introduction

Obesity, especially abdominal obesity, is a predominant phenotype of the aging Canadian. The prevalence of obesity throughout North America has increased dramatically in past decades such that now a clear majority of men and women over 65 are considered abdominally obese.<sup>1</sup> Of particular concern is that with aging, an expanding waistline represents a disproportionate increase in visceral adipose tissue -- an established independent predictor of morbidity<sup>2, 3</sup> and mortality,<sup>4</sup> and a major contributor to disease states common in the elderly and which add significantly to the burden of health care.<sup>5</sup> Furthermore, the sedentary lifestyle that is often associated with an abdominally obese profile exacerbates age-related muscle loss, which precipitates declining muscle function and an increased incidence of disability.<sup>6-8</sup>

Although clinicians routinely prescribe weight reduction programs for younger obese adults, uncertainty exists regarding the appropriate strategy for obesity reduction in the elderly. Because weight loss, especially that attained through caloric restriction, is commonly associated with lean tissue loss concurrent with fat reduction,<sup>9-13</sup> purposeful weight loss may not be an ideal prescription for an older patient in whom declining muscle mass may compromise mobility and functional capacity, and even lead to metabolic morbidity.<sup>14</sup> Evidence compiled from numerous studies shows that while weight loss induced by exercise alone may be modest in comparison to that obtained through caloric restriction, exercise training may provide a stimulus for preservation of skeletal muscle while mobilizing energy from risk-laden abdominal adiposity.<sup>10</sup>

While a reasonable prescription for health risk reduction in the elderly may be to focus on exercise alone, some uncertainty exists as to which modality of exercise yields optimal benefits. Whereas a program of progressive resistance exercise may have a profound effect on muscle mass, strength, and functional capacity, the energy expended per session may not be sufficient for reducing abdominal obesity and its associated metabolic risk. On the other hand, the energy expenditure of aerobic exercise may stimulate a more substantial reduction of abdominal obesity and metabolic risk, yet fail to provide the increased muscle mass and functional capacity typical of resistance exercise. Since either modality offers unique outcomes desirable for sedentary,

abdominally obese older persons, it is likely that the optimal exercise prescription would be one that incorporates both modalities. Indeed, currently-accepted exercise recommendations for the elderly acknowledge the benefits of both modalities and encourage a combination approach.<sup>15</sup> However, nearly absent from the literature are supporting studies which compare the independent effects of aerobic or resistance exercise against a program which combines the two exercise modalities.

In the two manuscripts contained in chapters 3 and 4, we report the independent and combined effects of resistance and aerobic exercise on abdominal obesity and insulin resistance, muscle mass and functional fitness in abdominally obese, sedentary older adults. With a tightly-controlled, randomized study design, we compared the effects of exercise modality using “gold standard” methodologies to measure the morphological, metabolic, and functional adaptations that underlie modest, exercise-induced weight loss. A novel aspect of our study design is our investigation of the effects of exercise, independent of caloric restriction, and a pragmatic approach to exercise prescription that is consistent with consensus recommendations. Our purpose in performing this trial, hereafter referred to as the Senior Study, was to provide empirical data to support an improved therapeutic strategy for the prevention and treatment of abdominal obesity, the reduction of health risk, and improved physical function in older men and women.

## **Chapter 2. Literature Review**

### **2.1.0. Introduction**

Fundamental to the aging process are the morphological changes that occur within the human body during later decades of life. Beneath the graying hair and wrinkles that are generally associated with the “golden years,” aging often brings a myriad of medical maladies that hamper quality of life and lead to increased disability, dependent living, and eventual death. Although medicine has made unprecedented progress over less than a century toward developing remedies and risk reduction practices, accounting for much of the over 30% increase of life expectancy in the United States<sup>16</sup> and Canada,<sup>17</sup> the resultant lifespan extension has brought to the forefront a new wave of senescence-related medical conditions, many of which are exacerbated by poor lifestyle choices. The challenge for today’s seniors is not simply living long enough, but striving for healthy aging: a lifestyle that includes independence from disease states and disability. This review discusses current methodologies employed to measure body composition for the purpose of assessing age-related health risk, details the health risks of a sedentary lifestyle in aging, and then compares effectiveness of lifestyle-based intervention strategies employed to improve health and quality of life in the elderly.

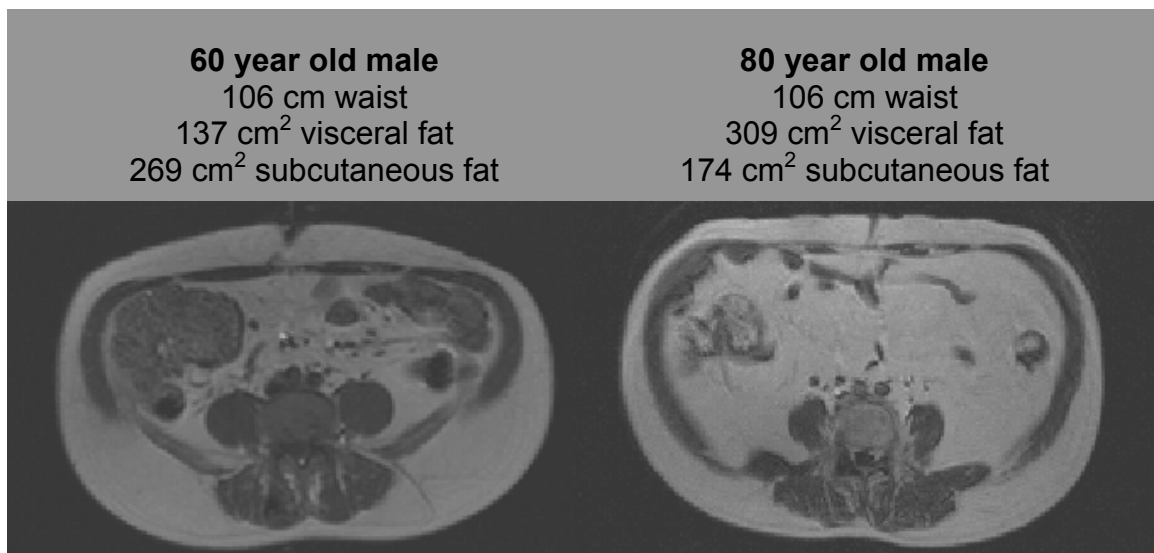
#### **2.1.1. The Aging Body**

The human body experiences subtle changes in morphology as it ages. Data from several classic cross-sectional population studies indicate that body weight and body mass index (BMI; weight in kilograms divided by height in centimeters squared) gradually increase through adulthood, peak at approximately 60 years, and then decline.<sup>18, 19</sup> This decline in weight could be attributed to the increased early mortality rate of obese persons,<sup>20, 21</sup> effectively “thinning” the surviving population as it ages. Prospective studies, however, generally confirm the cross-sectional results, indicating that beyond 60 years of age, body weight and BMI are either maintained or tend to decrease.<sup>22, 23</sup> Sometimes these decreases in weight over time in the elderly are misconstrued as an arrest in the progression of obesity, and, for many who have been

indoctrinated in the woes of weight gain, weight loss is considered an indication of improved health. With a closer look at the subtle changes occurring in various tissues in the aging body, however, one realizes that weight loss in the elderly may have deleterious health outcomes, depending on which tissue is waning.

Two major tissues in the body change in opposite directions with age: adipose tissue and skeletal muscle. Whole body adipose tissue or fat mass generally continues to increase over time,<sup>24</sup> and that increase has been measured at a rate of approximately 7.5% per decade in older men and women.<sup>25</sup> Age-related fat mass changes do not appear to be uniform throughout the body, since decreases of 17% in subcutaneous fat thickness are observed with concomitant increases in total body fat mass and waist girth over a decade.<sup>26</sup> A longitudinal study in 1300 Swedish women also demonstrated a progressive, approximately 0.7 cm per year increase in waist circumference, even in the oldest participants.<sup>27</sup> Studies conducted using computed tomography (CT) have demonstrated that this progressive increase in abdominal girth indicates growth of the intra-abdominal or visceral fat depot, which increases significantly with age in men and women despite reductions in subcutaneous fat.<sup>28-30</sup> Figure 1 illustrates how concomitant changes in visceral and abdominal subcutaneous fat may result in the same waist circumference in a 60-year-old versus an 80-year-old man.

**Figure 1.** Age-related changes in visceral and subcutaneous adipose tissue



Further investigations into regional fat deposition using CT and magnetic resonance imaging (MRI) have determined that aging is associated with concomitant increases in the amount of fat stored within metabolically active tissues such as muscle<sup>31</sup> and liver.<sup>32</sup> Fatty infiltration of lean tissue and growth of abdominal adiposity alongside thinning subcutaneous fat layers represents a progressive shift of lipid in the body from its “normal” storage depot toward “ectopic” storage of lipid: a phenomenon called lipodystrophy, describing the body’s inability to develop adequate adipose tissue mass to store lipid. The lipodystrophy of aging is associated with marked increases in metabolic risk.<sup>33</sup>

With lipid storage progressively increasing with age, how might one explain an observed maintenance or even reduction of weight over time in an elderly population? A major contributor to age-related weight reduction is a phenomenon called “sarcopenia,” a term coined by Irwin Rosenberg in 1988 to describe the steady, involuntary decline in skeletal muscle mass that occurs with aging.<sup>34</sup> Significant muscle loss is generally reported to begin occurring somewhere in the 5<sup>th</sup> decade of life and accelerate through old age.<sup>35</sup> Men usually carry more muscle than women in younger years, and the subsequent loss of that muscle is more rapid than women later in life.<sup>36</sup> Regardless of gender, the difference between young and old subjects is primarily seen in lower-body muscle.<sup>36</sup> Since muscle mass contributes substantially to overall body mass, particularly in men, sarcopenic reductions in skeletal muscle are at least partly responsible for observed weight and BMI declines in the elderly: perhaps even in spite of continued fat accumulation. Whereas metabolic health risk and disease are often linked to excessive obesity and lipodystrophy, insufficient skeletal muscle is also laden with its own debilitating consequences. That both phenomena progress simultaneously in the aging body is indeed a cause for concern, and presents a unique challenge for intervention.

The sections that follow will discuss the current methods available for measuring the subtle changes in body composition that occur with age, identify the health risks associated with age-related lipodystrophy and sarcopenia, and then discuss appropriate lifestyle modifications designed to reverse the progression of disease and disability in older men and women.

## **2.2.0. Methodologies for Measuring Body Composition**

For the purpose of acquainting the reader with the methods used in the literature for assessment of body composition in the elderly, this section will discuss and compare the various techniques available for quantification of fat and muscle, respectively, and describe their utility in characterizing obesity and sarcopenia in aging humans.

### **2.2.1. Measurement of Fat**

As interest in obesity escalates, methods of body composition assessment have also rapidly advanced, illuminating the intricacies of regional fat deposition and the lipodystrophy of aging. The measurement of fat has progressed from simple weight-by-height estimates to in-vivo whole body imaging for tissue identification. As described above, an inherent part of the aging process is a progressive reduction in fat-free mass and an increase in the ratio between fat and fat-free mass. Body mass index (BMI), a simple measure of weight that accounts for standing height, is a measure that is commonly used to assess health risk in younger populations because of its strong relationship with obesity. Since stature and skeletal muscle mass decrease while fat deposition is maintained or continues to increase in the aging population, weight and BMI are not as accurate health and mortality risk assessment tools for the elderly as compared to measurements of body composition.<sup>37, 38</sup> Currently there are no internationally-accepted thresholds for overweight and obesity by BMI specific to older men and women. Rather, it is widely accepted that various measures of fat distribution have greater predictive power for health risk assessment in aging, either coupled with or at the exclusion of BMI.<sup>39, 40</sup> An extensive review of the history and development of numerous body composition measures has recently been published,<sup>41</sup> and the reader is directed there for in-depth descriptions of the historical development and use of each measurement method. However, with regards to the assessment of fat in the elderly, a comparison of various techniques and their relative advantages and disadvantages for use in aging research is found in Table 1.

Because fat deposition changes with aging and the known health risk associated with excessive accumulation of abdominal obesity, methods capable of quantifying changes in

regional adiposity have the greatest utility for assessing fat-dependent health risk in the elderly. Hence, of the measures listed in Table 1, those which simply assess whole body volume have less clinical relevance in elderly populations. In previous decades, hydrostatic weighing was considered the gold standard method for determining whole body volume, a variable that can be used with body weight to determine whole body density, from which body fat percentage can be derived with various equations.<sup>42, 43</sup> Some of the technical limitations inherent to this method with the elderly are that difficulties may arise when the subject is particularly buoyant as a result of higher body fat stores and reduced muscle mass, and problems with compliance to protocol often occur when an elderly subject is required to expel as much air as possible from the lungs while underwater. Another alternative for whole body volume assessment is air displacement plethysmography, an alternative to underwater assessment that employs air chambers and adiabatic pressure to assess whole body volume. Three-dimensional body scanning, by laser refraction technology or by dual digital photography, is an emerging method of obtaining whole body volume, especially on oversized individuals. The utility of three-dimensional imaging is still unknown, as body composition validation studies have not yet shown to reliably compare with Hydro,<sup>44, 45</sup> but as the technology develops, it may potentially rival both Hydro and air displacement plethysmography due to its ability to obtain accurate abdominal or appendicular circumference data to describe regional fat distribution as part of the data acquisition process. Other anthropometric measures of regional girth, namely waist circumference, waist-to-hip ratio, and abdominal sagittal diameter are less expensive methods and have been more frequently used in the literature to describe the unique obesity characteristics of aging.

Several imaging techniques allow viewing of specific tissues that underlie circumferences and body volumes. Dual-energy x-ray absorptiometry (DEXA) is one that uses a low x-ray dosage to obtain a whole-body image and is capable of differentiating fat and lean mass by the relative density of appendicular and truncal regions. Some limitations to DEXA assessment of whole body fat have been documented, especially when comparing machines from different manufacturers<sup>46, 47</sup> or from pencil- and fan-beam technologies,<sup>48-50</sup> but overall, this method is considered reliable, repeatable, and reasonably accurate. Although not an imaging technique,

**Table 1.** Methods for measuring whole body and/or regional fat as a health outcome

Technique	Measured Quantity	Whole Body			Regional Advantages	Disadvantages
		Yes	No	Yes		
MRI	Cross-sectional fat quantification	Yes		Yes	Most accurate and repeatable; quantifies internal fat depots; non-hazardous; "gold standard"	Very expensive and time-consuming
MRS	Lipid content of various lean tissues	No		Yes	Actual quantification of muscle/liver fat	Very expensive and time-consuming
CT	Cross-sectional fat quantification; attenuation of x-ray energy estimates lipid content of lean tissues	No		Yes	Most accurate and repeatable; quantifies internal fat depots; qualitative muscle/liver fat assessment	Expensive; radiation exposure
DEXA	Relative attenuation of two x-ray energies	Yes		Yes	Fairly accurate and repeatable	Minimal radiation exposure; fair assessment of total abdominal fat
Ultrasound	Adipose tissue depth	No		Yes	Distinguishes between visceral and subcutaneous depots	Not widely used as a health outcome
3D body scanning	Body surface area/volume; circumferences	Yes		Yes	Regional girth measurements in addition to body volume	New technology; not widely used
ADP	Whole body volume	Yes		No	More tolerable than underwater weighing	Age-specific % body fat estimates not yet developed
Hydro	Whole body volume and density	Yes		No	Widely used in early studies	Expelling lung air underwater intolerable for some subjects
Bioelectrical impedance	Resistance and reactance of an alternating electrical current through body tissues	Yes		Yes	Inexpensive and widely used	Poor assessment of total abdominal fat; questionable reliability
Skinfolds	Thickness of a fold of subcutaneous fat	Yes		Yes	Site-specific regional measurement of subcutaneous fat	Certain regions difficult to assess with increasing obesity; between-tester reliability relatively low
Waist circumference	Abdominal girth	No		Yes	Correlates well with visceral fat volume	Combines visceral and subcutaneous
Waist-to-hip ratio	Ratio of abdomen to hip/buttocks girth	No		Yes	Indicates upper- versus lower-body fat; wide use in earlier population studies	Ratio sometimes fails to capture risk changes
Abdominal sagittal diameter	Distance between anterior and posterior trunk at iliac crest	No		Yes	Correlates well with visceral fat volume	Not as easily obtained as waist circumference

Abbreviations: MRI(S) = magnetic resonance imaging (spectroscopy); CT = computerized tomography; DEXA = dual-energy x-ray absorptiometry; Hydro = hydrodensitometry or underwater weighing; ADP = air displacement plethysmography.

bioelectrical impedance is another method that differentiates between fat and fat-free mass by measuring resistance and reactance of water-containing tissues of the body as an alternating electrical current passes through it. Various prediction equations for whole body fat mass have been derived from aging populations with DEXA as a reference.<sup>51-54</sup> Because most bioelectrical impedance equipment is inexpensive and portable, this method has gained popularity for use in epidemiological studies as well as for clinical and commercial facilities. Impedance tends to predict body composition well on a population level, but some have questioned its ability to predict body composition change on an individual level.<sup>55</sup>

Imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) are considered the most accurate and repeatable methods for in-vivo quantification of whole body obesity and have the added benefit of differentiating between and quantifying various internal fat depots. The two methods differ primarily in the manner in which the images are obtained. While both acquire cross-sectional images throughout the body, providing a view of internal lean and adipose tissue, acquisition of these images by CT requires ionizing radiation, which deters the use of CT for quantification of fat other than in specific regions of the body. On the other hand, MRI acquisition does not deliver any harmful radiation, but uses the interaction between hydrogen nuclei within bodily tissues and the magnetic fields created by the MRI system's instrumentation to generate a cross-sectional image of the body. The absence of radiation exposure in MRI increases its clinical utility and makes it the method of choice for whole body quantification of adipose tissue. Acquisition costs, availability, and time required to analyze the images prohibit use of MRI in larger epidemiological studies, however.

Although both CT and MRI were initially used to quantify the cross-sectional area of adipose tissue depots, they can also be used for in-vivo measurement of lipid deposition in lean tissue. Excessive lipid stored in tissues other than subcutaneous adipose tissue can be referred to as ectopic fat, meaning that its location is somewhere other than the customary site for most lipid deposition, namely subcutaneous fat. Several metabolically important ectopic fat depots have been shown to be independent risk factors for disease<sup>3, 56, 57</sup> and can be measured using MRI and/or CT technology. Two examples of ectopic depots are skeletal muscle and liver.

Traditionally, fat accumulation in these two tissues was measured by biopsy. However, biopsies may be painful<sup>58</sup> and impart additional risk of bleeding and other complications that may result in hospitalization or possible death.<sup>59</sup> Magnetic resonance spectroscopy, using the same machinery as MRI, is able to quantify lipid content in specific regions of lean tissue, and can differentiate between intra- and extramyocellular lipid in that region.<sup>60</sup> This technology is being used with increasing frequency in the literature to quantify lipid content of liver and skeletal muscle, and has been used in elderly subjects.<sup>32</sup>

Computed tomography may also be used to indicate the lipid deposition in skeletal muscle and liver. Measuring the extent of attenuation of x-ray particles as they pass through specific tissues, CT can detect the extent of lipid infiltration in lean tissue by virtue of the lean tissue's density. Not a quantitative method for measuring lipid content, CT assesses lean tissue quality, and has been used in studies linking liver<sup>61</sup> and muscle<sup>62</sup> lipid levels to metabolic risk. Although the accessibility and ease of acquisition is much greater in CT than magnetic resonance spectroscopy, CT imaging still delivers measurable radiation exposure to subjects, which again limits this method for frequent or repeated measurements. Until recently, studies measuring liver fat were left to their own devices in determining the amount and location of chest images to acquire a suitable image of liver for analysis. Also the location of specific regions of interest seemed to produce variable attenuation results.<sup>63</sup> Our research group at Queen's University, using data collected at the Cooper Institute in Dallas, Texas, produced a methodology paper that proposed a novel approach to CT liver acquisition.<sup>64</sup> Using 437 full-abdomen image sets of male and female subjects characterized by a wide range of age and obesity, we determined that the optimal image location for obtaining a simultaneous liver and spleen image in our sample was the intervertebral space between the 12<sup>th</sup> thoracic and 1<sup>st</sup> lumbar vertebrae (T12-L1). We also assessed the mean attenuation of liver and spleen in 8 different regions, respectively, for the purpose of determining optimal areas for placement of regions of interest. Because of the relative uniformity of density found throughout the liver, we proposed that attenuation of the whole liver visible on a single T12-L1 image, instead of using regions of interest, was the optimal approach for reducing analytical bias. This work established a procedure for liver fat acquisition that

minimizes radiation exposure and provides a uniform approach to liver analysis.<sup>64</sup> A full copy of this published manuscript is found as an appendix in section 7.2.0. of this dissertation.

In summary, an array of whole body and regional fat assessment tools are available for use with elderly subjects. The lipodystrophy of aging can be gauged by measures as simple as waist circumference, but radiological methods can quantify the different adipose tissue depots otherwise undetectable by circumferences. Furthermore, imaging technology allows for in vivo analysis of ectopic lipid deposition in metabolically active tissues like liver and muscle.

### 2.2.2. Measurement of Muscle

Measurement of body composition is often considered in reference to the health risk of obesity in younger populations, but a major contributor to the disability of aging is a reduced muscle mass, or sarcopenia. In aging studies, the quantity of muscle is a good indicator of muscle strength and thus, is a good indirect measure of functional capacity and health. Similar to obesity, a variety of skeletal muscle measurement methods are available for use in studies with elderly subjects. Several comprehensive reviews have detailed the advantages and disadvantages of each muscle measurement method.<sup>41, 65, 66</sup> A brief summary of these measurements follows to acquaint the reader with the methodologies commonly used to assess the health risk associated with sarcopenia. Table 2 provides a synopsis of the measurement methods discussed in this section.

As mentioned in the previous section on obesity, skeletal muscle mass cannot be measured directly by simple weight or BMI. In aging, however, observed declines in weight often indicate sarcopenic reductions in muscle mass. Thus, a very low BMI imparts an increased risk in older men and women, especially when controlling for waist circumference.<sup>40</sup> For similar reasons, the hip component of the waist-to-hip ratio may indicate gluteal muscle mass, which may explain the inverse association between hip circumference and health or disability risk. Appendicular circumferences, especially a triceps circumference with correction for skinfold thickness, were used widely in the literature for decades. The accuracy of this method was

**Table 2.** Methods for measuring skeletal muscle size/mass as a health outcome in the elderly

<b>Technique</b>	<b>Measured Quantity</b>	<b>Whole Body</b>			<b>Advantages</b>	<b>Disadvantages</b>
		<b>Body</b>	<b>Regional</b>	<b>Regional</b>		
MRI	Cross-sectional muscle size quantification; volume conversion to mass	Yes	Yes	Yes	Most accurate and repeatable; quantifies regional and whole body muscle; non-hazardous; “gold standard”	Very expensive and time-consuming
CT	Cross-sectional muscle size quantification	No	Yes	Yes	Most accurate and repeatable; quantifies regional muscle	Expensive; radiation exposure
DEXA	Relative attenuation of two x-ray energies	Yes	Yes	Yes	Fairly accurate and repeatable	Minimal radiation exposure
Whole-body counting/IVNA	Total body nitrogen Total body potassium	Yes	No	No	Noninvasive; minimal age or gender dependencies in prediction	High cost; restricted availability; variability in muscle estimation
Bioelectrical impedance	Resistance and reactance of an alternating electrical current through body tissues	Yes	Yes	Yes	Inexpensive and widely used	Variability in results on the individual level
Circumferences	Hips and appendicular girth, sometimes corrected for skinfold fat	No	Yes	Yes	Indicates upper- versus lower-appendicular muscle; used widely in early literature	Estimation error increases with increasing obesity

Abbreviations: MRI(S) = magnetic resonance imaging (spectroscopy); CT = computerized tomography; DEXA = dual-energy x-ray absorptiometry; IVNA = in vivo neutron activation.

examined in comparison to CT cross-sectional area of muscle at mid-humerus, and was found to overestimate muscle by 15-20% in normal weight individuals.<sup>67</sup> Even with revised, sex-specific equations that took into account humeral bone mass, the intra-individual error of circumferences was large and increased in those with higher body weights.<sup>68</sup> While circumferences give an indication of muscle mass, the inaccuracy associated with this measurement method, especially when monitoring subtle age-related declines in muscle mass, may undermine its utility in intervention studies.

Bioelectrical impedance was discussed earlier as a measure of whole body fat mass, yet in reality, bioelectrical impedance systems measure the voltage drop across a measured tissue bed, and since fat mass is a poor conductor of electricity, fat-free mass and total body water are the variables more directly assessed by this method. Because age-related changes in whole body muscle composition, which is the major appendicular conductor, impede the flow of electricity independent of muscle volume, age-specific formulas are required for appropriate bioelectrical impedance associations in older adults.<sup>69</sup> Indeed, prediction equations have been proposed for fat-free mass in the elderly such that bioelectrical impedance can be used as a viable measure of lean tissue in this age group.<sup>52, 53, 70</sup> However, some limitations still exist regarding variation of results on an individual level.<sup>55</sup>

Whole body counting and in-vivo neutron analysis are methods which were developed as a by-product of nuclear-based industrial testing of accidental radiation exposure in laboratory settings. Either by detecting the naturally occurring radioactive potassium-40 isotope or by activating various elements contained in human fat-free mass by neutron stream, these methods determine fat-free body mass with high correlations to DEXA and little need to apply age-dependent formulas.<sup>66</sup> Availability of and access to this technology, however, is limited.

Both whole body fat and lean tissues can be estimated in the elderly using DEXA. An added convenience to using this method in elderly populations is that it is the method of choice for osteoporosis screening -- a test that should be performed regularly, especially in postmenopausal women. Despite a low level of exposure to ionizing radiation inherent to x-ray technology, use of the DEXA is considered to estimate lean tissue mass well in the elderly.<sup>66</sup>

For reasons similar to those stated in the obesity measurement section, MRI and CT remain the methods of choice for quantifying muscle size. Using region-specific cross-sectional images, researchers can differentiate between fat, lean, and skeletal muscle tissue. Both MRI and CT have been used to obtain a single cross-sectional image of mid-thigh to estimate skeletal muscle quantity or adaptations to change. However, radiation exposure limits use of CT for more than single-slice or regional composition measures. Imaging and subsequent quantification of whole body skeletal muscle by MRI is possible by various multiple-image protocols.<sup>71, 72</sup> Using a whole-body, multiple-image approach, researchers are not only able to quantify skeletal muscle volume, but also organ, bone, and the various adipose tissue depots as described above. Although the cost and time-consuming analysis of MRI assessment of skeletal muscle remains prohibitive for large-scale studies, acquisition time is decreasing<sup>73</sup> and machines are becoming more prevalent.

As a summary of the methods available for use in the study of muscle size in the elderly, several stand out for different reasons. First, bioelectrical impedance machines can be purchased relatively inexpensively and give an indication of changes in total muscle volume, albeit with potential for variability in results. Second, whole-body DEXA scanning is growing in popularity, and couples a reliable measure of appendicular muscle mass with capacity for bone densitometry. Third, while expensive, MRI provides the most accurate and repeatable representation of skeletal muscle mass available, and can be considered the “gold standard” of in-vivo body composition measurement techniques.

### **2.3.0. Health Risk Associated with Age-Related Body Composition Changes**

Advances in body composition assessment permit the characterization of the lipodystrophy of aging and introduce methodologies capable of monitoring sarcopenic progression. These measures help investigators more clearly define the disease states and disability associated with aging. The following section on health risk in the elderly will discuss current knowledge with respect to age-related health risk as it is associated with regional lipid deposition and sarcopenia.

### 2.3.1. Obesity and Age-Related Health Risk

Obesity is a global health problem due to its increasing prevalence<sup>74-76</sup> and its association with morbidity and mortality from multiple chronic diseases.<sup>77</sup> The steep rise in overweight and obesity in Canada,<sup>76</sup> as in other industrialized nations,<sup>18, 78, 79</sup> has been referred to as nothing less than “epidemic,” perhaps owing to the increased incidence of cardiovascular disease, hypertension, diabetes, dyslipidemia, metabolic syndrome, gall stones, osteoarthritis, sleep apnea, and certain forms of cancer that have all been linked to overweight and obesity, as measured by body mass index.<sup>80, 81</sup> Risk of developing features in this extensive list of debilitating diseases is exacerbated in the obese elderly.<sup>82</sup> Considering that 1 in 4 Canadians between the ages of 65 and 74 now has a BMI that exceeds 30 kg/m<sup>2</sup>,<sup>83</sup> it is little wonder that although seniors comprise less than 15% of the Canadian population, they now account for a third of the nation’s health care expenditure.<sup>84</sup> In a prospective cohort study using questionnaires from over 17,000 healthy middle-aged men and women with a wide range of BMI, 26-year follow-up data showed a significant inverse-graded association between BMI and perceived health status or quality of life for those who were obese earlier in life.<sup>85</sup> Elevated mid-life BMI also increased later-life health care expenditures.<sup>86</sup> Within this same cohort, those who were obese at baseline assessment had a higher risk of hospitalization and mortality from heart disease and diabetes during the 26 years than those who were normal weight.<sup>87</sup> Clearly, a lifetime of obesity affects health risk and quality of life in later years.

#### *2.3.1.1. Health Risks of Abdominal Obesity*

Substantial evidence has established overweight and obesity as risk factors for developing heart disease and diabetes, yet not every person with excess weight presents with metabolic abnormalities. Certainly, regional fat deposition is not homogeneous throughout the population; two major whole-body obesity phenotypes have been likened to the characteristic shapes of fruits, with “pear-shaped” individuals having thinner waists and fatter hips while “apple-shaped” individuals are characterized by rounder abdomens and reduced hip and leg

circumferences. Apple-shaped people often possess greater metabolic disease and mortality risk than those with thinner waists.<sup>2, 88, 89</sup> The notion that body fat topography affects metabolic function was introduced in the literature over half a century ago by a French professor named Jean Vague, who noted that patients with increased fat deposition in the truncal region were more likely to display the metabolic abnormalities of obesity than those whose fat resided predominantly on hips and thighs.<sup>90</sup> Because of the increased health risk associated with abdominal obesity, and since waist circumference is a measure of abdominal girth, waist circumference is becoming increasingly recognized as an indicator of metabolic risk. Indeed, some studies have now shown that waist circumference may be a better predictor of risk than BMI for myocardial infarction,<sup>91</sup> type 2 diabetes,<sup>89</sup> medical care costs,<sup>5</sup> and all-cause mortality.<sup>92, 93</sup> The mounting evidence supporting the importance of abdominal obesity in the prediction of chronic disease and mortality has led to the incorporation of waist circumference instead of BMI for the clinical identification of the metabolic syndrome:<sup>94</sup> a cluster of metabolic abnormalities that also includes elevated levels of plasma triglycerides, cholesterol, blood pressure, and fasting glucose.<sup>95</sup> The focus of attention on centrally-located fat is further evident in the International Diabetes Foundation's adoption of even lower waist circumference cutpoints to identify risk, while instituting those thresholds as mandatory requirements for diagnosis of metabolic syndrome.<sup>96</sup> Overall obesity carries with it substantial health risk, yet central deposition of fat may be a key factor in the development of obesity-related co-morbidities. It is well established that the aging body progressively shifts lipid away from subcutaneous stores (on hips, legs, and arms) and deposits it centrally. This lipodystrophy may explain some of the increased metabolic risk that emerges in the elderly as opposed to younger adults with comparable BMI.<sup>97</sup>

#### *2.3.1.2. Health Risks of Excessive Visceral Adiposity*

The predictive power of waist circumference on health risk is thought to be linked to excessive visceral adipose tissue deposition, a centrally-located fat depot that is consistently reported to mirror changes in insulin resistance and other obesity-related co-morbidities independent of other adipose tissue depots.<sup>98</sup> Indeed, abdominal girth is often used as an

anthropometric surrogate for visceral adiposity because it estimates that specific fat depot better than BMI, weight, or waist-to-hip ratio.<sup>99</sup> Wide inter-individual variation in the ratio of subcutaneous to visceral fat in the abdomen, however, limits the prediction of visceral fat by waist circumference to about 35 to 50% of the variance explained (see Figure 1).<sup>100, 101</sup> Nevertheless, since waist circumference seems to predict both visceral adiposity and metabolic risk, it is logical to presume that visceral fat may be linked to the development of metabolic risk. Investigation of this notion through radiological quantification of abdominal adipose depots in elderly subjects confirms that visceral fat, not abdominal subcutaneous fat, is a common denominator in all features of the metabolic syndrome.<sup>102</sup> Furthermore, reduction of the visceral fat depot by surgical removal or through weight loss is associated with a marked improvement in insulin sensitivity<sup>103, 104</sup> and plasma lipid profile,<sup>105</sup> whereas surgical reduction of abdominal subcutaneous fat through liposuction has no effect on insulin sensitivity or other cardiovascular risk factors.<sup>106</sup> The visceral adipose depot is clearly linked to increased metabolic risk, and is an established independent predictor of morbidity<sup>2, 3</sup> and mortality.<sup>4</sup> These associations are of particular importance to seniors, who by virtue of the aging process, experience a disproportionate increase in visceral fat compared to abdominal subcutaneous fat for a given waist circumference.

While it is well established that measuring visceral adiposity is helpful in predicting health risk, the mechanisms by which visceral fat affects metabolic profile are yet unknown. In fact, whether visceral fat plays a causal role in elevated health risk or is simply a side effect of upstream metabolic dysfunction is still intensely debated.<sup>107, 108</sup> For years, the prevailing theory for the relationship between metabolic dysfunction and visceral fat was simply its proximity to the liver; in conditions of excessive abdominal adiposity, hypertrophied visceral adipocytes become resistant to the antilipolytic effects of insulin,<sup>109</sup> and increased the flux of free fatty acids into the portal vein, which drains directly into the liver. The overabundance of free fatty acids presented the liver directly from visceral adipocytes were thought to overwhelm hepatic metabolic processes, causing an increase in hepatic glucose production, decreased degradation of apolipoprotein B, and increased secretion of lipid-laden lipoproteins.<sup>110</sup> Significant doubt was

cast on the portal theory, however, when Nielsen et al.<sup>111</sup> observed the relative contribution of portally-delivered free fatty acids (FFA) from visceral and systemic sources. In obese subjects, only 20-25% of portally-delivered FFA was of visceral origin, and that percentage was even lower (5-10%) in lean subjects.<sup>111</sup> Additionally, the contribution of visceral lipolysis to total systemic FFA availability was less than 5%:<sup>111</sup> certainly insufficient stimulus to create the lipotoxic environment thought to be responsible for either  $\beta$ -cell dysfunction or peripheral insulin resistance.<sup>108</sup>

Another perhaps more plausible explanation for an altered metabolic profile in the visceraally obese is that adipose tissue also has many endocrine functions, and is known to release numerous proinflammatory molecules such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and C-reactive protein (CRP). Cross-sectional studies have shown that elevated plasma levels of these systemic inflammatory markers are associated with insulin resistance and type 2 diabetes mellitus,<sup>112-117</sup> and now longitudinal studies confirm that elevated levels of TNF- $\alpha$ , CRP and IL-6 predict the development of type 2 diabetes<sup>118-122</sup> and mortality.<sup>123, 124</sup> Elevated plasma CRP may also better predict myocardial infarction than traditional risk factor estimates.<sup>125</sup> One protein inversely associated with increasing obesity is adiponectin, an adipose-derived molecule that improves insulin signaling and provides protection against atherosclerosis.<sup>126</sup> Abdominally obese persons, especially those with high visceral fat distribution, are often characterized by increased proinflammatory markers TNF- $\alpha$ , IL-6, and CRP, and have reduced circulating adiponectin.<sup>127</sup> Although not dramatically, plasma levels of these inflammatory markers also increase with age, such that they contribute independently to morbidity and mortality, even after controlling for lifestyle factors and obesity.<sup>123</sup> Since visceral adipose tissue is known to release 2 to 3 times the amount of IL-6 than subcutaneous adipose tissue,<sup>128</sup> it stands to reason that the progressive increase of visceral adiposity in aging may influence inflammatory pathways. However, because both visceral obesity and inflammatory processes occur simultaneously, it is yet unclear which risk factor precedes the other.

### 2.3.1.3. *Health Risks of Ectopic Lipid Storage*

Perhaps because the visceral adipose tissue depot seems to correlate more highly to metabolic risk than other depots, subcutaneous adipose tissue is frequently overlooked as a significant player in the development of disease, when in fact, more than a few studies have shown that peripheral subcutaneous fat has a protective effect against the development of obesity's co-morbidities.<sup>129-134</sup> The inverse relationship between subcutaneous fat and metabolic risk seems paradoxical because metabolic disease usually increases proportionally to the degree or severity of obesity. By definition, lipodystrophy is a failure to develop adequate adipose tissue mass, resulting in lipid deposition in tissues other than the intended or metabolically favorable site for storage.<sup>135</sup> Subcutaneous adipose tissue is considered a "metabolically favorable site" for lipid storage, and under normal conditions, has the capacity to buffer lipid excess. In the lipodystrophy of aging, however, and for reasons not yet understood, the subcutaneous adipose tissue mass diminishes, and when available lipid exceeds the storage capacity of the subcutaneous fat mass, lipid is deposited in "ectopic" regions such as liver, heart, and skeletal muscle.<sup>136</sup> The visceral fat depot also appears to be a metabolically unfavorable site for excessive lipid deposition, and its growth may similarly be a marker of an upstream failure of subcutaneous adipose to appropriately deal with excessive fatty acid flux.<sup>98</sup> The mechanism by which thiazolidinediones operate supports this notion of metabolic dysfunction occurring when peripheral subcutaneous adipocytes reach filling capacity. Thiazolidinediones are medications which signal subcutaneous adipocyte cell division by binding to peroxisome proliferator-activator receptor- $\gamma$  (PPAR- $\gamma$ ), and thus reverse the lipodystrophic limitation of subcutaneous capacity by creating more adipocytes for lipid storage. What results is a reduction of circulating FFA,<sup>137</sup> redistribution of lipid from the visceral to subcutaneous depots,<sup>138-140</sup> decreased fatty liver and skeletal muscle triglyceride content<sup>141, 142</sup> and an improvement in hepatic and peripheral insulin sensitivity.<sup>141, 142</sup>

Metabolically active lean tissue is not incapable of storing some lipid. Most lean tissues maintain a small reserve of intracellular lipid for use as immediate energy and for repairing cell membranes. When faced with a constant barrage of FFA, however, these lean tissues are

infiltrated with excessive lipid, become insulin resistant, lose capacity to function normally, and eventually develop overt disease.<sup>143</sup> In the liver, lipid accumulation is referred to as hepatic steatosis, or “fatty liver.” Hepatic steatosis results in hepatic insulin resistance and elevated liver enzymes, and is related to the development of type 2 diabetes independent of obesity.<sup>3</sup>

Under normal conditions, skeletal muscle also has a small reserve of intramyocellular lipid available for energy production in oxidative pathways. With aging and inactivity, skeletal muscle has a decreased proportion of oxidative fibers and increased intramyocellular lipid. Despite increased availability of lipid within the myocyte, carnitine palmitoyltransferase remains the rate limiting step in the metabolism of fatty acyl-CoA,<sup>144</sup> and the transfer of long-chain lipid molecules into the mitochondria limits clearance or oxidation of intramyocellular lipid. Subsequent accumulation of intramyocellular lipid negatively affects peripheral insulin sensitivity and muscle glucose transport,<sup>145</sup> and independently predicts incidence of the metabolic syndrome in elderly subjects.<sup>2</sup>

Regardless of the mechanisms, accumulation of lipid in either visceral depot or lean tissue results in increased incidence of morbidity and mortality and must be prevented or treated in the elderly to avoid costly metabolic and lifestyle consequences.

### 2.3.2. Sarcopenia and Functional Impairment

The term sarcopenia was defined earlier as the steady and involuntary decline in skeletal mass that occurs with aging.<sup>34</sup> Not a rapidly-developing syndrome seen in more severe muscle wasting diseases caused by starvation, human immunodeficiency syndrome or the cachexia of congestive heart or renal failure, sarcopenia is more insidious in nature: acting as an underlying player in age-related disease and disability.<sup>146</sup> Its definition has grown to encompass such elicited causes as decrements in peripheral nervous system innervation, altered hormonal status, inflammatory effects, and altered caloric and protein intake.<sup>35</sup> These additional contributors to general skeletal muscle atrophy combine to explain much of the functional impairment, frailty, and disability commonly seen in older adults.<sup>147</sup> Not considered a diseased state, per se, the sequelae of disabling conditions which accompany clinical sarcopenia and undermine

independent living are cause for concern and should motivate prevention and treatment measures in the aging population.<sup>148</sup> Fortunately for the elderly, physical activity is a modifiable behavior associated with benefits that sometimes surpass existing pharmacological disease treatments.<sup>149</sup> The following sections will discuss in greater detail the prevalence and health toll of sarcopenia.

#### *2.3.2.1. Prevalence of Sarcopenia in Aging*

The prevalence of sarcopenia is difficult to quantify because its development is gradual, and there is truly no threshold level of lean tissue or skeletal muscle mass loss beyond which functional impairment dramatically increases. To dichotomize a continuous variable like age-related muscle loss is extremely difficult when some muscle loss is considered a natural phenomenon of aging, and when there is no simple and reliable anthropometric method of quantifying lean tissue. Various arbitrary thresholds have been proposed, however, and are currently widely used in population studies that employ imaging techniques capable of quantifying lean tissue or muscle mass. Through a population-based study conducted in New Mexico and using data from the Rosetta study<sup>150</sup> of healthy young adults as a reference, Baumgartner and colleagues<sup>151</sup> collected appendicular muscle mass data by DEXA in elderly Hispanics and non-Hispanic whites. Having no clinical definition for sarcopenia, the authors determined that muscle mass 2 standard deviations below the mean of the Rosetta population classified a subject as sarcopenic. Since individuals vary widely in skeletal structure, and a larger frame requires greater total skeletal muscle to accomplish a similar functional task, a relative skeletal muscle index was proposed using appendicular skeletal muscle in kilograms divided by height in meters squared.<sup>151</sup> The results of this study showed sarcopenia at a prevalence of 13.5% and 23.1% in white men and women, respectively, 65-69 years of age. This prevalence climbed steadily every half-decade through the over-80 group, within which 52.6% of men and 43.2% of women had a relative skeletal muscle index that was 2 standard deviations below the sex-specific mean standard provided by a younger population. Other epidemiological studies have since been conducted in various regions of the United States,<sup>8, 152-154</sup> Europe,<sup>155, 156</sup> and Asia,<sup>157</sup> using either

relative skeletal muscle index or a similar skeletal muscle index (skeletal muscle mass divided by total body mass, multiplied by 100) and standard deviation approach, yielding a similar increasing, age-dependent prevalence. These results, however, may be underestimates of the true population prevalence, as most studies only use healthy, non-institutionalized elderly subjects. Despite various limitations of the research to date, the message is clear: muscle loss occurs increasingly in the later decades of life, and a high percentage of our oldest old face an atrophy that would classify them as sarcopenic with reference to declining muscle mass.

Recent work by Janssen et al.<sup>158</sup> has questioned the wisdom of arbitrary cutpoints with reference solely to statistical deviation from “normal” muscle mass in younger populations, suggesting that cutpoints be made in relation to sarcopenia-induced disability. Using bioelectrical impedance data from the Third National Health and Nutrition Survey (NHANES III), these researchers examined the relationships between whole body mass estimates (indexed for height) and relative ability to perform activities of daily living. Receiver operating characteristics analyses of physical disability and skeletal muscle mass were used to derive three categories of disability risk.<sup>158</sup> From these analyses, cutpoints for moderately increasing and high disability risk were developed, creating new classifications based on disability standards: moderate (6.75 to 5.76 kg/m<sup>2</sup> in women, 10.75 to 8.51 kg/m<sup>2</sup> in men) and severe sarcopenia (<5.75 and <8.50 in men and women, respectively). Interestingly, previous sarcopenia cutpoints established by a 2 standard deviation variation from young Rosetta Study subjects<sup>151</sup> varied only slightly from these disability-based cutpoints for severe sarcopenia, yet still proved less predictive of physical disability.<sup>158</sup> By the new definitions, it was estimated that 35% of older Americans have moderate sarcopenia, and 10% have a severe degree of sarcopenia.<sup>158</sup>

#### *2.3.2.2. Functional Impairment with Muscle Loss*

The true clinical importance of sarcopenia is revealed when declining muscle mass translates into a loss of strength and capacity for work, or ultimately renders a person unable to accomplish the tasks of daily living. Quite literally, humans need a certain amount of muscle just to survive; earlier studies indicate that losing 40% of baseline lean mass is fatal.<sup>159, 160</sup> Loss of

muscle strength due to declining muscle mass is probably the most important detrimental effect of sarcopenia. Regardless of body weight and build, those who lack physical strength have higher mortality risk<sup>161</sup> and activities of daily life become increasingly more difficult. Ronenn Roubenoff, a leader in the field of sarcopenic research, suggests<sup>162</sup> that as sarcopenic seniors become weaker, greater effort is required to accomplish ordinary tasks, and the more difficult ones are eventually abandoned. This pattern of increasing disuse is self-perpetuating, as the foregone activities no longer provide stimulus for muscle maintenance. A vicious cycle of inactivity continues into disability, dependent living, and death. The previously-mentioned New Mexico study affirmed that sarcopenic men have 3.6 times higher risk of physical disability, while women had 4.1 higher rates, even after adjustment for age and a host of other possible confounders.<sup>151</sup> In this study, odds ratios for abnormalities in gait and balance, use of a cane or walker, recent falls, or having a history of bone fractures were all significantly greater in sarcopenic seniors.<sup>151</sup>

While the results from cross-sectional studies attest to the high risk of physical disability with sarcopenic levels of muscle mass,<sup>8, 151, 152, 158</sup> longitudinal study designs describe which characteristic precedes the other. Two recent longitudinal studies have investigated the development of mobility limitations and disability. Visser et al.,<sup>163</sup> from the Health, Aging, and Body Composition (Health ABC) Study, tracked an aging cohort of over 3000 men and women (ages 70-79) over a period of 2.5 years, measuring CT axial thigh images for muscle size and degree of fat infiltration. After control for lifestyle and health factors, men who had the smallest cross-sectional mid-thigh skeletal muscle area were 90% more likely to report increases in difficulty walking a quarter mile or climbing 10 steps over that time period, while women were 68% more likely, in comparison to their peers with the largest mid thigh muscle area. These investigators also included a measure of muscle strength in their analysis, and as expected, found that the relationship between muscle size and mobility limitations was indeed mediated by muscle strength. Muscle fat infiltration, as measured by muscle attenuation, was another independent predictor of decreased mobility.<sup>163</sup>

Ian Janssen,<sup>164</sup> using data from over 5000 older men and women in the Cardiovascular Health Study, examined the relationship between muscle mass as measured by bioelectrical

impedance and disability scores eight years later as indicated by self-reported increases in difficulty performing daily tasks. When the sarcopenia cutpoints Janssen and colleagues had earlier established<sup>158</sup> were applied, it was found that only the men and women with severe sarcopenia had a greater likelihood of developing disability than their counterparts with normal levels of muscle mass, and that increased likelihood for disability was only 27% greater.<sup>164</sup>

Although both of the two recent longitudinal studies showed sarcopenia preceding increased disability rates, neither reported rate increases of the magnitude reported in cross-sectional studies.<sup>8, 151, 152, 158</sup> This observation should not be construed as evidence refuting the relationship between sarcopenia and disability. On the contrary and as noted earlier, a self-perpetuating cycle of inactivity and muscle weakening suggests a bi-directional influence of either of these two health indicators on the other, and thus it might be expected that a temporal relationship between sarcopenia and disability would be difficult to establish.

### 2.3.3. Simultaneous Obesity and Sarcopenia

Until this point in this review, the health risks of obesity and sarcopenia have been discussed independently. In reality, both phenomena occur simultaneously in the human body as a result of aging, and not only are they difficult to measure independent of one another, but the metabolic risks and disabling characteristics associated with progression of either condition are exacerbated when both are manifest.

Richard Baumgartner, the lead investigator for the New Mexico Elderly Health Study, characterized a group of over 1000 seniors by measured or estimated body fat and appendicular skeletal muscle mass. Using the cutpoints for sarcopenia he had earlier established (>2 standard deviations from the mean of representative young adults),<sup>151</sup> and a median body fat percent of the study sample, he divided his subjects into four groups: normal, obese, sarcopenic, or sarcopenic obese. Of the four, the sarcopenic obese group was much more likely to be misclassified by population-based obesity indicators such as body mass index and waist-to-hip ratio, and had significantly lower grip strength relative to body weight, indicating progress toward functional disability. Serum testosterone and insulin-like growth factor were both elevated in men with

sarcopenic obesity, and elevated serum leptin was characteristic of the sarcopenic obese, regardless of gender. Furthermore, although either sarcopenia or obesity alone were associated with significant increases in odds ratios for developing three or more physical disabilities, those who were classified as sarcopenic obese had double and even triple the odds ratios (8.72 and 11.98 for men and women, respectively) for disability than they might have had with only obesity or sarcopenia, when all were compared to their normal counterparts. Further research is needed to discover the true prevalence of sarcopenic obesity on a population level, but the evidence from this study suggests that a simultaneous diagnosis of obesity and sarcopenia results in a synergistic effect of the negative consequences associated with each disease, resulting in a marked propensity for metabolic disease and disability.

#### **2.4.0. Treating Age-Related Health Risk through Lifestyle Intervention**

Although clinicians routinely prescribe obesity reduction programs that include caloric restriction for younger obese adults, uncertainty exists regarding whether this is an appropriate strategy for obesity reduction in the elderly. The principal concern with using caloric restriction as a method of inducing weight loss in the elderly is that senescence is associated with progressive reductions in muscle mass.<sup>36, 162</sup> While caloric restriction may be effective for reduction of risk-laden adiposity, diet-induced weight loss is associated with decrements in skeletal muscle size<sup>11, 13, 165-167</sup> and strength:<sup>167</sup> perhaps injurious side effects for older persons whose muscle mass is already compromised.<sup>8</sup> Thus, the viscerally obese and muscle-deficient older patient presents the clinician with a dual challenge for which a dietary treatment traditionally prescribed younger adults may not be optimal. Understandably, prescriptions for health risk reduction should be made on a case-by-case basis, using an approach that maximizes chances for successful improvements and incorporates the personal preferences or relative abilities of each senior, and proper management of nutrition should be a fundamental component of any lifestyle intervention. In order to ascertain the effects of exercise in a lifestyle intervention independent of caloric restriction, however, the following section will provide a summary of evidence to date supporting physical activity alone as a lifestyle modification designed to provide optimal health benefit to

previously sedentary, abdominally obese seniors. Comparisons of the effects of aerobic and resistance exercise will be made for the treatment of obesity, sarcopenia, and then for sarcopenic obesity.

#### 2.4.1. Treatment of Obesity in the Elderly

Several studies have investigated the independent effects of aerobic or resistance exercise on whole body fat in the elderly. A summary of the studies to date which report whole body obesity and associated health outcome changes as a result of performing aerobic exercise in the elderly is provided in Tables 3 and 4. In an attempt to investigate the independent effect of aerobic exercise on overall obesity and health, studies were included in these two tables if whole-body obesity measurements were performed on healthy, non-diabetic older (age exceeding 60 years) men and women before and after an intervention that included aerobic exercise independent of diet or other modifications. The first thing to notice about this collection of studies is that many of them are relatively recent. Whether due to technological improvements in measurement techniques (increased availability of DEXA for whole body measurement instead of hydrostatic weighing) or a recent increase in public awareness of health risk reduction in the aging population, the previous paucity of obesity reduction studies using aerobic exercise as a sole treatment strategy in the elderly has accumulated good evidence in recent years to create a clearer picture of the effects of aerobic exercise on whole body fatness. Most,<sup>168-174</sup> but not all studies,<sup>175, 176</sup> report that participation in at least a moderate-intensity aerobic exercise program 3 to 5 days per week induces a significant reduction in body fat over time in the elderly. All studies reporting a decrease in whole body fat content show a concomitant improvement in insulin resistance, as measured either by Bergman's minimal model,<sup>177</sup> homeostasis model assessment (HOMA),<sup>178</sup> or hyperinsulinemic, euglycemic clamp technique.<sup>179</sup> In these studies, maximal oxygen consumption on a graded exercise test to exhaustion (VO<sub>2</sub>max) invariably improved. Interesting to note, however, are the studies which failed to see a whole body fat reduction, yet observed beneficial metabolic outcomes. In the recent studies by Coker et al.<sup>175</sup> and DiPietro et

**Table 3.** Effect of aerobic exercise on whole body fat and health outcomes in the elderly: randomized controlled trials

First author	Study type	Duration (weeks)	#	Sex	Age (years)	Exercise description	Body comp method	Body fat $\Delta$	Metabolic health outcomes	Health outcome $\Delta$
Coker <sup>175</sup>	2006 RCT	12	7	M/F	70 $\pm$ 2	MI (50% VO <sub>2</sub> max), 1000 kcal/wk	DEXA	--	VO <sub>2</sub> max IR by clamp	$\uparrow$ --
DiPietro <sup>176</sup>	2006 RCT	39	9	F	73 $\pm$ 2	HI (75% VO <sub>2</sub> max), 1000 kcal/wk	DEXA	--	VO <sub>2</sub> max IR by clamp	$\uparrow$ $\downarrow$
					73 $\pm$ 3	MI (65% VO <sub>2</sub> max), 1200 kcal/wk	DEXA	--	VO <sub>2</sub> peak IR by clamp	-- --
					72 $\pm$ 3	HI (80% VO <sub>2</sub> max), 1200 kcal/wk	DEXA	--	VO <sub>2</sub> peak IR by clamp	-- $\downarrow$
					61 $\pm$ 7	MI (60-75% VO <sub>2</sub> max) 45 min, 4 d/wk (some RE suggested)	DEXA	$\downarrow$	VO <sub>2</sub> max IR by HOMA	$\uparrow$ $\downarrow$
Frank <sup>170</sup> Irwin <sup>171</sup>	2005 RCT	52	87	F	61 $\pm$ 7	MI (60-75% VO <sub>2</sub> max) 45 min, 4 d/wk (some RE suggested)	DEXA	$\downarrow$	Glucose, Trig Insulin, Leptin	-- $\downarrow$
Evans <sup>173</sup>	2001 RCT	39	18	F	66 $\pm$ 3	MI (70-85% HRmax) 30 min, 3 d/wk	DEXA	$\downarrow$	VO <sub>2</sub> max	$\uparrow$
Dengel <sup>180</sup>	1996 RCT	43	10	M	60 $\pm$ 2	MI (65-85% HRR)	Hydro	--	IR by clamp OGTT glucose OGTT insulin	$\downarrow$ -- $\downarrow$
Hersey <sup>181</sup>	1994 RCT	26	16	M/F	72 $\pm$ 2	MI (75-85% HRR) 35-45 min, 3 d/wk	Skinfolds	$\downarrow$	VO <sub>2</sub> max OGTT glucose OGTT insulin Lipid profile	$\uparrow$ $\downarrow$ $\downarrow$ $\downarrow$ --

Abbreviations: RCT = randomized controlled trial; # = number of subjects; M = male; F = female; RE = resistance exercise; MI = moderate intensity exercise, HI = high intensity exercise, VO<sub>2</sub>max = maximal oxygen consumption; VO<sub>2</sub>peak = peak oxygen consumption; HRmax = maximal heart rate; HRR = heart rate reserve; kcal/wk = kilocalories expended per week; min = minutes; d/wk = days per week; DEXA = dual energy x-ray absorptiometry; Hydro = hydrostatic weighing;  $\Delta$  = exercise-induced change over intervention period; IR = insulin resistance; clamp = hyperinsulinemic, euglycemic clamp; HOMA = homeostasis model assessment; OGTT = oral glucose tolerance test; Trig = triglycerides.

**Table 4.** Effect of aerobic exercise on whole body fat and health outcomes in the elderly: other study designs

First author	Year	Study type	Duration (weeks)	#	Sex	Age (years)	Exercise description	Body comp method	Body fat $\Delta$	Metabolic health outcomes	Health outcome $\Delta$
O'Leary <sup>172</sup>	2006	NR	12	16	M/F	63 $\pm$ 1	MI (85% HRmax) 60 min, 5 d/wk	Hydro	$\downarrow$	VO <sub>2</sub> max OGTT Leptin	$\uparrow$ $\downarrow$ $\downarrow$
Ferrara <sup>169</sup>	2006	NR	26	9	M	63 $\pm$ 1	MI (75-80% HRR) 45-50 min, 3 d/wk	DEXA	$\downarrow$	Adiponectin, TNF $\alpha$ VO <sub>2</sub> max IR by clamp	-- $\uparrow$ $\downarrow$
Evans <sup>168</sup>	2005	RNC	39	10	M/F	80 $\pm$ 3	HI (83% VO <sub>2</sub> peak) 58 min, 3 d/wk	DEXA	$\downarrow$	Glucose, Insulin VO <sub>2</sub> peak OGTT SI	-- $\uparrow$ $\uparrow$
Kohrt <sup>182</sup>	1992	NR	27	93	M/F	65 $\pm$ 2	HI (80% VO <sub>2</sub> max) 46 min, 4 d/wk	Hydro	$\downarrow$	TC, LDL HDL, Trig None	$\downarrow$ $\downarrow$ --
Schwartz <sup>183</sup>	1991	RNC	27	15	M	68 $\pm$ 6	HI (85% HRR) 45 min, 5 d/wk	Hydro	$\downarrow$	VO <sub>2</sub> max	$\uparrow$
Kahn <sup>174</sup>	1990	NR	26	13	M	68.6	HI (80-85% HRR) 45 min, 5 d/wk	Hydro	$\downarrow$	VO <sub>2</sub> max IR by minimal model	$\uparrow$ $\downarrow$

Abbreviations: NR = not randomized; RNC = randomized, but no control group; # = number of subjects; M = male; F = female; RE = resistance exercise; MI = moderate intensity exercise, HI = high intensity exercise, VO<sub>2</sub>max = maximal oxygen consumption; VO<sub>2</sub>peak = peak oxygen consumption; HRmax = maximal heart rate; HRR = heart rate reserve; min = minutes; kcal/wk = kilocalories expended per week; d/wk = days per week; DEXA = dual energy x-ray absorptiometry; Hydro = hydrostatic weighing;  $\Delta$  = exercise-induced change over intervention period; IR = insulin resistance; clamp = hyperinsulinemic, euglycemic clamp; HOMA = homeostasis model assessment; OGTT = oral glucose tolerance test; SI = sensitivity index; TNF $\alpha$  = tumor necrosis factor,  $\alpha$ ; TC = total cholesterol; L(H)DL = low (high) density lipoprotein; Trig = triglycerides.

**Table 5.** Effect of resistance exercise on whole body fat and health outcomes in older men and women

First author	Year	Study type	Duration (weeks)	#	Sex	Age (years)	Exercise description	Body comp method	Body fat $\Delta$	Metabolic health outcomes	Health outcome $\Delta$
Ferrara <sup>169</sup>	2006	NR	26	13	M	63 $\pm$ 1	6 exercises, 1 set UB, 2 sets LB, 8-12 reps, 3 d/wk	DEXA	--	VO <sub>2</sub> max IR by clamp Glucose, Insulin	-- $\downarrow$ --
Binder <sup>184</sup>	2005	RCT	13	53	M/F	83 $\pm$ 4	6 exercises, 3 sets, 8-12 reps, 3 d/wk	DEXA	--	None	--
Hunter <sup>185</sup>	2002	NR	26	14 12	M F	68 $\pm$ 4 66 $\pm$ 4	11 exercises, 2 sets, 10 reps, 3 d/wk	ADP	$\downarrow$	None	
Ryan <sup>186</sup>	2001	NR	26	11 10	M F	70 $\pm$ 1 69 $\pm$ 1	11 exercises, 1 set UB, 2 sets LB, 15 reps, 3 d/wk	DEXA	--	IR by clamp Glucose, Insulin Leptin in M Leptin in F	-- -- $\downarrow$ --
Trueth <sup>187</sup>	1995	NR	16	14	F	67 $\pm$ 1	12 exercises, 2 sets 12 reps, 3 d/wk	Hydro	--	VO <sub>2</sub> max Lipid Profile	-- --
Trueth <sup>188</sup>	1994	NR	16	13	M	60 $\pm$ 4	14 exercises, 2 sets 15 reps, 3 d/wk	DEXA Hydro	$\downarrow$ $\downarrow$	VO <sub>2</sub> max	--
Hersey <sup>181</sup>	1994	RCT	26	17	M/F	72 $\pm$ 2	10 exercises, 1 set 8-12 reps, 3 d/wk	Skinfolds	--	VO <sub>2</sub> max OGTT glucose OGTT insulin Lipid profile	-- -- -- --

Abbreviations: RCT = randomized controlled trial; NR = not randomized; RNC = randomized, but no control group; # = number of subjects; M = male; F = female; RE = resistance exercise; d/wk = days per week; UB = upper body exercises; LB = lower body exercises; reps = repetitions; VO<sub>2</sub>max = maximal oxygen consumption; DEXA = dual energy x-ray absorptiometry; Hydro = hydrostatic weighing; ADP = air displacement plethysmography;  $\Delta$  = exercise-induced change over intervention period; OGTT = oral glucose tolerance test; IR = insulin resistance; clamp = hyperinsulinemic, euglycemic clamp; Ins = fasting plasma insulin; HbA1c = glycosylated hemoglobin.

al.,<sup>176</sup> higher intensities of aerobic exercise induced significant improvements in insulin sensitivity, while lower intensities did not, despite equivalent energy expenditure during exercise and an absence of whole body fat loss in either group over a substantial intervention period. While a possible explanation for the lack of observed whole body fat change may be the low subject numbers in either study, it is also possible that fat mobilization may be preferentially reduced in a region-specific way during aerobic exercise such that significant regional fat changes could be occurring that are not detected by whole body measurement methods, and these changes could explain, or at least be correlated with the health benefits of exercise.

A similar collection of studies showing the effect of resistance exercise on whole body fat and health outcomes is shown in Table 5. Comparative inspection of these tables reveals interesting trends that highlight the difference between aerobic and resistance exercise in their relative ability to reduce whole body obesity and affect change in health-related outcomes. The first notable difference between aerobic and resistance exercise is that with the exception of only one non-randomized study, resistance exercise did not induce a significant change in whole body fat. Furthermore, no body composition study has observed a change in  $VO_{2max}$ , and only one of three studies report improvements in insulin resistance as a result of resistance exercise training. Also of note is the relative paucity of randomized controlled trials using elderly subjects; a majority of the studies to date lack randomization or a control group. In fact, the only randomized controlled trial in this population investigated body composition, but did not measure any metabolic outcomes.

A limitation to studying whole body obesity changes, especially in older men and women, is that measures of whole body fat may not be sensitive to regional deposition changes. Pursuant to the notion that adiposity in the elderly is characterized by a shift toward abdominal regions, and that significant health risk is associated with visceral fat accumulation, it is reasonable to argue that treatment strategies intended to reduce health risk in aging should focus predominantly on the reduction of abdominal fat depots and measure them for resultant change. Intervention trials performed in the elderly (mean age exceeding 60 years) wherein

measures of abdominal adiposity were specifically reported are summarized for aerobic and resistance exercise in Tables 6 and 7, respectively.

Similar to Tables 3 and 4, the research summarized in Table 6 provides evidence of fat reduction with aerobic exercise training in older men and women, yet not all studies agree. Of notable exception are the randomized controlled trials conducted by DiPietro et al.<sup>189</sup> and Dengel et al.,<sup>180</sup> which failed to observe exercise-induced abdominal fat changes over 4 and 10 months, respectively, while reporting significant improvements in cardiorespiratory fitness and insulin sensitivity measures. While both trials contained relatively few subjects and the latter relied on only waist-to-hip ratio, a rather crude measure of central adiposity, they comprise a majority of the few randomized controlled trials investigating abdominal change in a senior population. The remaining randomized controlled trial, the results of which are reported by both Frank et al.<sup>170</sup> and Irwin et al.,<sup>171</sup> contains many more subjects than the other two randomized controlled trials combined and finds a small yet significant change in abdominal fat depots accompanying meaningful fitness and metabolic improvements. Although the other studies in Table 4 either lack randomized design<sup>169, 172, 182</sup> or a comparative control group,<sup>183</sup> all demonstrate significant reductions in abdominal adipose tissue depots with concomitant health risk improvements in fitness and metabolic outcomes for senior men and women who train aerobically.

While the results of trials investigating the effect of resistance training on abdominal fat in the elderly (shown in Table 6) are also not unanimous, they stand in stark contrast to the results of aerobic exercise trials, with fully half of the studies failing to report significant reductions in abdominal adiposity,<sup>169, 184, 186</sup> including the only two trials which reported significant improvements in metabolic health outcomes: decreased insulin resistance<sup>169</sup> and decreased plasma leptin levels in men.<sup>186</sup> Furthermore, all but one of the trials were of non-randomized design, which brings into question the biases introduced regarding subject self-selection. The only randomized controlled trial investigating resistance exercise and changes in regional fat deposition in the elderly did not observe a change in abdominal adiposity, nor was any metabolic variable measured concurrently.

**Table 6.** Effect of aerobic exercise on abdominal fat and health outcomes in elderly men and women

First author	Study type	Duration (weeks)	#	Sex	Age (years)	Exercise description	Abdominal assessment method	Fat $\Delta$	Metabolic health outcomes	Health outcome $\Delta$
O'Leary <sup>172</sup>	2006 NR	12	16	M/F	63 $\pm$ 1	MI (85% HRmax) 60 min, 5 d/wk	VAT by CT ASAT by CT	↓ ↓	VO <sub>2</sub> max OGTT Leptin Adiponectin, TNF $\alpha$	↑ ↓ ↓ --
Ferrara <sup>169</sup>	2006 NR	26	9	M	63 $\pm$ 1	MI (75-80% HRR) 45-50 min, 3 d/wk	VAT by CT ASAT by CT WC	-- ↓ --	VO <sub>2</sub> max IR by clamp Glucose, Insulin	↑ ↓ --
Frank <sup>170</sup> Inwin <sup>171</sup>	2005 RCT 2003	52	87	F	61 $\pm$ 7	MI (60-75% VO <sub>2</sub> max) 45 min, 4 d/wk (some RE suggested)	VAT by CT ASAT by CT WC	↓ ↓ ↓	VO <sub>2</sub> max IR by HOMA Glucose, Trig Insulin, Leptin	↑ ↓ -- ↓
DiPietro <sup>189</sup>	1998 RCT	17	9	M/F	72 $\pm$ 1	MI (60-75% HRmax)	VAT by CT ASAT by CT WC, WHR	-- -- --	VO <sub>2</sub> peak Plasma FFA OGTT glucose OGTT insulin	↑ ↓ ↓ ↓
Dengel <sup>180</sup>	1996 RCT	43	10	M	60 $\pm$ 2	MI (65-85% HRR)	WHR	--	VO <sub>2</sub> max IR by clamp OGTT glucose OGTT insulin	↑ ↓ -- ↓
Kohrt <sup>182</sup>	1992 NR	27	93	M/F	65 $\pm$ 2	HI (80% VO <sub>2</sub> max) 46 min, 4 d/wk	WC	↓	None	
Schwartz <sup>183</sup>	1991 RNC	27	15	M	68 $\pm$ 6	HI (85% HRR) 45 min, 5 d/wk	VAT by CT ASAT by CT Chest by CT WC	↓ ↓ ↓ ↓	VO <sub>2</sub> max	↑

Abbreviations: RCT = randomized controlled trial; NR = not randomized; RNC = randomized, but no control group; # = number of subjects; M = male; F = female; RE = resistance exercise; MI = moderate intensity exercise, HI = high intensity exercise, VO<sub>2</sub>max = maximal oxygen consumption; HRmax = maximal heart rate; HRR = heart rate reserve; min = minutes; kcal/wk = kilocalories expended per week; d/wk = days per week; VAT = visceral adipose tissue; ASAT = abdominal subcutaneous adipose tissue; CT = computed tomography; WC = waist circumference; WHR = waist-to-hip ratio;  $\Delta$  = exercise-induced change over intervention period; IR = insulin resistance; clamp = hyperinsulinemic, euglycemic clamp; HOMA = homeostasis model assessment; OGTT = oral glucose tolerance test; TNF $\alpha$  = tumor necrosis factor,  $\alpha$ ; Trig = triglycerides.

**Table 7.** Effect of resistance exercise on abdominal fat and health outcomes in elderly men and women

First author	Year	Study type	Duration (weeks)	#	Sex	Age (years)	Exercise description	Abdominal assessment method	Fat $\Delta$	Metabolic health outcomes	Health outcome $\Delta$
Ferrara <sup>169</sup>	2006	NR	26	13	M	63 $\pm$ 1	6 exercises, 1 set UB, 2 sets LB, 8-12 reps, 3 d/wk	VAT by CT ASAT by CT WC	--	VO <sub>2</sub> max IR by clamp Glucose, Insulin	-- $\downarrow$ --
Binder <sup>184</sup>	2005	RCT	13	53	M/F	83 $\pm$ 4	6 exercises, 3 sets, 8-12 reps, 3 d/wk	VAT by MRI ASAT by MRI	--	None	--
Hunter <sup>185</sup>	2002	NR	26	14	M	68 $\pm$ 4	11 exercises, 2 sets, 10 reps, 3 d/wk	VAT by CT ASAT by CT	--	None	--
				12	F	66 $\pm$ 4	11 exercises, 2 sets, 10 reps, 3 d/wk	VAT by CT ASAT by CT	$\downarrow$ $\downarrow$	None	--
Ryan <sup>186</sup>	2001	NR	26	11 10	M F	70 $\pm$ 1 69 $\pm$ 1	11 exercises, 1 set UB, 2 sets LB, 15 reps, 3 d/wk	DEXA trunk	--	IR by clamp Glucose, Insulin Leptin in M Leptin in F	-- -- $\downarrow$ --
Trueth <sup>187</sup>	1995	NR	16	14	F	67 $\pm$ 1	12 exercises, 2 sets 12 reps, 3 d/wk	VAT by CT ASAT by CT WC, WHR	$\downarrow$ -- --	VO <sub>2</sub> max Lipid Profile	-- -- --
Trueth <sup>188</sup>	1994	NR	16	13	M	60 $\pm$ 4	14 exercises, 2 sets 15 reps, 3 d/wk	DEXA trunk WC	$\downarrow$ --	VO <sub>2</sub> max	-- --

Abbreviations: RCT = randomized controlled trial; NR = not randomized; RNC = randomized, but no control group; # = number of subjects; M = male; F = female; RE = resistance exercise; d/wk = days per week; UB = upper body exercises; LB = lower body exercises; DEXA = dual energy x-ray absorptiometry; VAT = visceral adipose tissue; ASAT = abdominal subcutaneous adipose tissue; CT = computed tomography; MRI = magnetic resonance imaging; WC = waist circumference; WHR = waist-to-hip ratio;  $\Delta$  = exercise-induced change over intervention period; VO<sub>2</sub>max = maximal oxygen consumption; IR = insulin resistance; clamp = hyperinsulinemic, euglycemic clamp.

Of the studies summarized in Tables 6 and 7, only one recently-published study compares groups of aerobic and resistance exercisers and their comparative body composition changes across time in the same trial. In this study conducted by Ferrara and colleagues,<sup>169</sup> two groups of older men were created by non-random assignment and performed either aerobic or resistance exercise three days per week for 6 months while adjusting calorie intake for weight maintenance throughout the intervention period. Despite a design that required recovery of exercise-induced energy expenditure through dietary means, aerobic exercisers lost a small but significant amount of body weight, while the resistance exercisers gained. Consistent with the results of other studies, aerobic training resulted in a 6.2% reduction of whole body fat mass, measured by DEXA, which was matched by a 7% abdominal subcutaneous fat loss, measured by CT.<sup>169</sup> Visceral adipose tissue did not change enough to achieve significance, which would have been an unexpected finding in middle-aged men and women due to reports of preferential reductions of VAT with aerobic exercise.<sup>11, 190</sup> However, studies conducted in the elderly are equivocal in their findings, with some showing significant reductions in visceral adipose tissue<sup>170-172</sup> while others fail to observe a change.<sup>189</sup>

The equivocal nature of the results to date regarding the comparative effects of aerobic or resistance exercise on body composition and reduction of health risk in older men and women reinforces the need for continued research. A few trends in the literature are noteworthy, however. First, aerobic training, especially of higher intensity, generally results in significant reductions in whole body fat and abdominal adipose tissue depots, and those changes accompany significant improvements in aerobic fitness and insulin sensitivity. Second, resistance training appears to be less effective at mobilizing the adipose tissue depots that are usually associated with age-related decreases in insulin sensitivity, and does not appear to improve aerobic capacity. While these generalized statements comparing aerobic or resistance exercise can be made with reference to various results available in current literature, there are currently no randomized controlled trials that simultaneously test these two exercise modalities for their independent effects on total or regional adiposity, nor has any such trial also investigated the

resultant metabolic changes that occur when previously sedentary abdominally obese seniors embark on either type of exercise program.

#### 2.4.2. Treatment of Sarcopenia in the Elderly

Inherent to the argument that weakness perpetuates inactivity (and vice versa) is the reverse notion that purposeful training of skeletal muscle serves to maintain its size and strength over time, which will also improve activity and mobility. Indeed, a well-known cross-sectional study in elderly master weightlifters has shown that participation in resistance weight training 3 days a week for at least 12 years showed a maintenance of muscle mass and strength that was comparable to youthful controls.<sup>191</sup> Interestingly, elderly master swimmers (who perform a predominantly aerobic activity) measured in that same study displayed comparatively significant decrements in muscle strength and size over 12 years.<sup>191</sup> This study and others<sup>192, 193</sup> that have investigated the physically active elderly versus their sedentary, age-matched peers suggest that no other exercise modality yields the same muscle-maintaining benefits as resistance exercise. Benefits of training are also not limited to the lifetime fitness enthusiasts. Sedentary and even frail elderly have experienced significant muscle hypertrophy as a result of resistance exercise: many with as short an intervention period as 12 weeks of progressive resistance training.<sup>194</sup>

Multiple reviews have been published in recent years summarizing the literature on the effects of resistance exercise training on elderly subjects.<sup>149, 194-196</sup> It should be noted that despite the seeming wealth of available data, many trials failed to control for confounding variables or do not report with sufficient detail the specifics of intervention such that summary statements can be made regarding the effect of resistance exercise on various outcome measures.<sup>195, 196</sup> However, an overriding theme throughout the studies was a significant strength improvement, especially in leg extensors.<sup>149, 194-196</sup> Lower-limb strength gains were reported relatively uniformly across the studies with significant improvements in gait speed and the ability to stand up from a chair or seated position.<sup>195</sup> These seemingly simple and practical outcome measures of walking speed or getting in and out of a chair represent improvements in lifestyle afforded by increased muscle strength and or power, and their utility is proven by the ease at which seniors are able to carry out

the activities of daily life.<sup>197</sup> Thus, it is now widely accepted that resistance training 2 to 3 days per week will lead to strength and muscle mass increases in the elderly, inasmuch that the American College of Sports Medicine recommends strength training as an integral part of physical activity programming for older adults, and in particular, for frail seniors who stand to derive the most benefit from improvements in muscle mass or strength.<sup>15</sup>

#### 2.4.3. Exercise Modalities for Treatment of Sarcopenic Obesity

Granted that only a small portion of the elderly population would be classified as sarcopenic obese by clinical standards, a majority of older men and women choose a sedentary lifestyle that predisposes them to escalating obesity and muscular atrophy. Despite ample evidence that aerobic exercise is an effective strategy for obesity reduction and that resistance exercise can be used to maintain and even restore functional capacity by increasing muscle mass in the elderly, only a third of people over 75 and half of seniors between 65 and 74 engage in any leisure time physical activity at all.<sup>198</sup> Which avenue should a practitioner take when prescribing a program of physical activity to a sedentary, senior population with an expanding waistline and muscle mass deteriorating from disuse? Is it aerobic exercise or resistance exercise which holds the most benefits for this population?

Owing to the specificity of training effects, a combination of the two modalities has been advocated for optimal physical function and health in the elderly.<sup>15, 199-201</sup> Interestingly, although these exercise recommendations are based on decades of research, few studies have been conducted in the elderly which directly compare the effects of aerobic or resistance exercise in the same exercise trial and employ measures that capture the relative benefits of each modality as they affect major health outcomes. The non-randomized exercise trial by Ferrara et al.<sup>169</sup> was the first to provide insight into the comparative insulin sensitivity and abdominal adaptations of an aerobic or resistance training in older, obese men. The authors reported significant strength gains were observed in both upper and lower body muscle groups in resistance exercisers by comparison to those in the aerobic group, despite no significance in appendicular lean tissue mass or mid-thigh skeletal muscle area.<sup>169</sup>

Several studies to date have documented substantial strength, endurance, and even metabolic improvements associated with a combined program of aerobic and resistance training in the elderly.<sup>202-207</sup> However, only one trial to date provides measures of aerobic capacity, muscular strength, and associated functional fitness change in a direct comparison between an aerobic exercise only, resistance exercise only, and a combination of the two exercise modalities in a group of previous-sedentary senior men and women. This randomized controlled design employed by Wood and colleagues<sup>208</sup> identified the independent treatment effect of both aerobic and resistance exercise as compared to control while also considering whether one modality may interfere with the benefits of the other when attempted concurrently.

The notion of one exercise modality interfering with the expected outcomes of another in a combined exercise training program has been investigated in studies with younger adults. While some studies report an impaired strength development when aerobic exercise is combined with an existing resistance training program,<sup>209-212</sup> others do not observed a compromise in relative strength gains.<sup>202, 208, 213, 214</sup> On the other hand, no study has yet shown that adding resistance training to an aerobic program interferes with improvements in aerobic endurance.<sup>202, 211, 212</sup> The study by Wood et al.<sup>208</sup> responds to the possible interference of aerobic training on strength gains by reducing the weekly volume of aerobic and resistance exercise in the combined group to match the volume performed by either modality alone. The results of this 12-week study showed no interference of aerobic exercise on strength or functional fitness gains when the modalities were combined.<sup>208</sup> In fact, the combined group outperformed the other exercise groups on strength and agility scores obtained by functional fitness testing.<sup>208</sup>

The results of this randomized controlled trial support the recommendations set forth by the American College of Sports Medicine (ACSM) position panel on exercise for older adults,<sup>15</sup> and seemingly provide answers to the questions regarding which modality or combination of exercises is most beneficial for functionality and strength in seniors approaching sarcopenic obesity. However, several questions still remain unanswered. First, the study by Wood et al.<sup>208</sup> failed to provide any measures of skeletal muscle mass and obesity, or more specifically, abdominal adiposity changes that may have occurred as a result of exercise intervention.

Second, although blood pressure was monitored, no other meaningful metabolic parameters were investigated which are known to be highly related to physical function, health, and disability such as insulin resistance or plasma markers of inflammation or disease. Lastly, the subjects composing each intervention group were of mixed gender, masking any possible gender-specific responses to exercise that may have driven the relationships found in the results. Despite its limitations, this study provides intriguing evidence that a combination of aerobic and resistance exercise improves functionality in seniors better than either exercise modality alone, and should be employed as a therapeutic strategy to prevent the onset of disability in the elderly.

### **2.5.0. Summary**

As a natural part of the aging process, but exacerbated by inactivity, abdominal obesity accumulates and appendicular muscle mass declines. Visceral fat deposition brings with it a host of debilitating metabolic diseases, including insulin resistance and dyslipidemia. Sarcopenia reduces functional capacity, threatens dependency on others, and increases risk of mortality. Simultaneous presentation of both conditions, a state termed sarcopenic obesity, results in a synergistic compounding of metabolic and disability risk. Aerobic training reduces whole body and abdominal adiposity, but has not been shown as an effective method of restoring muscle mass. Resistance training results in muscle hypertrophy even in the frail elderly and restores ability to perform activities of daily living, yet is not a potent stimulus for obesity reduction. It is thought that a combination of aerobic and resistance exercise should provide seniors with a therapeutic strategy that is tailored to the specific body compositional and functional needs of aging. However, only one randomized controlled trial to date has investigated the independent and combined effects of these two exercise modalities as they relate to strength and functional improvements in the elderly. Absent from the literature are randomized controlled trials investigating the separate and combined effects of aerobic and resistance exercise on visceral and subcutaneous adiposity, muscle mass, insulin resistance, or other metabolic outcomes in seniors. The effect of gender on these relationships has also not been directly investigated. The

results of trials investigating the type of lifestyle modification that provides most benefit to seniors currently on the pathway toward sarcopenic obesity are required.

The Senior Study responds to the paucity of data in the literature regarding the therapeutic use of exercise for the reduction of health risk in the elderly. Using a well-controlled, randomized design in an abdominally obese elderly population, the Senior Study investigates the effects of exercise using gold standard methodologies for determination of muscle mass, total and visceral fat, and insulin resistance. A novel aspect of the design is that the effects of aerobic exercise, resistance exercise, or a combination of the two modalities are observed and compared in the absence of caloric restriction. The results of this investigation provide the basis for improved therapeutic strategies for the prevention and treatment of abdominal obesity, reduction of health risk, and improvement of physical function in older men and women.

## **Chapter 3. First Manuscript**

**Effects of Exercise Modality on Visceral Fat, Skeletal Muscle and Insulin Resistance in  
Obese Older Men and Women: A Randomized Controlled Trial**

## **ABSTRACT**

**CONTEXT:** Aging is associated with marked increases in visceral obesity and associated insulin resistance concurrent with decreases in skeletal muscle mass and functional capacity. The optimal exercise modality for simultaneous treatment of abdominal obesity, insulin resistance and loss of muscle mass is unknown.

**OBJECTIVES:** To compare the effects of a six-month program of aerobic and/or resistance exercise without caloric restriction on changes in visceral fat, skeletal muscle, and insulin resistance in obese older men and women.

**DESIGN:** Randomized controlled trial.

**SETTING:** Queen's University Exercise Physiology Laboratory.

**PARTICIPANTS:** 136 sedentary, abdominally obese older (60-79 years) men and women.

**INTERVENTION:** Six months of progressive whole-body resistance exercise (RE), aerobic exercise (AE), a combination of the two modalities (RAE) or non-exercise control (C).

**MEASUREMENTS:** Whole body skeletal muscle and total and visceral fat were quantified by whole body magnetic resonance imaging. Insulin sensitivity was assessed by hyperinsulinemic euglycemic clamp.

**RESULTS:** Total abdominal and visceral fat were reduced in all exercise groups compared to controls ( $P < 0.01$ ). Muscle mass increased in RE and RAE groups by comparison to both AE and controls ( $P < 0.05$ ). Insulin sensitivity increased in AE and RAE groups ( $P < 0.05$ ), but not RE ( $P > 0.8$ ), by comparison to controls. The insulin sensitivity increase within the RAE group was also greater than RE ( $P < 0.001$ ).

**CONCLUSION:** In abdominally obese older men and women, the combination of resistance and aerobic exercise is the optimal treatment strategy for reducing abdominal obesity and associated insulin resistance concurrent to increases in skeletal muscle mass.

**Key Words:** exercise, aging, visceral fat, insulin resistance

## INTRODUCTION

The prevalence of abdominal obesity in older men and women is already high and increasing.<sup>1</sup> Of particular concern is that with aging, an expanding waistline represents a disproportionate increase in visceral adipose tissue, an established independent predictor of morbidity<sup>2, 3</sup> and mortality.<sup>4</sup> The increase in visceral adipose tissue with aging is at least partially responsible for the current epidemic of type 2 diabetes,<sup>215</sup> a disease that contributes substantially to the burden of health care in the United States.<sup>216</sup>

Diet-induced weight loss has been the cornerstone of a lifestyle-based treatment for obesity and its related chronic diseases.<sup>82</sup> While this strategy may effectively reduce abdominal obesity and related insulin resistance,<sup>107, 217</sup> weight loss induced by caloric restriction alone is also associated with decrements in skeletal muscle size<sup>11, 13, 165-167</sup> and strength.<sup>167</sup> For the elderly, a loss of skeletal muscle mass and strength is a detriment to functional capacity and increases the likelihood of disability.<sup>8</sup> Thus, a viscerally obese and muscle-deficient older patient presents a dual challenge to the clinician and raises questions as to the optimal treatment strategy for reducing abdominal obesity concurrent with a preservation and/or increase in skeletal muscle mass.

Although exercise is commonly associated with a decrease in abdominal fat and an increase in muscle, there is some uncertainty as to which modality of exercise is most beneficial for the reduction of metabolic risk in older adults. Performing aerobic exercise in the absence of caloric restriction has been shown to maintain muscle size and strength despite a significant reduction in body weight and obesity<sup>167</sup> and improves insulin resistance, likely through the mechanism of visceral fat reduction.<sup>171, 172</sup> Resistance exercise increases muscle mass and functional capacity in the elderly,<sup>218</sup> and has been shown to reduce visceral fat in several non-randomized trials.<sup>185, 187</sup> It has been suggested that combining the two exercise modalities is the optimal treatment strategy for health risk reduction.<sup>15, 199-201</sup> However, absent from the literature are randomized controlled trials comparing the independent and combined effects of aerobic and resistance exercise on visceral obesity and insulin resistance in elderly subjects.

We performed a randomized controlled trial to establish the independent and combined effects of resistance and aerobic exercise on abdominal and visceral fat, insulin resistance, and skeletal muscle in abdominally obese older men and women. Our goal was to evaluate modalities of exercise that were consistent with consensus guidelines and to implement them in the absence of caloric restriction with the intent to produce a modest, exercise-induced weight loss that would be associated with substantial improvements in all three outcomes.

## **METHODS**

### **Participants**

Non-smoking, sedentary, overweight senior men and women, 60 to 80 years of age were recruited from the Kingston, Ontario, Canada region. Inclusion criteria required a waist circumference of >102 cm in men and >88 cm in women and stable weight ( $\pm 2$  kg) for six months prior to study entry. Potential participants were excluded if they reported a history of heart disease, stroke, diabetes or any condition that would prevent them from engaging in an exercise study; currently dieting or intent to diet; or if they were already engaging in two or more planned exercise sessions per week. Blood pressure and lipid-lowering medications were allowed if maintained throughout the trial. All participants received medical clearance from a personal physician and signed an informed consent in accordance with ethical guidelines of Queen's University.

Eligible participants were allocated by computer-generated, sex-stratified random assignment into a non-exercise control or one of three exercise training groups: resistance exercise (RE), aerobic exercise (AE), or a combination of resistance and aerobic exercise (RAE). Randomized group assignment was issued upon completion of a majority of baseline assessments, and was not revealed to those conducting baseline tests. Of the 136 men and women randomized, nineteen did not complete their assigned six-month treatment (Figure 1). Discontinuation due to musculoskeletal pain was due primarily to arthritis or involved a joint injured prior to participation. Those who did not complete the trial did not differ significantly in any baseline anthropometric variable from those who completed ( $P > 0.10$ ).

### **Dietary Assessment**

During the baseline period, participants were taught by a nutritionist to continue a weight-maintenance calorie intake while recording their daily consumption of self-selected foods. A healthy balance of macronutrients (approximately 55% carbohydrate, 15% protein, and 30% fat) was encouraged, and body weight was monitored for approximately four weeks to ensure that daily calorie targets were appropriate for weight maintenance. During the intervention, participants were required to maintain calorie levels determined at baseline unless weight change

exceeded that predicted by exercise-induced energy expenditure. All participants attended nine one-hour seminars in which the nutritionist taught healthy food selection and preparation. Participants continued to keep and analyze detailed daily food records throughout the duration of the study (approximately 29 weeks). The nutritionist regularly reviewed records to assure compliance to established weight maintenance calorie targets, and upon completion of the study, analyzed two representative weeks of records (week 4 and week 20 of the intervention) by a computerized program (Food Processor, ESHA Research, Salem, Oregon) to assess accuracy of calculated results.

### **Exercise Regimen**

Aerobic and resistance exercise interventions were consistent with consensus recommendations for exercise-related health benefits<sup>15</sup> in older adults. All exercise sessions were by appointment and supervised within the facilities of the corresponding author.

Participants randomized into either the RE or RAE group performed resistance training 3 days per week. For each training session, the following nine exercises were performed: chest press, leg extension, shoulder raise, leg flexion, superpullover or lat pulldown (latissimus dorsi), triceps extension, biceps curl, abdominal crunch, and modified pushups. Subjects performed one set of between eight and fifteen repetitions to volitional fatigue for all exercises during each session. The weight lifted was increased when fifteen repetitions was exceeded. Relative strength increases were assessed by subtracting the weight lifted in the 4<sup>th</sup> week from the final week in the training, and expressed as a percentage of the 4<sup>th</sup> week's weight.

Those randomized to the AE group performed thirty minutes of moderate-intensity exercise (brisk walking or light jogging between 60 to 75% of peak oxygen uptake or 75 to 85% maximal heart rate), with five minutes designated for warm up and cool down, respectively, for a total of forty minutes on motorized treadmills, five days per week. Exercise intensity was monitored every five minutes using an automated heart rate monitor (Polar Oy, Kempele, Finland). Energy expenditure during the exercise program was determined using the heart rate and oxygen uptake data obtained from the baseline graded exercise test, which was adjusted using the results from a subsequent graded exercise test performed in the second month of

exercise. Participants in the RAE group performed the aerobic exercise protocol only three days per week in addition to the resistance exercise protocol.

### **Measurement of Body Composition**

Anthropometric measurements were taken at baseline and during the last week of intervention. Barefoot standing height was obtained to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass was measured on a balance scale calibrated to the nearest 0.1 kg with participants dressed in standard T-shirts and shorts. Waist circumference was obtained in a standing position using the average of two measures within 1.0 cm at the superior edge of the iliac crest.

Total and regional muscle mass and total fat mass were measured by magnetic resonance imaging (MRI) in a whole-body assessment protocol established elsewhere.<sup>12</sup> Images were obtained by a General Electric, 1.5-T magnet at baseline and follow-up. Once acquired, the MRI data were transferred to a stand-alone workstation for analysis using specially-designed computer software (Tomovision, Montreal, QC, Canada), the procedures for which have been described elsewhere.<sup>12, 219</sup> Volume units (liters) of tissues were converted to mass units (kilograms) multiplying the volumes by an assumed constant density for adipose tissue (0.92 kg/L) and fat-free skeletal muscle (1.04 kg/L).<sup>220</sup> Visceral and abdominal subcutaneous tissue masses were calculated using five equally-spaced cross-sectional images from five centimeters below to twenty centimeters above the L4-L5 intervertebral space.

### **Measurement of Cardiorespiratory Fitness**

Cardiorespiratory fitness (Peak  $\text{VO}_2$ ) was determined using a graded maximal treadmill test that employed a constant walking speed, progressive increases in treadmill grade, and the use of standard open-circuit spirometry techniques (SensorMedics, Yorba Linda, CA) at baseline, during the 2<sup>nd</sup> month of exercise, and in the final week of intervention. Peak  $\text{VO}_2$  was attained when the subject reached volitional fatigue and at least two of the following three criteria were achieved: no increase in  $\text{VO}_2$  despite further increases in treadmill grade, a respiratory exchange ratio in excess of 1.10, and a heart rate exceeding 85% of age-predicted maximum ( $208 - 0.7 \times \text{age}$ ).<sup>221</sup>

### **Measurement of Insulin Sensitivity and Glucose Tolerance**

Insulin sensitivity was assessed by 3-hour hyperinsulinemic euglycemic clamp according to standard laboratory procedures we have described previously,<sup>190</sup> with the exception that the elderly participants slept the previous night at their homes before being conveyed to the hospital with minimal arousal at 5:15 a.m. Upon arrival, they were instructed to relax or sleep in bed until testing commenced at 7:30 a.m. Post-intervention insulin sensitivity was assessed between 36-48 hours after the final exercise session.

Glucose tolerance was measured by a 2-hour glucose tolerance test after a 12-hour fast according to standard laboratory procedures previously published.<sup>190</sup> Those participants whose plasma glucose levels exceeded 11.1 mmol/L at 120 minutes were considered diabetic and excluded from the study.

### **Statistical Analysis**

The effect of intervention was evaluated by intent-to-treat analysis. Subjects for whom follow up data were unavailable were included in a multiple imputations procedure that estimated the missing data values randomly based on the multivariate normal distribution of the data within each gender-specific intervention group.<sup>222</sup> Analysis of variance (ANOVA) was used to determine differences between means of the treatment groups at baseline. Treatment-related changes in outcomes were adjusted for baseline values in an analysis of covariance (ANCOVA). The ANCOVA model was extended to include gender and treatment-by-gender interaction to determine whether the effects of treatment varied by gender. Tukey post hoc tests with adjustment for multiple comparisons were performed to determine the differences between interventions. Regression analysis was performed to determine the relationship between the changes in abdominal fat and changes in waist circumference. *P* values of <0.05 were considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

## **RESULTS**

### **Adherence to the Exercise and Diet Regimen**

Average attendance at the exercise sessions was  $91 \pm 9\%$  and did not vary significantly by gender or by exercise group ( $P > 0.3$ ). Aerobic exercise intensity did not differ between the AE and RAE groups (average exercise heart rate was 80% of maximum in both groups). Compliance to resistance exercise was manifest by significant strength gains. The RE and RAE groups improved whole body strength by 46 and 48%, respectively. Relative strength gains did not differ by group ( $P > 0.2$ ).

Sixty-six percent of participants completed more than 80% of their daily food intake records over the 6 month intervention. An additional 25% completed records at a rate of approximately two to three days per week. Computer analysis of a subset of 80 subjects verified self-reported results and confirmed that the total calorie and fat content of the diet did not change from the 4<sup>th</sup> to the 20<sup>th</sup> week of intervention and were not different from nutritional recommendations ( $P > 0.2$ ).

### **Baseline Characteristics and Gender Differences**

Subject characteristics at baseline are given in Table 1. The study sample was 98% Caucasian. Thirty-three percent of the sample was medicated for control of blood pressure; 19% was taking lipid-lowering medications. While men were different from women for many baseline characteristics, there were no significant differences between randomized groups within each gender for any baseline variable ( $P > 0.05$ ). With the exception of a greater magnitude of total and visceral fat reduction in men than women in the AE group only ( $P < 0.05$ ), men and women performing the same exercise treatments did not differ significantly in their response to exercise ( $P > 0.05$ ), and thus all treatment-induced changes were shown collapsed across gender.

### **Anthropometric Variables**

Body weight and body mass index (BMI) were reduced in the AE ( $-3.2 \pm 0.4\%$ ) and RAE ( $-2.8 \pm 0.4\%$ ) groups by comparison to both RE and controls ( $P < 0.01$ ), but did not differ from each other ( $P > 0.8$ ) (Table 2). The reduction in body weight and BMI within the RE group was not significant compared to controls ( $P > 0.1$ ).

Waist circumference was reduced in all exercise groups by comparison to controls ( $P<0.001$ ). The reduction within the AE group was greater than RE ( $P<0.05$ ), but not RAE ( $P>0.9$ ), which was not different from RE ( $P>0.1$ ). Collapsed across groups, waist circumference explained 30% of the variance in the changes in total abdominal fat volume ( $P<0.001$ ). Treatment changes for both abdominal fat and waist circumference are shown in Figure 2.

#### **Total Fat and Total Subcutaneous Fat**

Total fat was reduced in the AE and RAE groups ( $P<0.05$ ) by comparison to both RE and controls, but were not different from each other ( $P>0.7$ ) (Table 2). Total fat did not change in the RE group compared to controls ( $P=0.1$ ). Subcutaneous fat was reduced in the AE and RAE groups ( $P<0.01$ ), but not RE ( $P>0.1$ ) by comparison to controls. The reduction within the RAE group was greater than RE ( $P<0.01$ ), but not AE ( $P>0.4$ ).

#### **Abdominal Fat**

Total abdominal fat was reduced in all exercise groups compared to controls ( $P<0.05$ ) (Table 2). The reduction did not differ between groups ( $P>0.1$ ). Abdominal subcutaneous fat was reduced in AE and RAE groups ( $P<0.01$ ), but not RE ( $P>0.1$ ), by comparison to controls. The reduction was not different between AE and RAE ( $P=1.0$ ). Visceral fat was reduced in all exercise groups compared to controls ( $P<0.01$ ). The reduction did not differ between groups ( $P>0.2$ ).

#### **Skeletal Muscle**

Skeletal muscle mass increased in the RE and RAE groups ( $P<0.05$ ) by comparison to both AE and controls, but were not different from each other ( $P>0.8$ ) (Table 2). Skeletal muscle mass did not change in the AE group compared to controls ( $P=1.0$ ).

#### **Insulin Sensitivity**

Insulin sensitivity increased in the AE and RAE groups ( $P<0.05$ ), but not RE ( $P>0.8$ ) by comparison to controls (Table 2). The increase within the RAE group was greater than RE ( $P<0.001$ ), but not AE ( $P>0.2$ ). Percent increases in insulin sensitivity by exercise modality and corresponding muscle and visceral fat changes are shown in Figure 3.

### **Cardiorespiratory Fitness**

Cardiorespiratory fitness increased in AE and RAE groups by comparison to both RE ( $P<0.05$ ) and controls ( $P<0.001$ ), but did not differ from each other ( $P=1.0$ ) (Table 2).

Cardiorespiratory fitness did not change within the RE group compared to controls ( $P>0.1$ ).

## DISCUSSION

The primary finding of this trial is that independent of gender, the combination of resistance and aerobic exercise is the optimal treatment strategy for reducing abdominal obesity and associated insulin resistance concurrent with increases in skeletal muscle mass. However, it is also important that aerobic exercise alone was associated with a substantial reduction in visceral fat and insulin resistance and a preservation of skeletal muscle mass, and that resistance exercise was associated with a reduction in abdominal obesity concurrent with an increase in skeletal muscle mass. These findings offer options for clinicians who seek lifestyle-based treatment options for abdominally obese older men and women at substantially increased risk of diabetes and functional impairment.

Absent from the literature are randomized controlled trials comparing the extent to which aerobic exercise, resistance exercise, or the combination of those two modalities reduce visceral fat independent of caloric restriction in older subjects. Previous trials that have investigated the independent effects of aerobic exercise alone on visceral fat in older subjects,<sup>171, 189, 223</sup> report equivocal findings. In a study conducted by Irwin et al.,<sup>171</sup> 87 older women exercised aerobically 3.5 days per week for 12 months, yielding a 6.9% decrease in visceral fat. An earlier study by DiPietro et al.<sup>189</sup> reported no change in visceral fat, perhaps owing to a small sample size and shorter treatment duration. Both of these trials failed to measure or control dietary intake, which, if slightly increased over the intervention period, may have masked exercise-induced energy expenditure. Weiss and Holloszy<sup>223</sup> observed a 36% reduction in visceral fat following one year of aerobic exercise in 18 men and women. In that study, the authors rigorously controlled dietary intake to ensure a 16-20% increase in expenditure was achieved throughout the intervention. Although the energy expended during aerobic exercise training was likely substantially less in our trial, our results support the observations of Weiss and Holloszy,<sup>224</sup> demonstrating with twice the number of subjects a significant reduction of visceral fat as a result of aerobic exercise.

This is the first randomized controlled trial to report a significant reduction in visceral fat by resistance exercise alone in the elderly. Only one previous randomized trial in seniors, conducted in frail subjects over 78 years of age, reported no change in visceral fat as a result of

12 weeks of progressive resistance training.<sup>184</sup> It is possible that the short duration of the trial coupled with the extreme age or frailty of the subjects may have resulted in insufficient energy expenditure to reduce visceral fat significantly. Our findings extend previous work by providing a comparison of visceral fat changes induced by both aerobic or resistance exercise in the absence of caloric restriction, and offer novel evidence in support of a combined modality approach for the reduction of visceral fat.

To our knowledge, this is the first trial to compare the effects of exercise modality on insulin sensitivity using the hyperinsulinemic euglycemic clamp method in older subjects. An earlier trial by Dengel et al.<sup>180</sup> found that 10 months of aerobic exercise increased insulin sensitivity by 22% in 10 older men compared to controls. A larger trial by Frank et al.<sup>170</sup> also showed significant improvement in insulin sensitivity compared to controls using the HOMA method in 87 older women who performed aerobic exercise for a year. Although our results are consistent with the available randomized controlled trials investigating insulin sensitivity adaptations to aerobic exercise, the literature is not as well established regarding the effect of resistance exercise. Hersey et al.<sup>181</sup> conducted a 6-month randomized controlled trial in 52 older men and women, and reported that aerobic, not resistance exercise, improved fasting insulin and glucose tolerance compared to controls. The lack of a significant insulin sensitivity increase observed in our RE group confirms these results, yet the combination of resistance and aerobic exercise provided added insulin sensitivity benefit in comparison to aerobic exercise alone. That resistance exercise decreased visceral fat significantly while not improving insulin sensitivity points to mechanisms other than visceral fat as contributors to insulin resistance, possibly by lipotoxicity in muscle and/or liver that may not be modified by resistance training in the absence of aerobic exercise.<sup>225, 226</sup> More research is needed to determine the mechanisms underlying the differences in insulin sensitivity adaptations between exercise modalities.

An exercise-induced reduction in visceral fat of the magnitude observed in this study, especially when accompanied by maintenance or even increases in skeletal muscle, has important clinical implications for elderly men and women. It demonstrates that healthy body compositional adaptations can occur without caloric restriction and in the absence of substantial

weight loss. Specifically, while reducing body weight less than 3%, RAE participants experienced a significant reduction in visceral fat and regained muscle mass equivalent to five years' worth of "normal" age-related muscle loss, as estimated by a cross-sectional analysis of similar-aged men and women.<sup>36</sup> Certainly exercise alone, especially when combining resistance and aerobic exercise, is associated with marked reductions in visceral obesity and insulin resistance without necessitating caloric restriction.

These observations challenge the dogma that weight loss and caloric restriction need be the cornerstone of a lifestyle-based intervention, especially in the elderly. Indeed, if weight loss or BMI reduction were the sole indicators of health improvement and success in our participants, the efforts of the RE group would have been considered unsuccessful despite significant changes in muscle mass and abdominal obesity. The use of waist circumference as a clinical measure of successful obesity reduction may provide a clearer picture of progress to the clinician and to seniors whose exercise efforts may have induced meaningful body compositional changes while their BMI remained relatively constant. Given the concern of many clinicians that caloric restriction may be associated with malnutrition and loss of muscle mass, these results have vast clinical importance, and support the notion that measures of abdominal obesity such as waist circumference should become a standard clinical tool for the assessment of changes in obesity-related health risk.

It is important to highlight that the exercise prescriptions in this trial were consistent with current recommendations for exercise in the elderly.<sup>15</sup> The high compliance rate of our previously sedentary participants attests to the feasibility of the exercise prescriptions. That aerobic frequency was reduced from 5 days a week to 3 days when combined with resistance exercise further enhanced the palatability of the combined modality intervention for our senior participants and coincides with literature-supported evidence for an optimal exercise prescription in this age group.<sup>218</sup> The aerobic intensity maintained in daily exercise sessions by the participants was generally not considered burdensome, with a majority of the participants walking and only a few jogging in later stages of intervention. Although the commencement of and sustained compliance

to these exercise recommendations was well-tolerated by our participants, further research is needed to determine their effectiveness when recommended by health care providers.

In summary, our findings provide unequivocal support for a combined resistance and aerobic exercise program without caloric restriction as an optimal strategy for the simultaneous improvement of muscle mass, visceral fat, and insulin sensitivity in abdominally obese seniors. However, both aerobic and resistance exercise alone offer unique and meaningful health benefits. These observations provide the basis for an improved therapeutic strategy for the treatment of health risk associated with abdominal obesity and muscle loss in senior men and women: findings that apply directly to more than half of Americans over 65 years of age.<sup>1</sup> This evidence upholds consensus exercise guidelines and should encourage health care providers to promote exercise as a meaningful preventive measure for the development of diabetes and disability in seniors.

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**Table 1.** Subject characteristics at baseline

	Women				Men			
	Control (n=17)	Resistance Exercise (n=21)	Aerobic Exercise (n=20)	Resistance & Aerobic Exercise (n=21)	Control (n=11)	Resistance Exercise (n=15)	Aerobic Exercise (n=17)	Resistance & Aerobic Exercise (n=14)
<b>Anthropometric</b>								
Age (yrs)	67 (4)	68 (4)	69 (7)	67 (5)	67 (4)	67 (6)	69 (6)	67 (5)
Body mass index (kg/m <sup>2</sup> )	30.4 (3.2)	30.0 (3.4)	29.2 (3.7)	29.5 (3.0)	30.5 (2.0)	30.1 (2.6)	29.9 (3.0)	31.1 (3.1)
Waist circumference (cm)	104.9 (7.4)	104.3 (8.5)	104.2 (10.4)	102.8 (9.6)	* 112.8 (5.3)	111.0 (5.4)	113.0 (7.9)	114.1 (8.3)
<b>Magnetic Resonance Imaging</b>								
Skeletal muscle (kg)	20.6 (2.6)	19.9 (2.5)	19.3 (3.6)	19.0 (2.1)	* 29.5 (3.7)	32.2 (4.1)	30.3 (3.6)	30.0 (3.6)
Total fat (kg)	38.1 (7.5)	36.4 (6.8)	34.9 (7.2)	34.9 (6.8)	* 34.0 (6.1)	31.5 (4.5)	33.0 (9.2)	34.9 (6.8)
Subcutaneous fat (kg)	31.7 (6.7)	30.3 (5.7)	28.6 (6.2)	29.0 (6.3)	* 24.3 (4.5)	21.4 (3.3)	22.7 (7.9)	24.5 (5.6)
Total abdominal fat (kg)	8.5 (2.0)	7.8 (1.8)	7.6 (2.2)	7.5 (1.5)	* 9.0 (1.6)	8.2 (1.4)	8.9 (2.5)	9.1 (2.1)
Visceral fat (kg)	2.7 (1.0)	2.5 (1.0)	2.6 (1.0)	2.3 (0.7)	* 4.3 (1.3)	4.6 (1.1)	4.6 (0.9)	4.7 (1.1)
Abdominal subcutaneous fat (kg)	5.9 (1.5)	5.3 (1.1)	5.0 (1.5)	5.1 (1.2)	* 4.6 (0.9)	3.6 (0.7)	4.3 (2.2)	4.4 (1.4)
<b>Metabolic</b>								
Fasting glucose (mmol/L)	4.7 (0.5)	4.7 (0.4)	4.8 (0.7)	4.2 (0.9)	4.7 (0.4)	4.8 (0.5)	4.8 (0.6)	4.8 (0.06)
2-hr glucose tolerance (mmol/L)	6.7 (1.3)	7.6 (2.0)	7.3 (1.6)	6.7 (2.0)	6.1 (1.5)	7.0 (1.6)	7.6 (1.8)	6.7 (1.8)
Fasting insulin (pmol/L)	67.6 (41.5)	79.4 (46.6)	58.8 (30.6)	51.6 (25.0)	75.2 (61.4)	66.9 (24.3)	76.2 (32.9)	81.0 (31.3)
Insulin sensitivity (M/I)	4.4 (1.6)	3.4 (1.6)	4.4 (2.0)	4.9 (2.2)	* 3.7 (1.5)	3.2 (1.5)	3.1 (1.6)	2.7 (1.4)
<b>Cardiorespiratory fitness</b>								
VO <sub>2</sub> max (L/min)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	1.8 (0.4)	* 2.6 (0.4)	2.6 (0.5)	2.5 (0.4)	2.7 (0.5)
VO <sub>2</sub> max (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	21.1 (2.6)	21.0 (3.9)	21.8 (3.1)	23.5 (5.2)	* 28.3 (5.3)	27.8 (5.2)	26.9 (4.0)	28.1 (6.1)

Data are presented as group means (SD).

M/I = rate of glucose uptake per unit of plasma insulin per kg skeletal muscle (mg•L/pmol•min<sup>-1</sup>•kg<sup>-1</sup>•muscle x 100).

\* Baseline means in men are significantly different from women (p<0.05).

**Table 2.** Changes in selected morphologic, metabolic and fitness variables

Measured variables	Control [n=24(28)]	Resistance Exercise [n=30(36)]	Aerobic Exercise [n=30(37)]	Resistance & Aerobic Exercise [n=33(35)]
<b>Anthropometric</b>				
Body weight (kg)	0.3 (-0.4 to 1.0)	-0.6 (-1.4 to 0.1)	-2.8 (-3.4 to -2.1)*†	-2.3 (-3.0 to -1.7)*†
Body mass index (kg/m <sup>2</sup> )	0.1 (-0.2 to 0.3)	-0.3 (-0.5 to -0.0)	-0.9 (-1.2 to -0.7)*†	-0.8 (-1.1 to -0.6)*†
Waist circumference (cm)	-0.3 (-1.3 to 0.7)	-3.2 (-4.1 to -2.2)*	-5.1 (-6.0 to -4.2)*†	-4.6 (-5.5 to -3.7)*
<b>Magnetic Resonance Imaging</b>				
Skeletal muscle (kg)	-0.0 (-0.4 to 0.3)	0.8 (0.5 to 1.1)*‡	-0.0 (-0.3 to 0.3)	0.7 (0.4 to 0.9)*‡
Total fat (kg)	-0.5 (-1.2 to 0.3)	-1.6 (-2.3 to -1.0)	-3.0 (-3.7 to -2.3)*†	-3.4 (-4.0 to -2.7)*†
Subcutaneous fat (kg)	-0.3 (-0.9 to 0.3)	-1.2 (-1.7 to -0.7)	-1.9 (-2.4 to -1.3)*	-2.4 (-2.9 to -1.9)*†
Total abdominal fat (kg)	-0.0 (-0.3 to 0.2)	-0.5 (-0.7 to -0.3)*	-0.8 (-1.0 to -0.6)*	-0.8 (-1.0 to -0.6)*
Visceral fat (kg)	0.0 (-0.1 to 0.2)	-0.2 (-0.4 to -0.1)*	-0.4 (-0.5 to -0.4)*	-0.4 (-0.5 to -0.3)*
Abdominal subcutaneous fat (kg)	-0.0 (-0.2 to 0.1)	-0.2 (-0.4 to -0.1)	-0.4 (-0.5 to -0.3)*	-0.4 (-0.5 to -0.3)*
<b>Metabolic</b>				
Fasting Insulin	-2.0 (-10.6 to 6.5)	-6.7 (-14.5 to -1.1)	-10.0 (-18.6 to -1.0)	-10.5 (-17.7 to -3.3)
Insulin Sensitivity	0.1 (-0.3 to 0.5)	0.3 (-0.1 to 0.7)	0.9 (0.4 to 1.3)*	1.3 (0.9 to 1.7)*†
<b>Cardiorespiratory Fitness</b>				
VO <sub>2</sub> max (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	-1.2 (-0.3 to 0.2)	0.8 (-0.6 to 2.2)	4.2 (2.6 to 5.7)*†	3.8 (2.6 to 5.1)*†

Data are presented as group mean differences (95% confidence intervals).

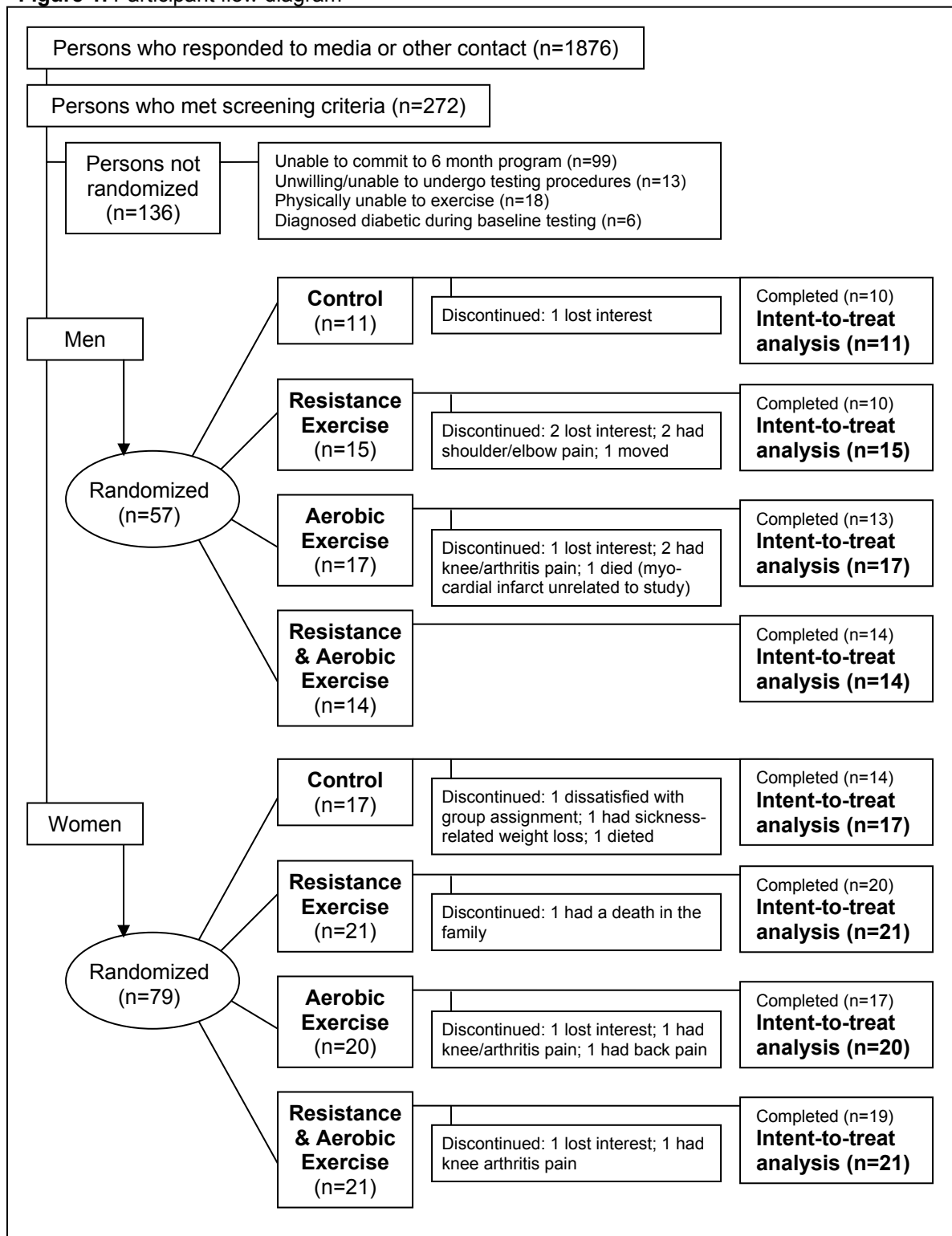
M = male; F = female; [n = number of participants completed (participants used in intent-to-treat analysis)].

\* Significant treatment differences (pre vs. post) compared with control (p<0.05).

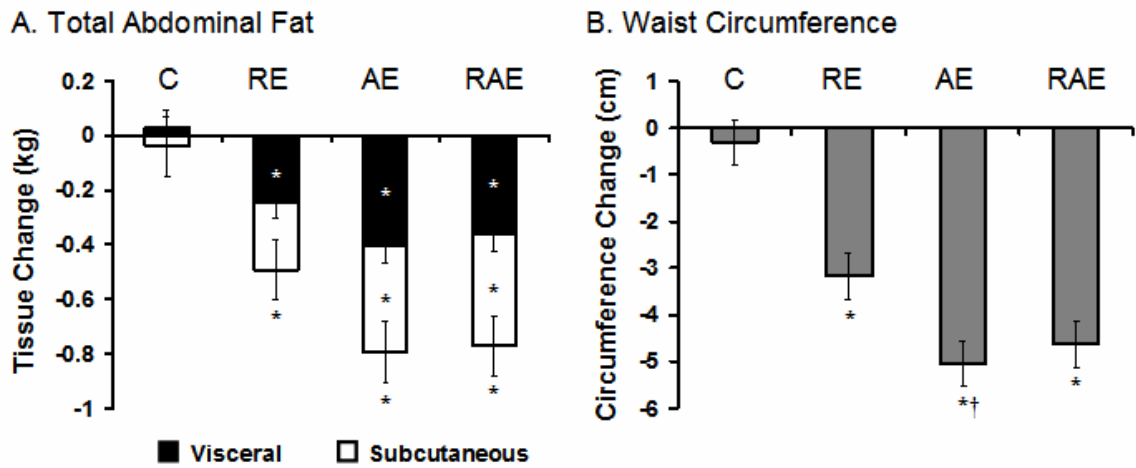
† Significant treatment differences (pre vs. post) compared with resistance exercise (p<0.05).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise (p<0.05).

**Figure 1.** Participant flow diagram



**Figure 2.** Changes in abdominal fat and associated waist circumference



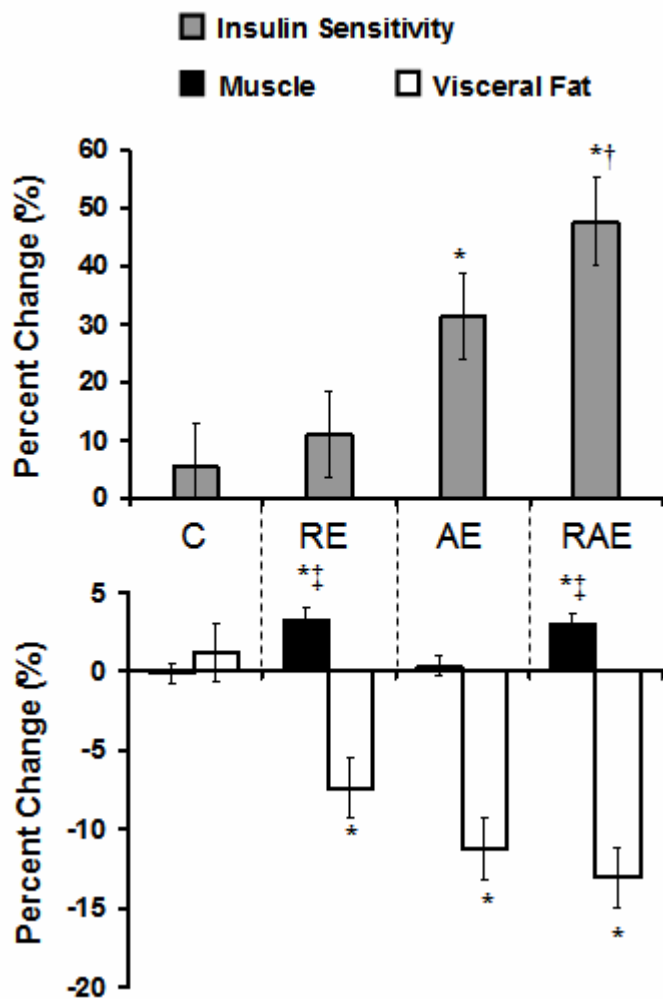
C = control; RE = resistance exercise; AE = aerobic exercise; RAE = resistance and aerobic exercise

\* Significant treatment differences (pre vs. post) compared with control ( $p < 0.05$ ).

† Significant treatment differences (pre vs. post) compared with resistance exercise ( $p < 0.05$ ).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise ( $p < 0.05$ ).

**Figure 3.** Percent changes in muscle, visceral fat, and insulin sensitivity



C = control; RE = resistance exercise; AE = aerobic exercise; RAE = resistance and aerobic exercise

\* Significant treatment differences (pre vs. post) compared with control ( $p < 0.05$ ).

† Significant treatment differences (pre vs. post) compared with resistance exercise ( $p < 0.05$ ).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise ( $p < 0.05$ ).

## **Chapter 4. Second Manuscript**

**Influence of Exercise Modality on Cardiorespiratory and Functional Fitness in Older Men  
and Women: A Randomized Controlled Trial**

## **ABSTRACT**

**CONTEXT:** Low cardiorespiratory fitness and decreased muscular strength are trademarks of aging, but can be modified with exercise. The optimal exercise modality or combination of modalities to be used as a treatment strategy to prevent physical disability in the elderly is still unknown.

**OBJECTIVES:** The primary objective was to examine the effects of aerobic and/or resistance exercise on cardiorespiratory and functional fitness. A secondary objective was to determine the extent to which changes in skeletal muscle and fat mass are related to functional performance in previously sedentary, abdominally obese older men and women.

**DESIGN:** Randomized controlled trial.

**SETTING:** Queen's University Exercise Physiology Laboratory.

**PARTICIPANTS:** 136 sedentary, abdominally obese older (60-79 years) men and women.

**INTERVENTION:** Six months of progressive whole-body resistance exercise (RE), aerobic exercise (AE), a combination of the two modalities (RAE) or non-exercise control.

**MEASUREMENTS:** Cardiorespiratory fitness (CRF) was assessed using a graded maximal exercise test. Four physical tests were used to assess functional fitness. Whole body skeletal muscle and fat were quantified by magnetic resonance imaging.

**RESULTS:** CRF increased in the AE and RAE groups by comparison to both RE and controls. Functional fitness improved significantly in all groups versus controls ( $P<0.001$ ). Improvement in the RAE group was greater than AE ( $P<0.01$ ) but not RE ( $P>0.1$ ). Muscle mass increased in RE and RAE groups by comparison to both AE and controls ( $P<0.05$ ). Total fat was reduced in AE and RAE groups by comparison to both RE and controls ( $P<0.05$ ). Both muscle gain and fat loss significantly and independently predicted improvements in functional fitness.

**CONCLUSION:** The combination of resistance and aerobic exercise is the optimal treatment strategy for simultaneous improvement of cardiorespiratory and functional fitness.

**Key Words:** aging, sarcopenia, obesity, fitness, aerobic exercise, resistance exercise

## INTRODUCTION

Over 46% of elderly Americans report no leisure time physical activity:<sup>227</sup> a lifestyle choice that, coupled with accelerated age-related declines in muscle strength and cardiorespiratory fitness,<sup>228, 229</sup> increases dramatically the likelihood of physical disability.<sup>7, 230</sup> Although it is clear that resistance exercise reverses age-related declines in muscle mass and strength,<sup>218, 231</sup> and that aerobic exercise improves cardiorespiratory fitness in elderly men and women,<sup>232</sup> the relative effects of resistance exercise on cardiorespiratory fitness and aerobic exercise on muscle mass and strength are not well understood. Uncertainty also remains regarding the efficacy of a combined aerobic and resistance training program for improving strength, functional ability and cardiorespiratory fitness in older adults.

Despite widely-accepted guidelines recommending that older adults incorporate both aerobic and resistance exercise into their daily activity,<sup>15</sup> only one randomized controlled trial has compared a combined modality program with aerobic and resistance exercise alone on strength, cardiorespiratory and functional fitness outcomes. Wood et al.<sup>208</sup> observed that a combined resistance and aerobic program resulted in strength gains similar to resistance exercise alone, and cardiorespiratory improvements similar to aerobic alone, with a synergistic effect of the two modalities on functional fitness.<sup>208</sup> While the results of Wood and colleagues provide promising evidence for an optimal exercise prescription for disability prevention in the elderly, the sample size was small, duration of treatment was short, dietary intake was not reported, the influence of gender was not considered, and intent-to-treat analyses were not performed.

In this study we compared 6 months of resistance and aerobic exercise combined to either modality alone in a large group of abdominally obese elderly men and women. To help isolate the effects of exercise modality on the primary outcomes, participants were asked to maintain calorie intake throughout the intervention. We hypothesized that the combination of aerobic and resistance exercise would induce significant improvements in functional performance and cardiorespiratory fitness compared to either modality alone. Ancillary aims were to investigate whether modality-driven outcomes differed by gender and whether exercise-induced changes in muscle and fat mass contributed to functional performance.

## **METHODS**

### **Participants**

Non-smoking, sedentary, overweight senior men and women 60 to 80 years of age were recruited from the Kingston, Ontario, Canada region. Inclusion criteria required a waist circumference of >102 cm in men and >88 cm in women and stable weight ( $\pm 2$  kg) for six months prior to study entry. Potential participants were excluded if they reported a history of heart disease, stroke, diabetes or any condition that would prevent them from engaging in an exercise study; currently dieting or intent to diet; or if they were already engaging in two or more planned exercise sessions per week. Blood pressure and lipid-lowering medications were allowed if maintained throughout the trial. All participants received medical clearance from a personal physician and signed an informed consent in accordance with ethical guidelines of Queen's University.

Eligible participants were allocated by computer-generated, sex-stratified random assignment into a non-exercise control or one of three exercise training groups: resistance exercise (RE), aerobic exercise (AE), or a combination of resistance and aerobic exercise (RAE). Randomized group assignment was issued upon completion of a majority of baseline assessments, and was not revealed to those conducting baseline tests. Of the 136 men and women randomized, nineteen did not complete their assigned six-month treatment (Figure 1). Those who discontinued participation due to musculoskeletal pain complained primarily of arthritis, previous joint injuries, or discomfort not directly attributable to the exercise requirements. Those who did not complete the trial did not differ significantly in any baseline anthropometric variable from those who completed ( $P > 0.10$ ).

### **Dietary Assessment**

During the baseline period, participants were taught by a nutritionist to continue a weight-maintenance calorie intake while recording their daily consumption of self-selected foods. A healthy balance of macronutrients (approximately 55% carbohydrate, 15% protein, and 30% fat) was encouraged, and body weight was monitored for approximately four weeks to ensure that daily calorie targets were appropriate for weight maintenance. During the intervention,

participants were required to maintain calorie levels determined at baseline unless weight change exceeded that predicted by exercise-induced energy expenditure. All participants attended nine one-hour seminars in which a nutritionist taught healthy food selection and preparation. Participants continued to keep and analyze detailed daily food records throughout the duration of the study (approximately 29 weeks). The nutritionist regularly reviewed records to assure compliance to established weight maintenance calorie targets, and upon completion of the study, analyzed two representative weeks of records (week 4 and week 20 of the intervention) by a computerized program (Food Processor, ESHA Research, Salem, Oregon) to assess accuracy of calculated results.

### **Exercise Regimen**

Aerobic and resistance exercise interventions were consistent with consensus recommendations for exercise-related health benefits<sup>15</sup> in older adults. All exercise sessions were by appointment and supervised within the facilities of the corresponding author.

Participants randomized into either the RE or RAE group performed progressive resistance exercises 3 days per week. For each training session, the following nine exercises were performed: chest press, leg extension, shoulder raise, leg flexion, superpullover or lat pulldown (latissimus dorsi), triceps extension, biceps curl, abdominal crunch, and modified pushups. Subjects performed one set of between eight and fifteen repetitions to volitional fatigue for all exercises during each session. The weight lifted was increased when fifteen repetitions was exceeded.

Those randomized to the AE group performed thirty minutes of moderate-intensity exercise (brisk walking or light jogging between 60 to 75% of peak oxygen uptake or 75 to 85% maximal heart rate), with five minutes designated for warm up and cool down, respectively, for a total of forty minutes on motorized treadmills, five days per week. Exercise intensity was monitored every five minutes using an automated heart rate monitor (Polar Oy, Kempele, Finland). Energy expenditure during the exercise program was determined using the heart rate and oxygen uptake data obtained from the baseline graded exercise test, which was adjusted using the results from a subsequent graded exercise test performed in the second month of

exercise. Participants in the RAE group performed the aerobic exercise protocol only three days per week in addition to the resistance exercise protocol.

### **Measurement of Cardiorespiratory Fitness**

Cardiorespiratory fitness (Peak  $\text{VO}_2$ ) was determined using a graded maximal treadmill test that employed a constant walking speed and the use of standard open-circuit spirometry techniques (SensorMedics, Yorba Linda, CA) at baseline, during the 2<sup>nd</sup> month of exercise, and in the final week of intervention. Peak  $\text{VO}_2$  was attained when the subject reached volitional fatigue and at least two of the following three criteria were achieved: no increase in  $\text{VO}_2$  despite further increases in treadmill grade, a respiratory exchange ratio in excess of 1.10, and a heart rate exceeding 85% of age-predicted maximum ( $208 - 0.7 \times \text{age}$ ).<sup>221</sup>

### **Measurement of Functional Fitness**

Status of physical function was evaluated using four of the six tests from the functional fitness test battery designed by Rikli and Jones,<sup>197</sup> consisting of items designed to assess the physiological parameters associated with independent living in older adults: thirty-second chair stand, arm curl, two-minute step, and 8-foot up-and-go. The remaining two tests evaluated flexibility outcomes were not directly targeted by our exercise intervention: stretching was encouraged, but not required following each exercise session. Performance on the four functional tests was evaluated not only by raw scores, but by changes in percentile rankings when compared to age- and gender-specific normative values from a representative older population of over 7,000 older subjects who completed the same battery of tests.<sup>233</sup> An overall functional fitness improvement score was derived using a mean percentile ranking increase from all four strength and agility tests.

### **Measurement of Body Composition**

Anthropometric measurements were taken at baseline and during the last week of intervention. Barefoot standing height was obtained to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass was measured on a balance scale calibrated to the nearest 0.1 kg with participants dressed in standard T-shirts and shorts. Circumference measures were obtained in a standing position using the average of two measures within 1.0 cm: thigh at the midpoint between

inguinal crease and the proximal edge of the patella; hip at the greatest protrusion of the buttocks as viewed from the side; waist at the superior edge of the iliac crest.

Total and regional muscle mass and total fat mass were measured by magnetic resonance imaging (MRI) in a whole-body assessment protocol established elsewhere.<sup>12</sup> Images were obtained by a General Electric, 1.5-T magnet at baseline and follow-up. Once acquired, the MRI data were transferred to a stand-alone workstation for analysis using specially-designed computer software (Tomovision, Montreal, QC, Canada), the procedures for which have been described elsewhere.<sup>12, 219</sup> Volume units (liters) of tissues were converted to mass units (kilograms) multiplying the volumes by an assumed constant density for adipose tissue (0.92 kg/L) and fat-free skeletal muscle (1.04 kg/L).<sup>220</sup> Skeletal muscle was divided into upper and lower-body segments at the L4-L5 intervertebral space.

### **Statistical Analysis**

The effect of intervention was evaluated by intent-to-treat analysis. Subjects for whom follow up data were unavailable were included in a multiple imputations procedure that estimated the missing data values randomly based on the multivariate normal distribution of the data within each gender-specific intervention group. Analysis of variance (ANOVA) was used to determine differences between means of the treatment groups at baseline. Treatment-related changes in outcomes were adjusted for baseline values in an analysis of covariance (ANCOVA). The ANCOVA model was extended to include gender and treatment-by-gender interaction to determine whether any treatment effects varied by gender. Tukey post hoc tests with adjustment for multiple comparisons were performed to determine differences between randomized groups. Regression analysis tested the independent associations of fat and muscle changes to functional fitness changes. Fat and muscle tertile group comparisons were made by ANCOVA controlling for baseline, age, and gender with Tukey adjustment for multiple comparisons. *P* values of <0.05 were considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

## RESULTS

### Baseline Characteristics and Gender Differences

The study sample was 98% Caucasian. Thirty-three percent of the sample (24 of 57 men; 21 of 79 women) was medicated for control of blood pressure; 19% (11 of 57 men; 15 of 79 women) was taking lipid-lowering medications. While there were differences in baseline values between men and women, randomly-assigned groups within each gender did not differ significantly ( $P>0.05$ ), and baseline characteristics are shown collapsed across group in Table 1. Men and women did not differ in response to exercise modality for any of the physical or functional fitness variables, with the single exception of a greater total fat reduction in men ( $4.4\pm0.5$  kg) than women ( $1.7\pm0.4$  kg) within the aerobic exercise group only ( $P=0.04$ ). Accordingly, mean changes for all variables are shown collapsed across gender (Table 2).

### Dietary Intake

Approximately 66% of participants completed more than 80% of their daily food intake records over the 24-week intervention. An additional 25% completed records at a rate of approximately two to three days per week. Computer analysis of a subset of 80 subjects verified calculated results and confirmed that the total calorie and fat content of the diet was not different from nutritional recommendations, and did not change from the 4<sup>th</sup> to the 20<sup>th</sup> week of intervention ( $P>0.2$ ).

### Exercise Programs

Average attendance at all exercise sessions was  $91\pm9\%$  and did not vary significantly by gender or by exercise group ( $P>0.3$ ). Aerobic exercise intensity did not differ between the AE and RAE groups (average exercising heart rate was 80% of maximum in both groups, regardless of gender). Men expended more energy during each aerobic exercise session ( $354\pm58$  kcal) than did women ( $245\pm47$  kcal) ( $P<0.001$ ), but within gender, AE and RAE did not differ in energy expenditure per treadmill session ( $P>0.2$ ).

Compliance to resistance exercise was evidenced by significant strength gains in both men and women. The RE and RAE groups improved upper body strength by 39% in men; in women, the RE and RAE groups increased by 40% and 46%, respectively. Men increased lower

body strength by 59% and 62% in the RE and RAE groups, respectively; women increased by 62% in both RE and RAE groups. Percent strength gains did not differ by gender or between RE and RAE ( $P>0.2$ ).

### **Anthropometric Variables**

Body weight and body mass index (BMI) were reduced in the AE and RAE groups ( $P<0.01$ ) by comparison to both RE and controls, but did not differ from each other ( $P>0.8$ ) (Table 2). The reduction in body weight and BMI within the RE group was not significant compared to controls ( $P>0.1$ ).

### **Cardiorespiratory Fitness**

Absolute cardiorespiratory fitness (expressed in L/min) increased in the AE and RAE groups ( $P<0.001$ ), but not RE ( $P>0.1$ ), by comparison to controls (Table 2). The increase within the AE group was greater than RE ( $P<0.05$ ), but not RAE ( $P>0.9$ ). When expressed relative to body weight (milliliters of oxygen per kg body weight per minute), cardiorespiratory fitness increased in AE and RAE groups by comparison to both RE ( $P<0.05$ ) and controls ( $P<0.001$ ). The RE group did not increase compared to controls ( $P>0.1$ ).

### **Functional Fitness**

Performance on the four functional fitness tests improved significantly in all exercise groups compared to controls ( $P<0.01$ ) (Table 2). Improvements within the RAE group were greater than the AE group on chair stands, arm curls and the 2-minute step test ( $P<0.05$ ), but were not greater than AE on the 8-foot up-and-go ( $P>0.3$ ). The AE and RE groups did not differ from each other on any functional fitness test ( $P>0.5$ ), nor did RAE differ from RE ( $P>0.05$ ). Improvements in age- and sex-specific percentile rankings compared to a reference population are shown in Figure 2. The mean percentile ranking increase from the four functional fitness tests was greater in the RAE group compared to AE ( $P<0.01$ ), but not RE ( $P>0.1$ ) (Figure 2e). Percent change in percentile rankings are shown by randomized group as they coincide with changes in cardiorespiratory fitness, skeletal muscle, and total fat in Figure 3.

### **Skeletal Muscle**

Both whole body and upper body skeletal muscle mass increased in the RE and RAE groups ( $P<0.05$ ) by comparison to AE and controls, but RE and RAE were not different from each other ( $P>0.8$ ) (Table 2). Muscle mass did not change in the AE group compared to controls ( $P=1.0$ ). Lower body skeletal muscle mass did not increase significantly in any of the exercise groups compared to controls ( $P>0.2$ ).

### **Total Fat**

Total fat was reduced in the AE and RAE groups ( $P<0.05$ ) by comparison to both RE and controls, but were not different from each other ( $P>0.7$ ) (Table 2). Total fat did not change in the RE group compared to controls ( $P=0.1$ ).

### **Associations between Muscle, Fat, and Functional Performance**

Collapsed across groups, changes in muscle mass and total fat were significantly associated with corresponding changes in performance on all four functional fitness tests, albeit in opposite directions ( $n=121$ ,  $P<0.05$ ). Both fat loss and muscle gain were independent predictors of improvements in functional fitness, but fat loss was a stronger predictor in all but the 8-foot up-and-go test (Table 3). Figure 4 further illustrates the relationship between changes in functional performance and muscle and total fat change using groups defined by high, middle, or low muscle and total fat change. On all four functional fitness tests, mean improvement on performance was greater in subjects in the highest tertile of fat loss and muscle gain compared to those in the lowest tertile in both tissues ( $P<0.05$ ) (Figure 4).

## DISCUSSION

The primary finding of this study was that performing aerobic and resistance exercise for 6 months produced optimal improvements in functional performance and cardiorespiratory fitness in previously sedentary, abdominally obese senior men and women. Performing aerobic exercise alone was associated with a similar increase in cardiorespiratory fitness but lesser functional fitness benefit, while resistance exercise alone did not significantly increase cardiorespiratory fitness but improved functional performance similarly when compared to the combined exercise group. Regardless of modality, however, exercise produced significant and meaningful improvements in functional performance compared to controls. All exercise-induced cardiorespiratory and functional fitness changes occurred independent of gender. That these observations were derived from exercise strategies that are consistent with consensus guidelines reinforce the clinical utility of the findings and offer the clinician alternatives for the prevention and treatment of disability in the elderly.

Our primary observation that a combination of aerobic and resistance exercise resulted in optimal cardiorespiratory and functional fitness outcomes supports the findings of Wood et al.,<sup>208</sup> which demonstrated in a smaller sample of elderly men and women that the strength and cardiorespiratory fitness adaptations attained by either aerobic or resistance exercise were not attenuated when the two modalities were combined. While some previous randomized trials in younger subjects have reported an “interference” effect of modality-specific adaptations,<sup>210, 212</sup> our findings and those of Wood et al.<sup>208</sup> demonstrate that not only are the strength gains achieved by elderly subjects performing resistance exercise alone, and the cardiorespiratory improvements attained consequent to aerobic training alone not affected when combined with the other modality, but a synergistic enhancement of functional performance is achieved with simultaneous resistance and aerobic training. A possible explanation for the lack of interference in these two studies with elderly subjects is that in both cases, aerobic exercise session frequency was reduced to three instead of five or more sessions per week, which allows for adequate recuperation from muscle damage caused by resistance training, especially muscle groups used in both exercise modalities.<sup>218</sup> Although a recent meta-analysis recommends a resistance

exercise frequency of two days per week to obtain full muscle recovery in the elderly, specifically in older women,<sup>234</sup> our results show no significant compromise in strength or muscle hypertrophy with a frequency of three days per week during six months of combined training.

Whereas the strength and functional fitness benefits of resistance exercise are well established,<sup>218</sup> the benefits regarding cardiorespiratory fitness are unclear.<sup>196</sup> Other randomized controlled trials have investigated the effects of resistance exercise alone on cardiorespiratory fitness outcomes in elderly subjects. Vincent et al.<sup>235</sup> compared 6 months of high and low intensity resistance training to controls, and found that both intensities increased cardiorespiratory fitness significantly by over 20%. Using a training protocol similar to Vincent's high intensity program, Hersey et al.<sup>181</sup> compared six months of resistance exercise to aerobic exercise, and observed a 20% increase in cardiorespiratory fitness with aerobic exercise and no improvement in the resistance group. The resistance training protocols of both previous trials match ours in intensity and duration, yet our results support Hersey et al.<sup>181</sup> and contradict those of Vincent et al.<sup>235</sup> One plausible explanation for differences between these trials is the possible variance in subjects' participation in free-living physical activity, which has been documented to increase concurrent to longer-duration resistance training programs,<sup>236</sup> but was not quantified or reported to be controlled in these studies.

This is the first randomized controlled trial to compare modality-specific adaptations in both muscle and fat and how they relate to functional fitness improvements in the elderly. Visser et al.<sup>237</sup> demonstrated in a large cross-sectional study that both low muscle mass and high body fat are related to poor physical function. The significant differences in muscle and fat change between treatments, shown in Figure 3, demonstrate the distinct physical adaptations that are associated with either aerobic or resistance exercise. That functional fitness improvement appears to be greatest in modalities that induce the greatest concurrent changes in muscle and fat implies that these adaptations independently contribute to enhanced performance. Indeed, we examined further the associations between functional performance and body compositional change and found that both fat loss and muscle gain significantly and independently predicted performance improvement, such that the subjects who lost more fat and gained more muscle

were more likely to enhance functional performance (Figure 4). These findings highlight the importance of simultaneously developing muscle and reducing fat in seniors to prevent functional decline.

Consensus exercise guidelines for older adults already recommend participation in both aerobic and resistance exercise for optimal health benefits.<sup>15</sup> For the clinician wishing to personalize exercise prescription for a variety of elderly patients, however, the results from this study provide evidence to support more than one viable treatment option. An obese older patient may choose to focus on the cardiorespiratory fitness-enhancing, fat-reducing, morbidity-compressing benefits associated with aerobic exercise, for example, while a frailer senior may prefer the muscle hypertrophy and strength benefits that a resistance-only program provides. Understanding that resistance exercise alone may have minimal effects on cardiorespiratory fitness, and that aerobic exercise alone may not yield the maximal functional fitness benefit without resistance exercise provides a framework upon which informed treatment decisions can be made. Regardless of preference, significant functional fitness benefits can be achieved with either exercise modality alone. However, our results clearly show that the combination of resistance and aerobic exercise provides an optimal assembly of cardiorespiratory and functional fitness benefits, due in part to its favorable influence on both muscle and fat mass.

A notable limitation to our study may be our exclusion of non-abdominally obese seniors. Though our sample represents a majority of the aging population in North America, our conclusions regarding the relative benefits of exercise modalities in this sample may not apply to elderly populations with substantial anthropometric differences from our sample. Furthermore, an evaluation of the effect of race on study outcomes was not possible with our predominantly Caucasian sample of elderly men and women. Also, this study compared the efficiency of exercise modality programs which contained aerobic or resistance components, and did not assess the results of a program in which resistance exercise is modified to incorporate aerobic attributes. Circuit training, for example, may or may not produce the same results achieved by our combined aerobic and resistance exercise program. Further research is required to assess the comparative utility of such modifications.

In conclusion, the findings of our study present unequivocal evidence that the combination of resistance and aerobic exercise, performed according to consensus recommendations, is the optimal treatment strategy for simultaneous improvement of cardiorespiratory and functional fitness in abdominally obese older adults. However, substantive body compositional and functional fitness benefits were associated with either exercise modality alone. These observations provide the clinician with options for needs-based exercise prescriptions for the prevention of disability in the elderly.

## **ACKNOWLEDGEMENTS**

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**Table 1.** Subject characteristics at baseline

	Men (n=57)	Women (n=79)
<b>Anthropometrics</b>		
Age, yr	67.7 (5.1)	67.7 (5.1)
Waist Circumference, cm	112.7 (6.9)	104.0 (9.0)*
Body Mass Index, kg/m <sup>2</sup>	30.4 (2.7)	29.7 (3.3)
Body weight, kg	94.6 (10.6)	78.7 (10.1)*
<b>Cardiorespiratory Fitness</b>		
VO <sub>2</sub> max (L/min)	2.6 (0.5)	1.7 (0.3)*
VO <sub>2</sub> max (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	27.7 (5.1)	21.9 (4.0)*
<b>Functional Fitness</b>		
Chair Stands, reps in 30 seconds	15.4 (3.6)	12.5 (3.4)*
Percentile Ranking	50.6 (24.3)	40.0 (25.7)*
Arm curls, reps in 30 seconds	19.8 (3.8)	15.3 (3.4)*
Percentile Ranking	62.0 (23.0)	49.4 (22.5)*
Steps in place, reps in 2 minutes	113.1 (15.1)	90.5 (19.1)*
Percentile Ranking	71.0 (24.5)	52.7 (24.5)*
8-foot up-and-go, seconds	4.1 (0.6)	5.2 (0.8)*
Percentile Ranking	75.4 (12.9)	61.6 (18.7)*
<b>Magnetic Resonance Imaging</b>		
Total Muscle Mass, kg	30.6 (3.8)	19.7 (2.8)*
Upper Body Muscle, kg	12.6 (1.8)	7.4 (1.1)*
Lower Body Muscle, kg	18.0 (2.2)	12.3 (1.8)*
Total Fat Mass, kg	33.3 (7.0)	36.0 (7.0)*

Values as presented as Mean (SD).

\* Women are significantly different from men,  $P<0.05$ .

**Table 2.** Changes in selected anthropometric, cardiorespiratory and functional fitness variables over 6 months of treatment

Measured variables	Control [n=24(28)]	Resistance Exercise [n=30(36)]	Aerobic Exercise [n=30(37)]	Resistance & Aerobic Exercise [n=33(35)]
<b>Anthropometric</b>				
Body weight (kg)	0.3 (-0.4 to 1.0)	-0.6 (-1.4 to 0.1)	-2.8 (-3.4 to -2.1)*†	-2.3 (-3.0 to -1.7)*†
Body mass index (kg/m <sup>2</sup> )	0.1 (-0.2 to 0.3)	-0.3 (-0.5 to -0.0)	-0.9 (-1.2 to -0.7)*†	-0.8 (-1.1 to -0.6)*†
<b>Cardiorespiratory fitness</b>				
VO <sub>2</sub> max (L/min)	-0.1 (-0.2 to 0.0)	0.0 (-0.1 to 0.2)	0.3 (0.2 to 0.4)*†	0.2 (0.1 to 0.3)*
VO <sub>2</sub> max (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	-1.8 (-2.5 to 0.2)	0.8 (-0.6 to 2.2)	4.2 (2.6 to 5.7)*†	3.8 (2.6 to 5.1)*†
<b>Functional fitness</b>				
Chair stands (repetitions)	0.4 (-0.7 to 1.5)	4.2 (3.1 to 5.3)*	3.9 (2.9 to 4.8)*	6.1 (5.0 to 7.2)*‡
Arm curls (repetitions)	0.1 (-1.6 to 1.7)	6.5 (4.9 to 8.0)*	5.1 (3.8 to 6.4)*	8.1 (6.5 to 9.7)*‡
2-minute step (steps)	1.8 (-2.8 to 6.4)	19.7 (15.0 to 24.4)*	16.7 (12.8 to 20.6)*	27.3 (22.9 to 31.7)*‡
8-foot up-and-go (seconds)	-0.1 (-0.2 to 0.1)	-0.6 (-0.7 to -0.4)*	-0.4 (-0.6 to -0.3)*	-0.6 (-0.8 to -0.4)*
<b>Magnetic Resonance Imaging</b>				
Skeletal muscle (kg)	-0.0 (-0.4 to 0.3)	0.8 (0.5 to 1.1)*‡	-0.0 (-0.3 to 0.3)	0.7 (0.4 to 0.9)*‡
Upper body muscle (kg)	-0.1 (-0.3 to 0.2)	0.7 (0.3 to 1.1)*‡	-0.5 (-0.9 to -0.2)	0.6 (0.2 to 0.9)*‡
Lower body muscle (kg)	0.0 (-0.4 to 0.5)	0.5 (0.1 to 0.9)	0.3 (-0.1 to 0.7)	0.2 (-0.2 to 0.5)
Total fat (kg)	-0.5 (-1.2 to 0.3)	-1.6 (-2.3 to -1.0)	-3.0 (-3.7 to -2.3)*†	-3.4 (-4.0 to -2.7)*†

Data are presented as group mean differences (95% confidence intervals).

\* Significant treatment differences (pre vs. post) compared with control ( $p<0.05$ ).

† Significant treatment differences (pre vs. post) compared with resistance exercise ( $p<0.05$ ).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise ( $p<0.05$ ).

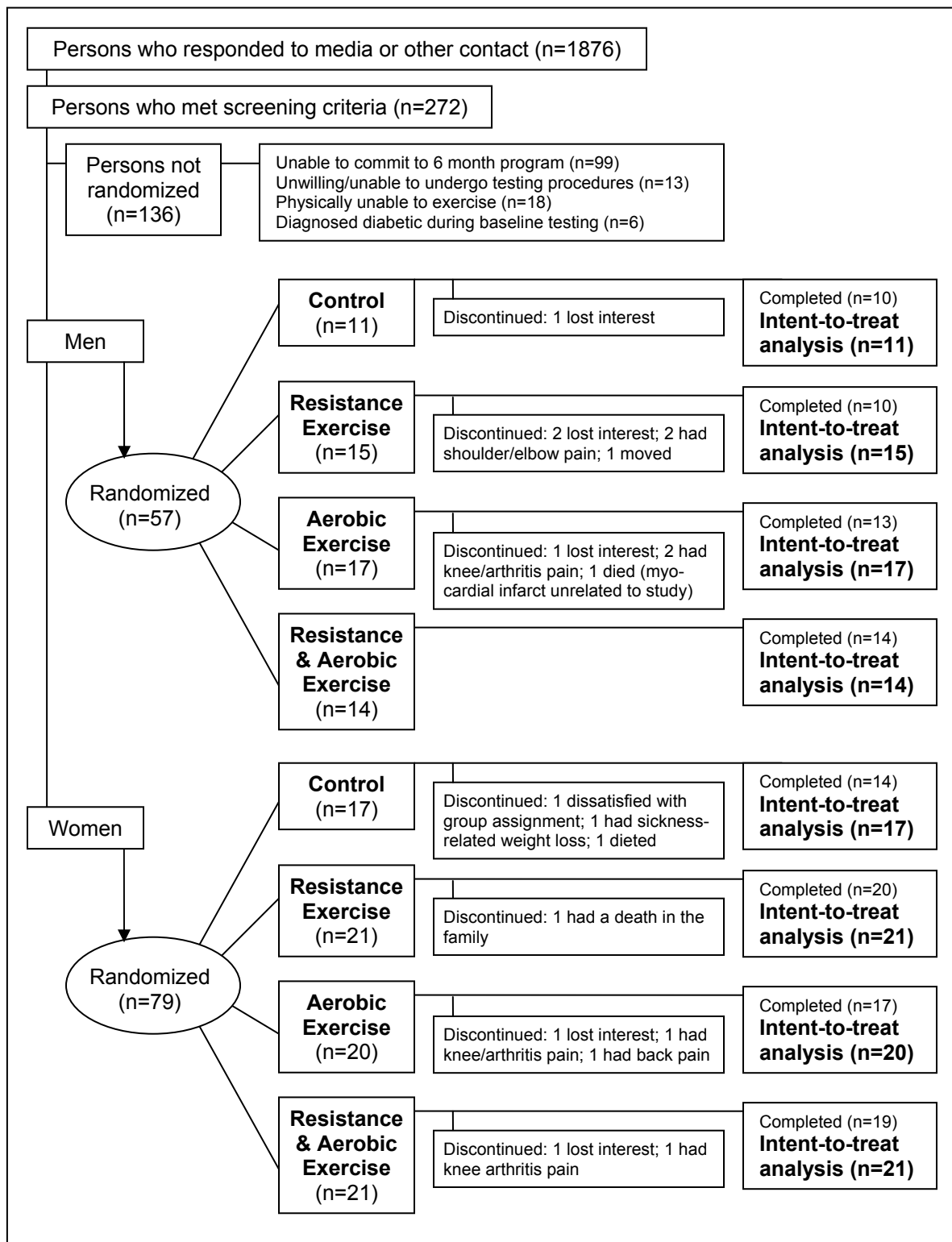
**Table 3.** Associations between changes in muscle, fat, and functional performance improvement

Functional Fitness Test	Skeletal Muscle Changes		Total Fat Changes		Combined Changes	
	$R^2$	<i>P</i> -value	$R^2$	<i>P</i> -value	$R^2$	<i>P</i> -value
<b>Chair stands</b> (repetitions)	0.038*	0.04	0.093*†	<0.001	0.149	<0.001
<b>Arm curls</b> (repetitions)	0.057*	0.01	0.095*†	<0.001	0.175	<0.001
<b>2-minute step</b> (steps)	0.039*	0.03	0.093*†	<0.001	0.151	<0.001
<b>8-foot up-and-go</b> (seconds)	0.058*†	0.01	0.037*	0.04	0.110	<0.001

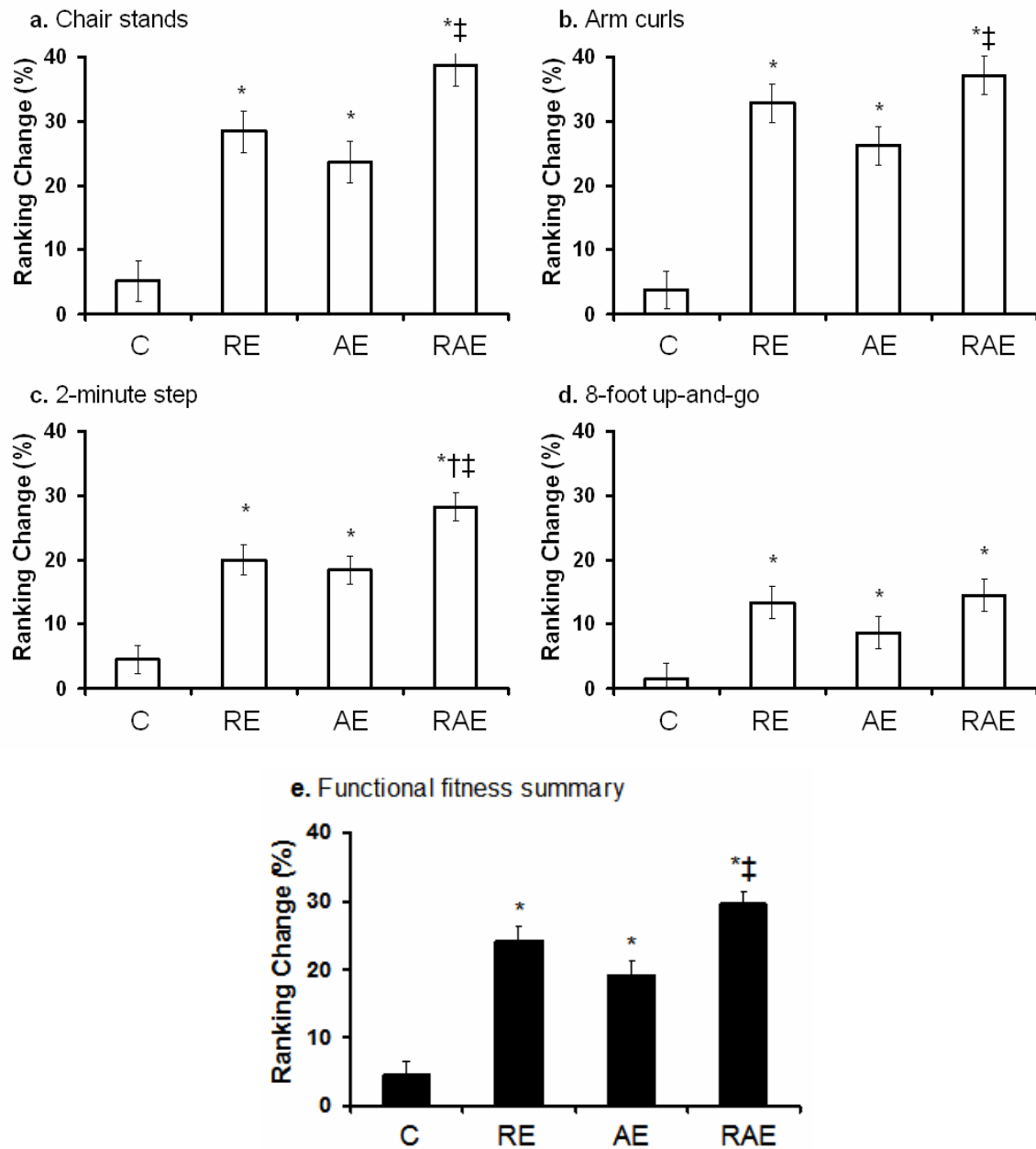
\* Change independently predicts functional fitness change.

† Stronger predictor of functional fitness change.

**Figure 1.** Participant flow diagram



**Figure 2.** Changes in age- and sex-specific ranking on four functional fitness tests



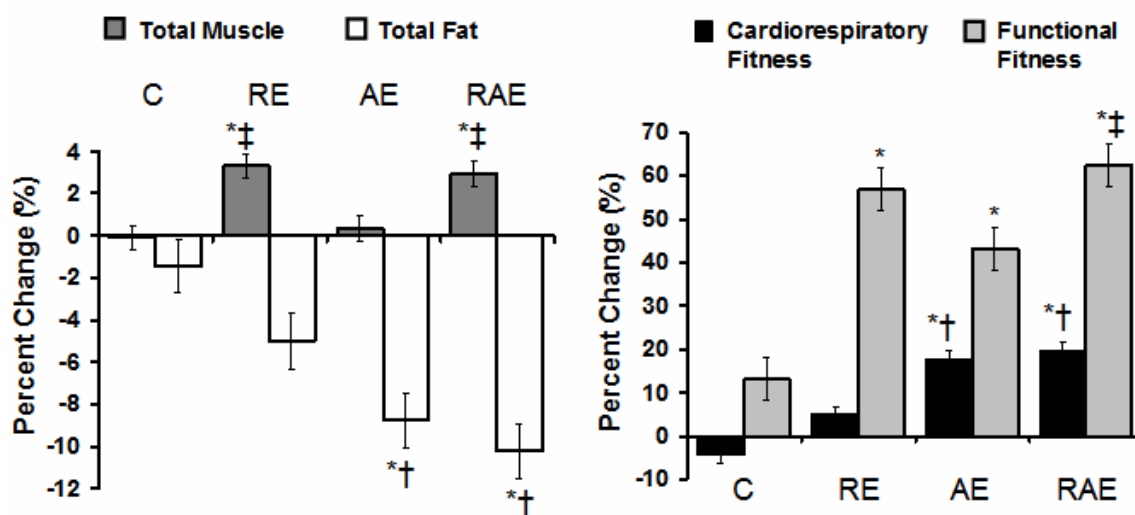
C = control; RE = resistance exercise; AE = aerobic exercise; RAE = resistance and aerobic exercise

\* Significant treatment differences (pre vs. post) compared with control ( $p < 0.05$ ).

† Significant treatment differences (pre vs. post) compared with resistance exercise ( $p < 0.05$ ).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise ( $p < 0.05$ ).

**Figure 3.** Percent changes in cardiorespiratory and functional fitness, total muscle and fat with exercise modality



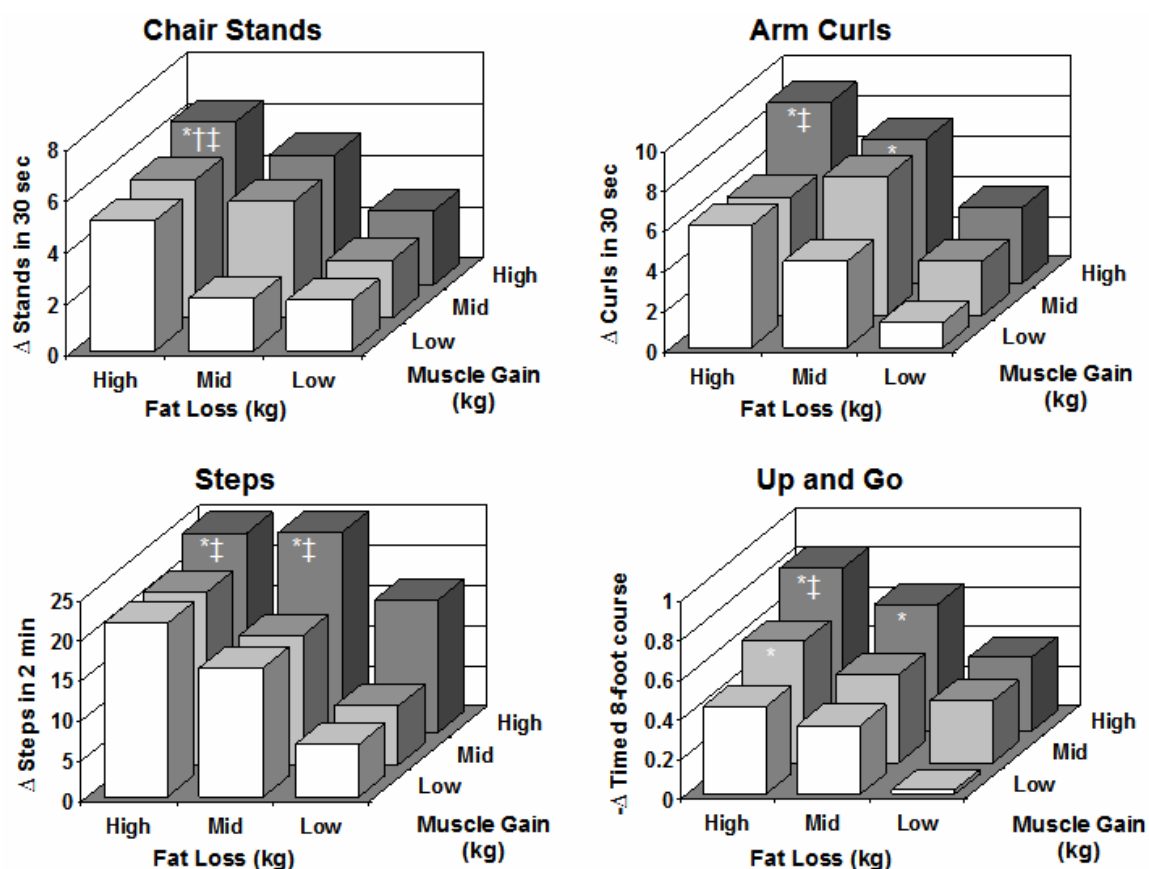
C = control; RE = resistance exercise; AE = aerobic exercise; RAE = resistance and aerobic exercise

\* Significant treatment differences (pre vs. post) compared with control ( $p < 0.05$ ).

† Significant treatment differences (pre vs. post) compared with resistance exercise ( $p < 0.05$ ).

‡ Significant treatment differences (pre vs. post) compared with aerobic exercise ( $p < 0.05$ ).

**Figure 4.** Functional fitness performance by muscle and fat change tertile groups



Δ = change; -Δ = inverted change scores; High = highest tertile of muscle or fat change; Mid = middle tertile of muscle or fat change; Low = lowest tertile of muscle or fat change; sec = seconds; min = minutes.

\* Tertile mean is greater than low-fat low-muscle change tertile ( $p < 0.05$ ).

† Tertile mean is greater than mid-fat low-muscle change tertile ( $p < 0.05$ ).

‡ Tertile mean is greater than low-fat mid-muscle change tertile ( $p < 0.05$ ).

## Chapter 5. General Discussion

The results from these two manuscripts establish that independent of gender and without caloric restriction, performing a combination of aerobic and resistance exercise over a period of 6 months results in marked improvements in body composition, insulin resistance and functional capacity, and may be considered an optimal treatment strategy for the reduction of metabolic risk and functional disability in the elderly. However, either aerobic or resistance exercise alone provides distinct body compositional, metabolic, and functional benefits, offering viable exercise modality options to clinicians seeking lifestyle-based prevention and treatment for the diabetes and functional impairment commonly observed in abdominally obese older men and women.

The message to clinicians regarding the therapeutic treatment of older men and women is clear. The dogma that caloric restriction is fundamental for the reduction of health risk in abdominally obese seniors has now been challenged. Through moderate exercise alone consistent with consensus guidelines and with minimal weight loss, older adults may enjoy a substantive reduction in abdominal obesity and related insulin resistance, a marked increase in cardiorespiratory fitness, and muscle hypertrophy concurrent with total fat loss resulting in a reversal of the functional impairment commonly associated with aging. This evidence and the encouraging clinical message it provides is relevant to a majority of older adults.

The Senior Study provides conclusive evidence confirming the efficacy of exercise as a fundamental part of a therapeutic strategy to reduce health risk in abdominally obese senior men and women. Indeed, the use of a rigorously-controlled randomized design, criterion measurement methodology, well-managed exercise facilities and motivating support staff to ensure compliance to the study protocol, strengthens our findings and elevates the quality of research so that dissemination of our interpretation of the results can be more widespread. The controlled attributes of a laboratory setting, although essential to establishing the efficacy of a treatment strategy, do not provide information regarding the success of that intervention when applied within the everyday living environment of the elderly in the absence of an “obligation” to comply with an imposed research protocol. Essentially, our results provide a clear message of

the efficiency of exercise in providing substantial health benefit, but in so doing, are unable to speak to the effectiveness of physical activity. Would the marked physical and functional improvements we observed in each of the exercise treatment groups have materialized without supervision of exercise and constant external motivation to continue?

One method of testing the applicability of a successful laboratory protocol in a home-based environment is to continue observation of participants for a period of time after the structured laboratory intervention. Dunstan et al.<sup>238</sup> conducted a 1-year trial in older diabetic men and women in which 6 months of supervised gym-based resistance exercise and dietary intervention was followed by 6 months of unsupervised home-based diet and resistance exercise. The improvement in glycemic control observed after the first 6 months was abolished under a home-based resistance exercise program, with the authors citing a reduced volume and intensity of exercise and other non-compliance issues as possible explanations for the lack of success at home.<sup>238</sup> Another randomized trial by the same research group compared a year of home-based resistance exercise to similar training performed in a community fitness and recreation center, both of which were prefaced by two months of observed exercise in a laboratory setting.<sup>239</sup> Again, the home-based exercise program failed to provide significant glycemic control while the community-based exercisers at least maintained the glycemic benefits they derived from the 2-month laboratory training.<sup>239</sup> Investigations have been conducted comparing various other modalities of exercise and physical activity interventions, many of which report that home-based exercise programs are not as effective as center-based or observed exercise.<sup>240-243</sup> However, there is some evidence that, assuming sustained compliance over longer intervention periods, home-based programs may produce similar results to structured or observed exercise<sup>244, 245</sup> and further research is needed to establish their long-term effectiveness.<sup>246</sup>

From the research cited above regarding the comparative effectiveness of observed or community-based versus home-based exercise programs, coupled with the observation that many of the seniors sought to exercise together during the program and some even arranged to continue an exercise routine with their fellow participants after they concluded the study, it appears that a key component for successful maintenance of an exercise program is social

support. A need for social interaction within this demographic may be answered by group participation in physical activity, and may satisfy innate social desires while providing substantial health benefits.

Interest in whether these exercise interventions are sustainable in a “real world” environment stems from observations of the Senior Study participants as they attempted to transition their newly-developed lifestyle of physical activity into an old framework fraught with sedentary habits. Their responses to the cessation of our laboratory program varied substantially, with some concluding the study hopeful and excited to continue physical activity in other surroundings, some doubtful and fearful that they couldn’t sustain a physically active lifestyle without daily external motivation, and others just glad to have one less thing to worry about in their busy, yet sedentary lifestyles. With such variation in attitudes toward a lifestyle that includes physical activity, even within our sample of seniors who successfully became “physically fit” though completing 6 months of sustained exercise, it is no wonder that such high rates of physical inactivity prevail in the elderly population.

In other seniors for whom the commencement of exercise is not conveniently facilitated through joining an exercise intervention trial, starting a new exercise program may be difficult without the encouragement of a health care provider. It was our impression when obtaining medical consent for the subjects’ participation in the study that most primary care physicians were fully supportive of their patients’ involvement in a lifestyle-based intervention designed to improve physical and metabolic function, yet perhaps lacked the time, information, or resources to adequately prescribe that kind of intervention for their patients without resorting to an existing program. Fostering good communication with health care providers and making available options for implementing viable lifestyle-based treatments for at-risk elderly patients will facilitate the advocacy of the medical community, which will likely increase the success rate of seniors who wish to improve their health through exercise.

Disseminating to clinicians our recommendation for the optimal treatment strategy for abdominal obesity and age-related muscle decline is only one step toward implementation of exercise in seniors whom the message would most benefit. Further research is required to

determine the effectiveness of exercise recommendations when advocated by primary care physicians, and to determine an environment in which seniors are best able to sustain regular physical activity.

## Summary and Conclusions

Aging is associated with a progressive accumulation of abdominal fat and an accelerated decline in muscle mass and strength, which are associated with substantially increased risk of metabolic disease and functional disability. These studies establish that performing a combination of resistance and aerobic exercise without caloric restriction and in accordance to consensus guidelines is an optimal treatment strategy for abdominally obese older men and women. The distinct benefits associated with each modality combine to produce a simultaneous reduction in obesity and muscle hypertrophy associated with marked improvements in insulin sensitivity and cardiorespiratory and functional fitness. That substantial benefits were associated with only moderate exercise-induced weight loss challenges the dogma that caloric restriction and weight loss need be the cornerstone of a lifestyle-based strategy for health risk reduction in the elderly. Rather, the notion of tracking waist circumference instead of weight changes as a clinical tool for assessment of exercise-induced changes in abdominal obesity is reinforced. While these data support a combination of resistance and aerobic exercise as the optimal treatment strategy in abdominally obese older adults, more research is needed to determine the effectiveness of this exercise prescription when advocated by physicians and conducted in a non-laboratory setting.

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## **Appendices**

## **7.1.0. Senior Study Manual of Procedures**

### **7.1.1. Introduction**

Inherent to successfully conducting intervention trials in humans is a need for strict adherence to a protocol that minimizes opportunities for bias, ensures proper treatment of participants, and provides uniformity in intervention and assessment. When I began as a new doctoral student in Dr. Ross's exercise physiology laboratory at Queen's University, the Senior Study had recently been awarded federal funding, and I was expected to begin learning the ropes of laboratory testing, establish study procedures, and recruit study participants as soon as possible. Fortunately, I began this effort in the wake of two other major intervention trials: a recently-completed diet and exercise study in women, nicknamed the MRC women study; and the Caffeine study, an ongoing trial investigating insulin resistance in diabetics being directed by So Jung Lee. With this immediate opportunity to learn assessments, I began compiling a personal laboratory testing procedures manual, which I have used extensively as a reference and a teaching tool over the years of Senior Study data collection. The following manual of procedures explains the behind-the-scenes work of conducting a randomized controlled trial and provides step-by-step instructions for carrying out recruitment, assessment, management, and data analysis for the Senior Study.

### **7.1.2. Key Personnel**

Essential to the study are the major decision makers. First and foremost, Dr. Robert Ross was the principal investigator and funding supervisor, and provided the final word on all major decisions regarding the study. In matters of a medical nature, he would consult Dr. Robert Hudson, who was head of the medical team and was also a co-investigator listed on the funded grant. The medical team included doctors, nurses, and medical technicians as listed below, along with their specific duties:

1. Dr. Robert Hudson – Provided approval of medication use, attended a majority of clamp procedures, signed imaging requisition forms, acted as liaison with participant physicians

2. Dr. Katherine Kilpatrick – Attended all maximal exercise tests, assisted in approval of participant medical questionnaires, was attending physician for 1/3 of all clamp tests
3. Dr. Armita Rahmani – Attended clamp tests on occasion
4. Tammy Scott-Zelt – Head clamp nurse, charge of inventory at Hotel Dieu hospital for blood draws and clamp procedure
5. Lesley Rooke – Assistant clamp nurse, filled in on double clamp mornings
6. Leann Cunningham – Assistant clamp nurse toward the end of the study
7. Diana Hall – Consultant laboratory technician for proper handling of freezer samples
8. Cindy Little – Head MRI technician, attended many whole-body MRI acquisitions, only technician trained to perform MRS procedure, trained her staff of technicians and developed program for MRI scan acquisition on newly-acquired magnet partway through data collection
9. Joyce Devette-McPhail – Manager of CORELAB at KGH, which facility made possible blood specimen analysis for blood gases, lipids, insulin, and for liver and inflammatory markers

Management of the study participants was made possible by a team of students and employees in Dr. Ross's laboratory. Over the 4-year data collection, we cycled through various project staff which filled roles that were essential to the successful completion of the trial. I shared much of the day-to-day management of the study with a project coordinator: a vital member of the team who often doubled as a study nutritionist. In chronological order of their employment, the following served as project coordinators:

1. Ann-Marie Kungl – Project coordinator of previous studies, aided in adapting an existing nutritional guidance package for Senior Study use, assisted in recruitment of subjects through arranging for advertisements and telephone screening, performed all nutritional education sessions and monitored dietary intake records during first 1.5 years of the study, scheduled testing appointments, and arranged personnel for observation of exercising seniors.

2. Shelley Atkinson – Began as study nutritionist and developed the nutritional package to accommodate a greater mass of study participants, assumed role of project manager in Ann-Marie's absence while continuing her role as study nutritionist, assisted extensively in study recruitment efforts, and aided me in providing feedback packages to seniors who had completed.
3. Amanda McDougall – Completed the study as project coordinator and nutritionist in Shelley's absence and performed detailed analysis of dietary records for a majority of participants.

Most testing appointments were attended or performed by me personally for the first year of the study, but as the recruitment effort and volume of ongoing participants increased, I delegated some of my testing responsibilities to other graduate students in the lab. The following is a list of graduate students and their involvement in testing procedures during the study:

1. Jennifer Kuk – performed a majority of the senior women's anthropometric and functional fitness assessments and attended MRI/MRS appointments on a rotational basis with other graduate students.
2. Kate McMillan – performed anthropometric and functional fitness assessments on a few of the senior women, attended MRI/MRS on rotation with other graduate students, helped conduct VO<sub>2</sub>max tests for a year and a half, and upon completion of her Masters degree, helped analyze MRI images.
3. Peter Janiszewski – Conducted VO<sub>2</sub>max tests for 2 years, attended CT scan sessions often throughout that time, and attended MRI/MRS on rotation with other graduate students.
4. SoJung Lee – performed anthropometric and functional fitness assessments on a few of the senior women, and attended MRI/MRS and CT on rotation with other graduate students.

5. Meghan Watts – Assisted me with VO<sub>2</sub>max tests for a year, attended CT scan sessions often throughout that time, and attended MRI/MRS on rotation with other graduate students.
6. Suzy Wong -- attended MRI/MRS on rotation with other graduate students.

Each exercise session completed by the seniors was monitored by a graduate student, undergrad, or hired exercise monitor. During the first year or so of the study, while the Caffeine study was still underway, I monitored a majority of the resistance exercise sessions (which required the monitor to accompany the participant to the Queen's exercise facilities downstairs) and shared the responsibility of upstairs monitoring with the other graduate students. Occasionally, undergrads seeking volunteer hours or even an hourly wage would stand in for the upstairs monitoring. Gradually, as recruitment accelerated, I trained some of the graduate students and a few trustworthy undergrads to help with the downstairs resistance sessions, and we began to share the load of exercise monitoring relatively equally. During the 3<sup>rd</sup> year of the study, we decided to hire a part- to full-time graduated physical education student as a more permanent exercise monitor to ease the burden of monitoring from me and the other graduate students. It was mandatory that a graduate student was available in the event of an emergency, so each graduate student signed up for various hours throughout the week and made him/herself easily accessible to either fill in while the permanent exercise monitor was downstairs, or was able to assist if called on for an emergency. The laboratory purchased walkie-talkies to ensure quick communication, and often the graduate students were able to maintain their studies in their laboratory offices while leaving the exercise monitor to interact with the seniors alone.

The exercise monitor obviously played a pivotal role in motivating the exercising seniors, and we were fortunate enough to have consistently hired dedicated and energetic monitors for this position. Our first official monitor was Erin Armitage, whose work ethic and love for the seniors set the stage for the others: Claire Kilgallon, Mika Johnson, and Nicole Bobbette. Each of these monitors provided motivating encouragement to the exercisers, and was essential to the success of the study during her respective tenure as part of our research team.

### 7.1.3. Recruitment Strategies

Over the four years of recruitment, we tried numerous recruitment strategies to attract eligible participants for the study. Listed below, in order of efficacy, are some of the methods we employed:

1. Newspaper advertisements – Our first wave of recruits was summoned by small advertisements placed in a few of the local newspapers. These smaller advertisements caught only the avid newspaper readers, and efficacy began to wane after the first surge of recruits called in. We maintained those smaller advertisements while trying other means until later in the study, when we became desperate for a response and went to larger advertisements with pictures and testimonials of current participants. This latter means brought more calls than any other, and while expensive, was the single greatest recruitment method. Examples of smaller and larger advertisements can be found in section 7.1.13., Appendix 1. We also encouraged exercising seniors to submit short promotional articles to local publications, relating their feelings about participation in the study and encouraging other like-minded seniors to take part. Two participants, Bora Hincer and Dr. Peter Froud, were eager to help and produced pieces for submission in The Kingston's Whig Standard and in online form for the Retirees Association of Queen's, respectively (see section 7.1.13., Appendix 2). These promotional articles did not generate as much response as the picture advertisements, however.
2. Health fair booth – Another highly effective recruitment opportunity was posting an information booth at a health fair held by Christ's Church in Kingston. A representative from the church contacted the School of Physical and Health Education, asking for graduate students to display current research. No other graduate student in our school at the time was half as interested as I was at interacting with the community, so I was allowed an entire booth space to attract senior recruits. One of the current exercisers, Bob Wells, was eager to join me at the fair, and we had some very large and colorful posters made up for the occasion. We posted pictures of seniors exercising in the lab (all with written permission, of course) and had a sign-up sheet available for eligible seniors

to indicate their interest in the study. Bob Wells was phenomenal: he talked up the program so well (even flexing his muscles for a few undecided seniors) that we went away with 30 or so names in only 4 hours worth of work! The power of a testimonial is supreme.

3. Posters – Early in the study, I created a flyer that became our trademark poster throughout the study (see section 7.1.13., Appendix 3). We had it slightly enlarged, printed in color on good-quality paper, and posted it in strategically-located places throughout the community in hopes of attracting the senior eye. We posted in medical facilities, malls, bookstores, libraries, churches, and Kingston's senior centre: anywhere we could get permission. Although we don't have statistics on which poster had the most hits, I recall that one posted near a coffee shop in the Cataraqui Town Centre seemed to bring in more calls than any other over an extended period of time.
4. Public speaking opportunities – Our first occasion to double a public speaking opportunity with recruitment was when we arranged for Dr. Ross to speak as part of the "Learn and Linger" program at the Senior Centre in Kingston. We expected the opportunity to be a fruitful one, with Ann-Marie and I performing simple functional fitness tests afterwards so that people could get to know us and hopefully respond to the recruitment flyers we were prepared to give them. Dr. Ross's speech went very well and was extremely well received. However, due to a time conflict, we had to hurry away to another engagement immediately after the presentation and fitness tests without leaving much time for further mingling. We received only one phone call resulting from that event; the subsequent write-up of the discourse in the Senior Centre monthly journal, *Vista*, was extremely complimentary, but was also of limited recruitment consequence (see article by Pat Galasso in section 7.1.13., Appendix 4). In time, however, we learned to make opportunities for one-on-one discussion with attendees, and public speaking became a worthwhile venture. Dr. Ross spoke at one more luncheon put on by Rotary International, and later I put together a PowerPoint presentation for a different rotary club luncheon and for two other invited church gatherings.

5. Word of mouth – A few of our participants were directed to the program by family members. Meetings with Rotary International, for example, were public speaking events which often made the grown children of seniors concerned for the health of their parents, who would be given our pamphlets or number to call. With all of the foot travel that I did between the university and the two hospitals, I often stopped to talk with seniors fitting the description of the study and asked them if they would be interested in becoming involved. That method alone brought in several successful participants. Sometimes study participants became so excited about the changes they had made that they recruited their friends and colleagues. The effect of word of mouth recruitment is difficult to assess, especially later in the study, when recruits may have seen posters and advertisements well before finally being approached by someone and invited to join the study.
6. Radio and television – On two occasions, I was interviewed on local radio and television programs, extolling the virtues of the study and expressing our need for participants. Previous studies from our lab had had success with Dr. Ross targeting a younger population on the radio waves, but somehow this method did not seem as productive in the Senior Study. One of our early participants, Beverly Spencer, was chosen as a senior spotlight on a national cable network show. She was followed around by cameras as she explained her new lifestyle in the Senior Study; while the program was well-produced and provided glowing praise for the study, these methods did not yield substantive recruiting results.

#### 7.1.4. Screening of participants

Not everyone fits the criteria we are looking for in our study. In advertising, however, we were cautious not to screen out too many candidates initially, so that we would not lose eligible participants who may not think they fit our criteria. Our advertisements encouraged interested people to call the laboratory number and ask for the project coordinator, who would screen the callers by asking them specific questions and recording the answers in an Excel database. Major

explanation of the project details did not usually occur over the phone, but was rather deferred to the recruitment meeting, where I could be more thorough and present the ideas and reasons for the study more fully.

The screening spreadsheet was computer based and had a column for each of the inclusion criteria. For the CIHR Senior Study, the criteria were the following:

Age: 60-80 years

Residence status: self-sufficient, community dwellers

Activity level: sedentary

BMI: 27-34.9

Waist circumference: >88cm for women, >102cm for men

Weight stable: change not greater than  $\pm 2$  kg for 6 months prior to study

Non-smokers

Non-diabetic

For women: no hormone replacement therapy within 3 months

Other medical restrictions were noted, recording the dosage of the medication and how long the participant had been taking it. The candidate was also asked about intended medication changes. The following questions were typical during these phone conversations:

Are you having any joint/mobility concerns?

Have you ever been prescribed nitroglycerine (spray, patch or sublingual tablet)?

Has your doctor ever said that you have cardiovascular disease?

Have you ever experienced angina?

Have you had a heart attack, stroke, or bypass surgery?

Have you ever had a stress test? How long ago? What were the results?

Our medical team requested that we screen out the following during the telephone screening process:

1. Anyone with angina
2. A cardiac history unless approved by Dr. Kilpatrick
3. Diabetics taking medication for glucose control

4. Prednisone – it affects glucose/insulin levels
5. Blood pressure meds, specifically beta blockers: metoprolol, atenolol, propranolol, sotalol
6. Hydrochlorothiazides if over 50mg – only allowed if dose remains constant
7. Cholesterol meds (which we began allowing in Sept 2003): lipitor (atorvastatin), zocor (simvastatin), pravacol (pravastatin), niacin, crestor, lipidil
8. Any new medications – must wait 4-6 weeks before undergoing pre testing

The medications column was included last in the screening spreadsheet to allow for a long list of medications and explanations for those medications. Any questionable medications were highlighted and sent to Dr. Hudson for individual approval. Screening over the phone was done so that ineligible people would not be invited to the recruit meeting and be disappointed when we didn't allow them into the study. A column for subject status (called, not called, not available until next Thursday, etc) was also in the spreadsheet, so that the project manager and I could both operate from the same sheet and not duplicate efforts when or the other was not available to do phone work.

#### 7.1.5. Orientation meetings

When candidates successfully passed the eligibility criteria, orientation meetings were scheduled. I conducted all of these meetings personally since the initial overview presentation was vital to the seniors' understanding of the project and was often pivotal in their decision-making. It was preferable to have five or so candidates meet together in the downstairs conference room of the PEC, room 154. In actuality, we rarely had five in one meeting, and meetings were often performed with one or two potential participants in my office when scheduling of the conference room proved difficult.

The orientation meeting educated each candidate fully as to the procedures performed, the time commitment required, and the potential risks and benefits for involvement in the study. I was careful to hold no detail back and to present the information as concisely as possible. An example of the PowerPoint presentation used for orientation meetings in the CIHR Seniors study is available in section 7.1.13., Appendix 5.

The three documents given the subjects upon arrival to the meeting are listed below and copies of these documents are found in the appendices:

1. Orientation Meeting Information Sheet (section 7.1.13, Appendix 6)
2. Informed Consent (section 7.1.13, Appendix 7)
3. Medical Questionnaire (section 7.1.13, Appendix 8)

In the final minutes of the orientation session, I would explain each of the above documents and what the potential participant should do with them. The information sheet was turned in and used for recording the screening anthropometrics (height, weight, and waist circumference). The informed consent was to be read carefully with a spouse or friend before it was signed and returned to the project coordinator. The medical questionnaire was filled out by the potential participant and taken to a personal physician for approval.

While some physicians had seen their senior patients for yearly check-up recently enough, most of the potential participants' physicians preferred performing a complete physical before giving signed approval. The signed paperwork and in some cases the physical, which in previous trials had been covered as a standard medical visit by the Canadian health care system, was no longer covered due to recent legislation. We instructed the seniors to bring the receipts for such fees into the project coordinator for reimbursement. The fees varied from a \$20 paperwork fee to well over \$200 in some cases.

When performing a larger orientation meeting, I would have the project coordinator and/or a few graduate students available at the meeting to help me conduct anthropometric screening measurements on the candidates in the laboratory. Otherwise I would personally perform the following on interested candidates after the meeting:

1. Waist circumference – usually done in the wet lab for privacy. This measurement was often done over the top of clothes with the tape should be positioned horizontally at the iliac crest. Those candidates who were “close” to the abdominal obesity cutpoints were asked if they wouldn't mind submitting to another measurement wearing loose-fitting Queen's athletic shirt and shorts for this measurement.

2. Weight – in kilograms with clothes on (shoes off) on the lab scale.
3. Height – by the wall-mounted Holtain Limited to the nearest centimeter.

The measurements were recorded on the information sheet (section 7.1.13, Appendix 6).

BMI was calculated immediately by dividing kg body weight by height in meters squared.

Because we measure height in centimeters, the decimal was shifted 2 columns to the left before squaring height.

Before inclusion into the study, these information sheets were examined carefully (by Dr. Hudson, if necessary, for medications) to screen out any candidates who do not fit the inclusion criteria. When a medication list did not match either the version received over the phone or the list provided in the medical questionnaire, the project coordinator investigated the discrepancies.

#### 7.1.6. Nutritional meetings

Having handed in the information sheet, a signed consent, and having at least a scheduled appointment to see a physician, participants began meeting with the study nutritionist for the nutritional run-in period. Key messages during these first few meetings were the following:

1. This is a physical activity intervention, not a weight loss program
2. Participants are expected to maintain weight during the baseline period run-in period and calorie intake throughout the course of the study
3. Participants must be willing to participate in any of the four randomly-assigned groups
4. Participants must inform the lab if a medication change occurs
5. Participants must not make any changes to their current way of eating.

The nutritionist then explained Canada's Food Guide, including the rainbow design and the focus on variety. She reviewed the four food groups and the "other" category, identifying which food groups provide major macronutrients. She explained the importance of choosing whole grains, brightly-colored fruits and vegetables, low fat dairy products, and leaner meats and meat alternatives. She discussed unhealthy fats (saturated and trans) and identified sources. The participants were taught to quantify portion sizes and to understand measurements. They were

taught to understand serving sizes and to identify the fat and calorie content on a label. Participants were instructed and practiced using the T-factor booklet while filling out a diet record, with focus on how to report a combination of foods and how to break food down to individual components. Each run-in session concluded with a weigh-in on the laboratory scale.

After the introductory session, participants took home a nutritional binder containing a picture of Canada's food guide, a T-Factor or H book, fast food brochures on nutrition breakdown of food, daily food intake records, a sheet giving instructions on how to improve accuracy of diet records, and a frequently used food list. An appointment was scheduled for a return visit within the next three days to assess diet records and to measure body weight. An example of one completed day of dietary recording is found in section 7.1.13, Appendix 9.

For a period of three to sometimes five weeks, the nutritionist/project coordinator and each participant met 2 to 3 times per week to discuss the accuracy of the food records and to obtain a current body weight. The intent of this process was to determine the total calories required to keep that particular participant weight stable under "normal" or sedentary conditions. When a satisfactory calorie intake was determined, the participant was encouraged to maintain that target calorie level throughout the study. Only when calorie intake and weight were both stable was the participant allowed to begin baseline assessments.

After baseline testing, the nutritionist checked in regularly with exercising seniors and would collect a packet of completed dietary records from each senior on a weekly basis. Seniors in the control group would drop in once a week to weigh in and drop off the previous week's dietary records for review. Exercisers and controls alike were expected to maintain their target calorie intake throughout the study. When waist circumference and/or weight changed dramatically to an extent unexplained by the prescribed exercise treatment, the nutritionist would investigate the issue, determine whether excessive or insufficient calorie intake was driving the changes, and provide counsel accordingly. On rare occasions, the calorie target was deemed incorrect and needed to be adjusted.

Along with regular monitoring of weight and checking accuracy of diet records, the nutritionist provided all participants with a series of educational sessions on the fundamentals of

maintaining a healthy diet according to Canada's Food Guide. A total of nine nutritional packages were delivered during the course of the study. A summary of the goals for each nutritional session is provided in section 7.1.13, Appendix 10.

#### 7.1.7. Randomization

Our method of randomly assigning new participants into one of four treatment groups was to prepare a list of assignments in random order at the beginning of the trial, and place each new participant into one of two master lists (stratified by gender) in the order that he/she completed baseline testing, thus assigning treatment. Because of the potential for bias that arises if a single person were able to schedule baseline testing (which determines placement in the list) while also having access to the master list of assignments, the project coordinator and I divided responsibilities. The project coordinator, who worked with the participants during the run-in period and determined the schedule of baseline assessments, was not allowed access to the randomized treatment list. When a group of participants had progressed through baseline assessments and was ready to begin treatment, the project manager assigned a subject number to each participant by gender and by order of estimated completion of baseline testing, and approached me with the names and assigned numbers. My mandate was to reveal to the project manager the group assignment from the master list that was associated with each participant's subject number by telling her which treatment group was associated with the subject numbers she had given me. To avoid the possibility of my rearranging assignment order, I was made accountable by having an archival copy of the original randomized lists that was burned onto a compact disk and kept in storage.

Partway through the study, we decided that married couples should be assigned to the same group to avoid the potential for "treatment envy" or the likelihood that one member in the relationship might compete with the other, even subconsciously, to achieve similar benefits despite undergoing different treatments. To maintain integrity of the randomization, the project manager decided which member of a couple I was to randomize, and then the spouse would also assume that randomized assignment.

The randomized lists were generated before the study began. In an Excel spreadsheet, I created 100 group assignments (25 of each treatment) in one column. In the adjacent column, I inserted “=rand()”. This function assigns a computer-generated random number between 0 and 1 in each cell. I then sorted both columns by random number in ascending order, thus shuffling the group assignments randomly. In a separate spreadsheet, I performed the same operation again for the other gender. To the left of the group assignments, I entered a column for subject number: 001 through 100 for women, and 101 through 200 for men. After these procedures, I created the archival copy.

#### 7.1.8. Assessments

The following subsections (7.1.8.1 through 7.1.8.12) summarize the laboratory procedures followed for the assessments performed on Senior Study participants and constitute my laboratory manual as a graduate student.

##### *7.1.8.1. Anthropometrics*

Anthropometric measurements should be recorded on the Anthropometric Data Collection Form (see 7.1.13, Appendix 11).

#### **Weight and Height**

Anthro Weight (kg): on Detecto scale

Standing Height (cm): stand with heels against metal plate below Holtain Limited hung on wall in dry lab. Instruct subject to stand tall and take a deep breath in, record measurement given on dial.

Acromion Height (cm): have subject sidestep so that the R acromion process is at the edge of the measurement board. Deep breath in.

Arm length (cm): with tape, measure acromion to longest fingertip

Sitting Height (cm): seat subject on green-topped table (73.3 cm tall), deep breath in.

Knee Height (cm): measure from heel to the top of the knee, with both foot and knee flexed to 90 degrees.

### **Skinfolds (mm)**

Mark the midpoint on the lateral side of the upper arm between the acromion and olecranon processes.

Wrap the tape around the upper arm and transfer that midpoint to the anterior (bicep) and posterior (tricep) surfaces of the arm

Do the following 3 times, measuring within 4 seconds of pinch (longer results in fluid displacement in tissue):

1. Subscapular – diagonal fold, just inferior to the inferior angle of the scapula.
2. Tricep – vertical fold, at midpoint mark
3. Bicep – vertical fold, at midpoint mark subject's palm facing anteriorly

Do these together:

1. Mid-Axillary – subject's R hand on left shoulder, arm elevated (ensure no trunk flexion); horizontal fold on mid-axillary line at level of the xiphi-sternal junction.
2. Iliac Crest – immediately superior to iliac crest along mid-axillary line (p.63)
3. Abdomen – horizontal fold; 3 cm to the right of the umbilicus, 1 cm inferior

Do these together:

1. Thigh – mark midpoint between inguinal crease and proximal patella; vertical fold.
2. Calf – have subject put foot on chair (90 degrees flexion), mark medial calf at widest point; vertical fold.

### **Circumference Measures (cm):**

Hip: should be called “buttocks” measure – at the level of farthest posterior protrusion of the buttocks. Be sure tape does not sag.

Standing Waist, Last Rib: physically find the bottom of the ribcage. Mark it on the R side; Use tape -- do not compress skin and be sure the tape is horizontal.

Standing Waist, Iliac Crest: horizontally at the most superior tip of the iliac crest (palpation will require pressing in firmly with both hands laterally at subject's waist). Mark the level on the R side. Instruct subject to relax and breathe normally. If measurement changes with breathing, take the measure at the end of normal exhalation. Do not compress skin with tape.

Do these together:

1. Bicep: R side, use skinfold mark; L side, create mark between olecranon and acromion
2. Forearm: subject's palms facing anteriorly; measure at maximal circumference

Do these together (subject's weight evenly on both legs):

1. Proximal thigh: horizontally around thigh, immediately distal to gluteal furrow.
2. Midthigh: horizontal at level of skinfold mark
3. Distal thigh: just proximal to femoral condyles

Calf: horizontally at skinfold mark

Supine Waist, Last Rib: take subject into wet lab and have him/her recline supine on padded table (put tape down before the subject lies down) with arms crossing chest. Physically find last rib and measure after normal exhalation.

Supine Waist, Iliac Crest: Physically find superior-most edge of iliac crest and measure circumference vertically at that level.

### **Sagittal Diameters (cm):**

Supine, Last Rib: warm caliper arm first; place end without arm on padded table without depressing vinyl, measure diameter at point of last rib marking after exhalation

Supine, Umbilicus: move caliper inferior to umbilicus, measure after exhalation

Standing Last Rib: insert other caliper arm and warm it; measure at last rib mark with subject standing (on exhalation)

Standing Umbilicus: move calipers inferiorly and measure horizontally at umbilicus (on exhalation)

#### 7.1.8.2. Functional fitness

The functional fitness test outcomes should be recorded on the FFT Data Sheet (7.1.13, Appendix 12). Instructions for the testing procedure are summarized from the *Senior Fitness Test Manual*, a book produced in 2001 by Roberta Rikli and Jessie Jones, who developed this battery of tests. The functional fitness test was a battery of 6 physical tests performed immediately following the anthropometrics measurements.

### 1. 30-second chair stand

- a. Equipment needed
  - i. Stopwatch
  - ii. Stable chair, no arm rests, seat height 17 inches
- b. Protocol
  - i. Place back of chair against wall
  - ii. Have subject sit in the middle of the chair, back straight, feet flat on the floor about shoulder-width apart, arms crossed at wrists and held against chest
  - iii. At your signal of “go,” the subject rises to a full stand, then returns to seated position
  - iv. Subject repeats movement as many times as possible within 30 seconds
- c. Scoring
  - i. Administer only one trial
  - ii. Count number of stands in 30 seconds

### 2. Arm curl

- a. Equipment
  - i. Stopwatch
  - ii. Stable chair

- iii. 5-lb dumbbell for women, 8-lb for men

- b. Protocol

- i. Have subject sit on the chair, back straight, feet flat on floor, shifted slightly to the dominant side of the seat to allow for arm movement
- ii. Subject holds the dumbbell in the dominant hand, arm hanging down beside chair in a handshake grip
- iii. On your signal of “go,” the subject lifts and lowers the weight as fast as possible (yet in a controlled manner)
- iv. Hand position should be facing the chest in full flexion, then return to handshake in extension
- v. Subject repeats movement as many times as possible within 30 seconds

- c. Scoring

- i. Administer only one trial
- ii. Count the number of curls completed in 30 seconds

### **3. Chair sit-and-reach**

- a. Equipment needed

- i. Stable chair, placed against a wall for stability
- ii. 18-inch ruler

- b. Protocol

- i. Have subject sit on the edge of the chair, with one foot flat on the floor and the other leg extended with foot flexed (toe pointing up)
- ii. Subject slowly reaches forward, bending at the hips, and slides the hands (one on top of the other with tips of middle fingers even) down the extended leg in an attempt to touch the toes or reach beyond them
- iii. If the extended knee starts to bend, the subject should sit back slowly until the knee is straight before you record a score

- c. Scoring

- i. After giving the subject two warm-up practices, administer two test trials and record the better test score
- ii. Measure the distance from the tips of the middle fingers to the top of the shoe to the nearest half-inch (or cm)
- iii. If the reach is short of the toes, record the distance as a minus (-) score; if the fingers touch the toes, record a score of "0"; and if the reach is past the toes, record the distance as a plus (+) score

#### **4. Back scratch**

- a. Equipment needed
  - i. 18-inch ruler
  - ii. Perhaps a an ink pen to aide in positive measures
- b. Protocol
  - i. In a standing position, keeping the back as straight as possible, the subject reaches one hand over the shoulder and down the back (elbow up, palm down) and reaches the other hand (palm facing up) behind the back and up as far as possible in an attempt to touch or overlap the middle fingers of each hand
- c. Scoring
  - i. After giving the subject two warm-up practices, administer two test trials and record the better test score to the nearest half-inch (or cm)
  - ii. Measure the distance of overlap (positive (+) score) or distance between the tips (negative (-) score) of the middle fingers; fingertips touching receives a "0" score

#### **5. Eight-foot up-and-go**

- a. Equipment needed
  - i. Stopwatch

- ii. Stable chair, placed against a wall in a clear, unobstructed area
  - iii. Cone, placed exactly 8 feet (measured from the back of the cone to the front edge of the chair) in front of the chair
- b. Protocol
  - i. Subject sits in the middle of the chair with feet flat on the floor and hands on thighs
  - ii. On your signal of “go,” the subject pushes off and walks (but does not run) as quickly as possible around the cone, then walks back and sits down
- c. Administer one practice and two test trials. Record the better test time to the nearest 1/10<sup>th</sup> of a second.

## **6. Six-minute walk**

- a. Equipment
  - i. Stopwatch
  - ii. 4 cones in a 20 x 5-yard rectangle, with 6 cones or other markers showing 5-yard increments along the long sides
- b. Protocol
  - i. Give each subject a marked Popsicle stick and instruct each to track his/her own laps by moving a thumb to uncover the lap number written sequentially on the stick
  - ii. On your signal of “go,” the subject walks as fast as possible (no running) around the course as many times as he or she can within the six-minute time limit
  - iii. Administrator should “call out” when there are 3, 2, and 1 minutes remaining
  - iv. Subjects should walk around the course for another minute to cool down
- c. Scoring

- i. Give the subject a practice trial on a day prior to the test; on test day, administer only one trial.
- ii. The score is the total number of yards walked in six minutes to the nearest 5-yard indicator
  - 1. Each lap = 50 yds; each subsequent cone passed = 5 yds
- iii. If necessary, the subject may rest and start again during the six minutes, but the clock should keep running

**7. 2-minute step** (Used instead of six-minute walk because of limited space)

- a. Equipment
  - i. Stopwatch
  - ii. Tape measure and piece of masking tape for a wall marker.
- b. Protocol
  - i. Find midpoint of the thigh (already marked if anthropometrics done previously) and place the masking tape on an adjacent wall to mark the stepping height
  - ii. On the “go” signal, subject begins stepping in place, raising each knee to the indicated height. Do not allow the subject to run.
- c. Scoring
  - i. The score is the number of full steps completed in 2 minutes (counted each time the right knee reaches the target height).

*7.1.8.3. Glucose tolerance*

We screened our participants for undiagnosed diabetes by having them undergo a 2-hour oral glucose tolerance test (OGTT) at our metabolic facilities in the Hotel Dieu Hospital. Participants were instructed to eat a normal to high-carbohydrate meal the evening before, followed by a 12-hour fast prior to testing. I would meet participants personally at 8:00 a.m. at the Brock Street entrance of the Hotel Dieu and escort them to our laboratory on the third floor.

There introduced them to the study nurse, who would seat them and prepare to draw fasting blood samples from a retrograde venous catheter she inserted into an antecubital vein. The seniors were given a specially-prepared drink containing exactly 75g of glucose and were asked to drink it all in less than 10 minutes. When they had finished drinking, a “0-time” blood sample (5mL volume) was taken from the catheter. Samples were taken every 30 minutes thereafter until 120 minutes had passed. During this time, I took the opportunity to answer any more questions they had about the trial or any upcoming tests. For most, however, I spent a majority of the two hours processing plasma samples for the Hoffman-LaRoche study, which will be described in section 7.1.8.13. We had a small collection of reading material or movies available for the participants to pass the time until the end of the test, after which the nurse removed the catheter and fed them a light snack. I escorted the participants to the front doors of the hospital.

Using a YSI glucose analyzer, the nurse determined blood glucose for each of the samples taken at 30-minute intervals. The two most important samples for diagnosing Type 2 diabetes are the fasting or “0-time” sample and the sample taken 2 hours after ingestion of the glucose drink. Fasting samples which were greater than 7.0 mmol/L or a 2-hour glucose level greater than 11.1 mmol/L is diagnostic of diabetes, according to the 1999 World Health Organization (WHO) diabetes criteria. If either of these cutpoints were exceeded, Dr. Hudson was notified and he communicated the finding to the participant’s personal physician. While diagnosis of diabetes at baseline was considered cause for exclusion from the study, all six of the seniors found to be diabetic with this test continued participation in the study in an exercise intervention. We performed a repeat OGTT on one of the diabetic participants after completing the trial, and his 2-hour blood glucose level was reduced from 12.3 to 10.6 mmol/L (slightly below the diabetes threshold) as a result of 6 months of resistance training.

After separating out the plasma by centrifugation, samples from the OGTT were stored at -80°C in a deep freezer located in our laboratory at the Hotel Dieu Hospital.

#### *7.1.8.4. Cardiorespiratory fitness test ( $VO_2max$ )*

Measuring changes in aerobic capacity requires a comparison of maximal performance on a graded exercise test. For seniors who have never been on a treadmill and are unaccustomed to pushing themselves physically, obtaining meaningful results can prove difficult. During the run-in period, I familiarized each senior with the treadmill and assess his/her ability and balance while they demonstrated a few minutes of walking on the treadmill (usually just after the functional fitness and anthropometrics tests). For some, this required more than one session of practice. The more they comprehended the test and what was required of them, the better the participants would respond when encouraged to exercise “to fatigue” during the test.

$VO_2max$  tests were performed once a week, on an evening when Dr. Kathie Kilpatrick could attend (usually Monday nights). We scheduled a half hour to 45 minutes per participant, and often had 3-4 tests per session. The seniors changed into Queen’s athletic shirt and shorts, and wore a pair of comfortable shoes suitable for brisk walking or jogging. We gave them a Polar heart rate monitor to wear so that we could record heart rates every 20 seconds throughout the test. The test usually lasted 12-15 minutes, beginning with a relatively brisk pace at level grade, increasing grade to 2% at the 3<sup>rd</sup> minute, and then further increasing the grade by 1% every odd minute thereafter. Heart rates were observed by a graduate student, who held a receiver watch while standing close to the participant, and who recorded them on a data sheet (see section 7.1.13., Appendix 13).

Breath-by-breath analysis of respiratory gases was also recorded throughout the test. The following is the step-by-step process of operating the Vmax machine and other computers used in our laboratory for data collection and analysis of this test:

#### **Startup**

Turn the power on to the Vmax console and laptop.

Allow 30 minutes of warming time before calibration and testing.

The Vmax program automatically loads upon startup. If the computer was already on, locate the Vmax program icon and double-click it.

## **Patient Demographic Information**

Be aware that any new calibration data or test data will be added to the current patient file. You don't want that unless your subject is doing back-to-back exercise tests – not likely. You have two choices:

1. Make a New Patient File
  - a. Select “2 New Study” on the Vmax Main Menu
  - b. Enter the subject's information
    - i. ID
    - ii. Date – computer will automatically generate today's date
    - iii. DOB – enter/select birthdate; Age is calculated automatically
    - iv. Gender – drop-down list
    - v. Race – choose from list
    - vi. Height – either inches or centimeters
    - vii. Weight – enter today's weight (kg or lbs)
    - viii. Physician – select Kathie, None, or Big Bob
    - ix. Tech – select your name
    - x. Medication – enter up to 5 medications
  - c. Select “F3” to store the information and return to the Main Menu
2. Retrieve a Previous Patient
  - a. Select “2 New Study” on the Vmax Main Menu
  - b. Press “F1” to search for previous patient's demographic data
  - c. The “Last Name” Data Window will automatically be selected when the Patient File Search Box is initially displayed
  - d. Type the subject's last name (not case sensitive)
  - e. Select “F1” to begin the search
  - f. Select the desired subject name with the mouse
  - g. Select “F2” to run a new VO<sub>2</sub> test on the subject

- h. Change any information (likely weight will change in these studies, perhaps age)
- i. Select "F3" to store the information and return to the Main Menu

### **Flow Volume Calibration**

Select "1 Flow Sensor Calibration" on the Main Vmax Menu.

The Mass Flow Sensor Zero Box will be displayed.

Attach the calibration syringe to the Mass Flow Sensor.

Press "F1" to start calibration.

Stroke the syringe 2 times to purge the Mass Flow Sensor with room air.

Select "Space Continue"

Excessive movement of the Mass Flow Sensor or the Sensor Cable during calibration can affect your accuracy and success at calibration: Ensure that airflow is minimal around Vmax.

A ten-second timer will count down to zero before continuing to the Zero routine.

The Mass Flow Sensor will be automatically calibrated to zero gas flow.

When the Zero routine is complete, the Flow Volume Calib Screen will be re-displayed.

### Calibration Strokes

With the syringe piston initially in, move the piston in and out for 5 full strokes.

The display will not show the first full stroke

A screen with flow ranges will show whether you have averaged a certain stroke speed

Be sure to turn all ranges from yellow to green with the allotted strokes

Strokes should be done smoothly and consistently: don't bang the syringe!

Hint: for slow strokes, twist the syringe head slightly as you go – keeps it from sticking

Keep each stroke within 3-6 LPS (0.5-1.0 second stroke duration)

### Verification Strokes

Perform 5 more strokes.

At least one of the last 4 should have an average flow rate of  $< 0.5$  LPS

At least one of the last 4 should have an average flow rate of  $> 3.0$  LPS

The red dotted lines should help you achieve these requirements.

If you failed the Verification Criteria ( $\pm 3\%$  of known piston volume) then start again: Press "F1"

Press "F3" to accept calibration values.

Remove the syringe.

**Verification only** (used between consecutive tests)

Select "F2" on the Flow Volume Calibration Screen.

Attach the calibration syringe to the Mass Flow Sensor using the calibration adapter.

Perform 6 strokes of the syringe piston (flow rate between 20-720 LPM)

At least one of the last 4 should have an average flow rate of  $< 0.5$  LPS

At least one of the last 4 should have an average flow rate of  $> 3.0$  LPS

The red dotted lines should help you achieve these requirements.

If a Warning Message Box appears, you generally have to perform the complete Cal. Procedure

Remove the syringe.

**Gas Analyzer Calibration**

Select "4 Exercise/Metabolic Test" from the Main Menu

Select "Exercise Protocol", then Press "F1"

Use the tool to turn the Span 1 and Span 2 valves on completely (2 full turns counterclockwise)

Connect sample line (braided) to the Calibration Fitting on the front of the Pneumatics Module.

Select "F1" to initiate the O<sub>2</sub> and CO<sub>2</sub> analyzer calibration sequence

Both analyzers will initially sample 3 gas concentrations and calculate correction factors (step 1):

16% O<sub>2</sub>, 4% CO<sub>2</sub> (Cal 1 gas)

26% O<sub>2</sub>, 0% CO<sub>2</sub> (Cal 2 gas)

20.94% O<sub>2</sub>, 0.05% CO<sub>2</sub> (room air)

The correction factors are then verified by sampling the same three gas concentrations (step 2)

The Verification sequence (step 2) is displayed graphically in the O<sub>2</sub>% vs. Time Window and the CO<sub>2</sub>% vs. Time Window.

The values are updated at the end of the verification sequence.

If you get a warning, follow directions. Do *not* test someone until this calibration is successful.

Reconnect the sample line to the sample fitting on the Mass Flow Sensor.

Press “F3” to accept calibration values and begin test.

#### **Verification only** (used between consecutive tests)

Connect sample line (braided) to the Calibration Fitting on the front of the Pneumatics Module.

Select “F2 Verify” to initiate the O<sub>2</sub> and CO<sub>2</sub> analyzer verification sequence

If you get a warning, complete a full Gas Analyzer Calibration procedure.

Reconnect the sample line to the sample fitting on the Mass Flow Sensor.

Press “F3” to accept calibration values and begin test.

Test screen will pause until you have the subject hooked up and start the VO<sub>2</sub>max test

#### **Equipment Check**

You'll need a clean mouthpiece and spit drain connected to the Mass Flow Sensor

The spit drain is assembled by stuffing gauze in the drain and sealing the end with tape

Wrap a clean pad around the forehead section of the headpiece.

Snap the headpiece onto the Mass Flow Sensor and carefully lay aside so it will not fall.

Have a heart rate monitor and receiver (watch) ready to give to the subject

Have two extra pieces of tape ready for the subject's nose and to secure the lines to the treadmill display panel

#### **Subject Preparation**

Thoroughly explain the entire procedure to the subject, including:

- a. stop mechanisms for treadmill
- b. subject should not try to talk – use hand signals instead
- c. subject should terminate test if feels pain in chest or dizziness

Fit the heart rate monitor snugly around the subject's ribcage (about at bralaine)

Ensure that the receiver (watch) reads a normal heart rate

Have the subject familiarize him/herself with the treadmill and warm up for at least 5 minutes

Treadmill should be at 0% grade and a speed that induces a HR of about 135 BPM

Use the speed you determined (in practice sessions) for the treadmill test speed

Stretch the major leg muscles with the subject in preparation for the test

Fit the headgear snugly and adjust the wires so that the mouthpiece is supported

Tape the tubes (with some slack toward the subject) to the display panel on the treadmill

Place a nose clip on the subject (may require tape first if subject will sweat profusely)

### **Maximal Graded Exercise Test**

Simultaneously select "F8" and the Start button on the treadmill.

Immediately adjust the treadmill to the desired speed.

Manually record HR every 20 seconds throughout the test

Provide encouragement to the subject, reassurance, and step-by-step explanations

The ramp protocol is included as an appendix to this section

Instruct the subject to press the stop button or grab hold of railings with both hands as a signal to stop the test.

Be watching for signs of fatigue and be ready to offer a steadying hand at the subject's back

Do the following upon completion of the test:

Select "Exit/Pause" on the Top Menu

Select "Y to End Test"

Data collection will terminate, and the Exercise/Indirect Calorimetry End of Test Comments Box will be displayed.

Disconnect subject from breathing circuit and perform your routine post-test subject care

### **Cleaning Equipment**

Detach headpiece from breathing circuit.

Run a beaker full of water and add proper amount of cleaning solution

Detach the Mass Flow Sensor and gently place it into the solution

Remove the tape and gauze from the spit drain and discard

Place the mouthpiece and spit catch in the solution as well

BEWARE: leaving the Mass Flow Sensor in a cleaning solution for too long may damage it!

Not leaving it in long enough may be damaging in the long run too:

Let it soak for 10 minutes, then VERY GENTLY rinse

Remove forehead pad from headpiece, and repeatedly saturate with soapy water and rinse.

Leave all breathing circuit equipment on the towel to dry

Wash, rinse, and thoroughly dry the heart rate monitor. Lay it out on the towel for the next test.

### **Formatting File and Saving for Data Entry** (immediately after testing)

From Main Menu, select "4 Exercise/Metabolic Test"

Select "1 Tabular Edit"

You'll need to generate a one-page summary; change the Average section from None to 20 Sec.

Select "F5" to print the file (you really don't print with this selection)

A Print To File Window appears, with "\*.prn" highlighted

Change the "\*.prn" to "<subjectlastname>.prn"

Change the Drive from C: to A: and insert a floppy disk. Press OK.

Remove the floppy.

Hit Esc twice to return to Main Menu

Exit the Vmax program and shut the computer down

### **Finding File, Formatting and Saving for Data Entry** (when other tests have since occurred)

From Main Menu, select "A Find a Patient"

Type the last name of the subject in the available field

Select "F1"

Tests completed on that subject will appear. Click on the appropriate test.

Select "F3" to retrieve patient data. The Main Menu will appear.

Follow the directions above in Formatting File and Saving for Data Entry

## **Data Entry**

Insert the floppy that has the subject's VO<sub>2</sub>max data on it.

On Viewsonic, go to Lance's file.

Open folders: Queens PhD → CIHR Seniors → VO<sub>2</sub>max results

Select folder for subject's cohort, and find name. An Excel worksheet will appear.

Click on the appropriate tab: Pre, Mid, or Post.

Check to see that the name is correct and enter the test date.

File, open. View "All Files"

Select "3½ floppy A:\<subject\_name>.prn"; press OK.

Change option from "Fixed width" to "Delimited"; press Next.

Choose "Tab" and "Space" delimited; press Finish.

Drag and right click the entire data set from 00:00:20 to the last interval of testing

(Check to see that the last few intervals are really valid data points)

Copy the highlighted area

Close the "3½ floppy A:\<subject\_name>.prn"

Click on cell "A8" and Paste.

Enter HR values you from the VO<sub>2</sub>max data sheet. *Double-check for errors.*

Click on each of the yellow boxes and change all "\_99" values to the number of the last row of data for this test. Example "\_69"

Formulas will generate valid numbers to be used for updating the lab's stand-alone computer.

Save changes, Exit.

## **Updating The Stand-Alone Computer**

In the Results section of the VO<sub>2</sub> datasheet, find the "kcal/HR" formula output.

Double-check that the row numbers represent the data set.

Write the Slope and Intercept numbers shown onto a piece of paper.

Walk over to the stand-alone computer in the main lab room.

On the desktop, select the icon representing the subject's cohort.

Find the subject's worksheet and the current date.

Click on the kcal column of the next exercise day.

Input the numbers into the formula shown in the cell window:

Where R# = mean HR during exercise

$$=((Slope*R#)-Intercept)*Q\#$$

And Q# = minutes exercised

Change the "Eq(Equation) Source" to represent the latest test VO<sub>2</sub> test performed: Pre, Mid, Post

Copy a few more days with the updated formula, Save changes, Exit.

### **Paperwork**

Print out a hard copy of the VO<sub>2</sub>max summary for the current VO<sub>2</sub>max test.

Staple it to the front of the heart rate record.

Insert the test into the cohort folder under the label "VO<sub>2</sub>max"

Sort alphabetically by subject's last name and then by chronology.

An example of the VO<sub>2</sub>max summary data printout is given in section 7.1.13., Appendix 14.

Each VO<sub>2</sub>max test in the senior study was evaluated by standard criteria. A true maximum was achieved when two of the three criteria were met.

1. A plateau in oxygen consumption was observed despite further increases in workload
2. Respiratory exchange ratio (VCO<sub>2</sub> expired / VO<sub>2</sub> consumed) was greater than 1.1.
3. Maximal heart rate was greater than 85% of age-estimated maximum:  $208 - 0.7 (\text{Age})$ .

#### *7.1.8.5. Magnetic resonance imaging*

Body composition was assessed in the Senior Study by whole body magnetic resonance imaging (MRI). Whole body MRI is considered by many to be a gold standard technique for determining whole body muscle and total and regional fat deposition. Through Dr. Ross's connections with the Queen's University medical school and with Kingston General Hospital

(KGH), we had access to a 1.5 Tesla magnet for testing of seniors before and after their 6-month interventions.

The project coordinator made appointments for whole body testing with the MRI technicians at KGH. These appointments were made outside of the normal hours of medical use on the magnet, and were usually on Saturday mornings. A graduate student met the seniors at the main entrance of KGH and escorted them to the imaging department. The seniors changed into hospital gowns to eliminate clothing-related artifact in the images. In a process that took 30-40 minutes, the technician performed at least 11 scans (including scouts) to acquire 45-47 cross-sectional images of each participant. The whole body acquisition protocol and scan specifications are detailed in section 7.1.13., Appendix 15.

The acquired images were burned to compact disk and taken back to an image analysis computer at Queen's University. For each set of scans, I examined the images, identified the 45-47 images to be used for analysis, arranged them sequentially from inferior (foot images) to superior (finger images), and adapted a program (or script) for the computer to retrieve the images in sequence for tissue analysis. An example of the script file can be found, in part, in section 7.1.13., Appendix 16. Using the table coordinates obtained during scan acquisition, I calculated the spacing between the femoral head image and the adjacent superior image, and the spacing between the humeral head image and the adjacent inferior image: the only gaps in our whole-body protocol that are usually not 4 cm. The spacing between the 45-47 images is used for interpolating total tissue volume from the tissue areas observed on each 1 cm-thick image. The worksheet used to arrange the images and to calculate the two variable gap distances is in 7.1.13., Appendix 17. Procedures for calculating gap distances in abnormal situations (how to deal with overlapping images, etc.) are given in 7.1.13., Appendix 18.

Determination of tissue area (muscle, fat, organ, etc.) on each image was accomplished using specially-designed image analysis software called Slice-O-Matic, a product of Tomovision (Montreal, Canada). A technician viewed the cross-sectional image and identified muscle, fat, and other lean tissues shown in the image, tracing the gray-level image and tagging the visible tissue area with specific colors. A completely analyzed mid-thigh image, for example, would have

tag colors identifying lower extremity bone, muscle, lean tissue (large veins, nerves, etc.), intramuscular fat, and subcutaneous fat, and the voxel area of the tag labeling each tissue could be quantified, indicating the volume of tissue found in that cross-section of the body that was 1 cm thick. If the images were contiguous, simply adding the voxels of a specific tissue tag throughout the body would yield whole body tissue volume. However, since the images were not contiguous, but rather placed 5 cm apart, the 4 cm of body tissue between images was interpolated mathematically using data from adjacent images. See section 7.1.13., Appendix 19 for a visual representation of inter-image interpolation and formulas used for the volume calculations.

Using voxel summary data from the 45-47 images on each whole body scan, I used Excel spreadsheets to run interpolation formulas and calculate whole body tissue volumes. Because each tissue varies in density, I employed tissue-specific conversions to express volumes as masses (in kilograms). For example, skeletal muscle and adipose tissue volumes were converted to masses by multiplying them by 1.04 and 0.92, respectively.

#### *7.1.8.6. Magnetic resonance spectroscopy*

Magnetic resonance spectroscopy (MRS) can be used to quantify the adipose tissue deposition within skeletal muscle. Because intramuscular triglyceride levels appear to affect metabolic function and play a role in insulin resistance, we intended to perform an MRS assessment of intramuscular triglyceride in anterior tibialis muscles of the seniors before and after the 6 month intervention. Encountering some technical difficulty, we only collected MRS data on approximately half of our sample.

The MRS test required a 40-minute extension of the time spent in the imaging unit on the day of the MRI. The test required essentially the same conditions, but was a different application of the magnet, and only a specially-trained technician could perform the procedure. Since the results of the MRS acquisition will not be discussed in this dissertation, the procedures of this test will not be provided in detail.

#### 7.1.8.7. Computed tomography

Computed tomography (CT) images of liver and thigh were used in the senior study to assess the quality of hepatic and skeletal muscle tissue, respectively. The travel of x-ray particles emitted by a CT scanner is attenuated as the particles pass through more dense bodily tissues; because liver and muscle tissue are more dense than fat, they have comparatively higher attenuation values. Under conditions of high visceral adiposity or insulin resistance, both liver and muscle tissue are often infiltrated with lipid and decrease in attenuation value. Although CT cannot directly quantify lipid content of lean tissue, it measures the extent of lipid infiltration and provides an *in vivo* and non-invasive assessment of metabolic risk.

The Senior Study used CT images at mid-thigh and chest (at the T12-L1 intervertebral space) for analysis of muscle and liver tissue quality, respectively. The measured variables at mid-thigh were the following:

1. Adipose tissue area (total, deep, and subcutaneous)
2. Low attenuation skeletal muscle area
3. Normal attenuation skeletal muscle area
4. Mean attenuation of skeletal muscle

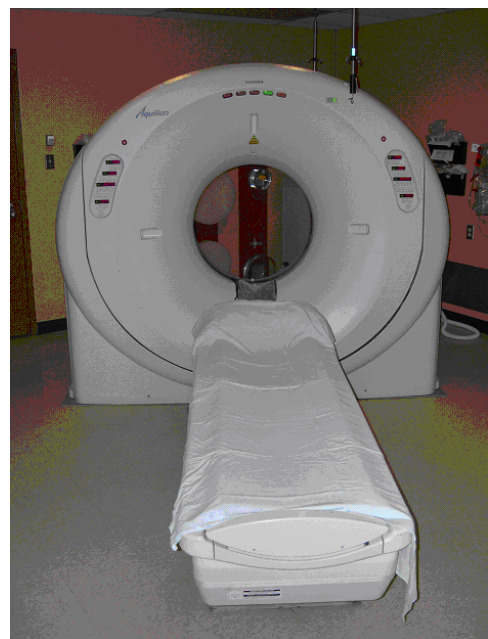
These variables were measured in the liver:

1. Mean liver attenuation
2. Mean spleen attenuation
3. Liver-to-spleen ratio

#### Measurement Device

Aquilion TSX-101A Whole-Body X-Ray CT Scanner from Toshiba Medical Systems (New York, NY), located at Hotel Dieu Hospital, Kingston, Ontario.

CT scanner at HDH  
Kinsman CT Suite



## Measurement Procedures

### *Preparing the participant*

1. The participant was met by a graduate student 10 minutes prior to the appointment in the main lobby of the Hotel Dieu Hospital and then escorted to the Kinsman CT Suite, level 0.
2. The graduate student provided the participant with appropriately-sized Queen's athletic shorts to change into in the washroom located in the CT Suite.
3. The participant was asked to remove all metal or other artifact-inducing materials.

Graduate student measures  
mid-thigh mark



4. The graduate student marked an "x" on the participant's skin at the midpoint of the right thigh. This was performed by having the participant stand with full body weight on the left leg, relaxing the right leg so that both hip and knee joints are in slight flexion. The graduate student then used a plastic tape measure to assess thigh length anteriorly from the inguinal crease to the base of the patella. When midpoint was determined, a clear mark was drawn on the skin of the participant's anterior mid thigh.

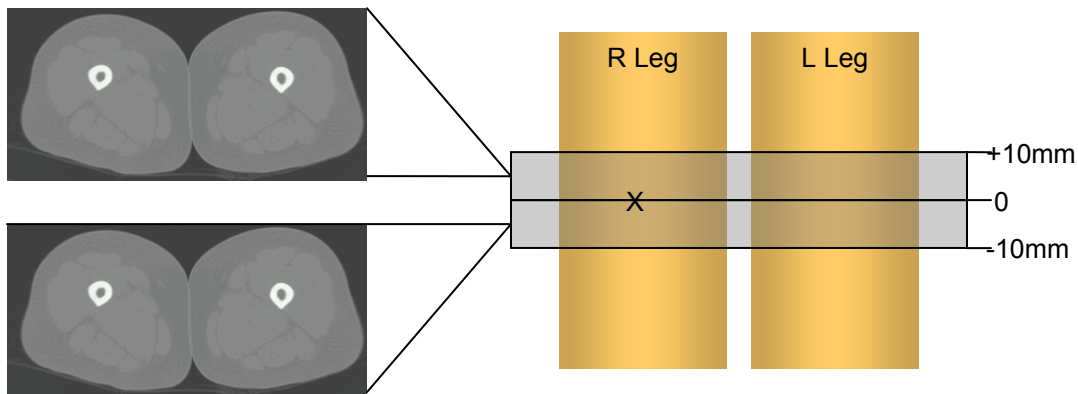
### *Preparing the Aquilion computer*

The graduate student provided the radiology technologist with a CT requisition form which had been completed by the project coordinator and signed by the study physician (see section 7.1.13., Appendix 20). The technologist entered the subject's Pre test ID number where it asked for ID and the Pre test ID number preceded by "ZZ" where it asked for name. Beside "Attending Physician" the technologist typed in ROSSPROTOCOL. With this information, the computer automatically performed thigh and abdominal scans under the following technique:

1. Thigh – 120 kV, 250 mA, LL, 480 FOV
2. Abdominal scout – 100 kV, 250 mA, approximately 320 mm
3. Liver – 120 kV, 250 mA, LL, 480 FOV

*Performing the scan: Thigh*

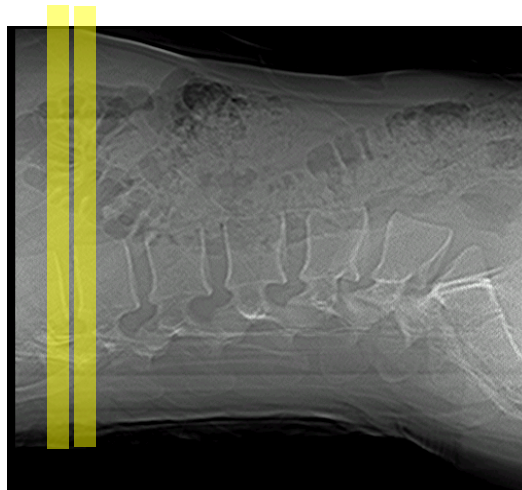
The technologist instructed the participant to lie supine on the examination table with feet pointed into the barrel of the CT scanner and the right mid-thigh mark exposed. The technologist adjusted the table until the laser guide superimposed the mid-thigh mark. Two 10mm-thick images were obtained, centered 5mm to either side of the mark, as shown on the following diagram:



*Performing the scan: Liver*

The participant was instructed to follow the recorded message to “breathe in and hold your breath” at the appropriate times. During this timed breath hold, a “scout” scan of the participant’s lumbar vertebrae was performed for the purpose of land-marking the T12-L1 intervertebral space. This scout was performed at 100 kV, 10 mA, and has an approximate length of 320 mm. The technologist located the L5 vertebra and counted up to the T12-L1 intervertebral space. The image acquisition box was positioned at the center of this space to obtain two 10mm-thick cross-sectional images at the T12-L1 intervertebral space. The scan was then performed during another breath hold.

Locating the T12-L1  
intervertebral space  
using a scout image



Like in most radiological procedures, there is some health hazard associated with CT. However, the total exposure of this entire procedure was below 1.5 mSv, which is well below the 5 mSv/year considered the upper “safe” limit.

#### *Data transfer*

All images acquired were immediately sent to the Galileo imaging database at the Hotel Dieu Hospital. The Galileo system has a pre-programmed link to an FTP site on the firewall of the Ross Laboratory at Queen’s University. Within 24 hours, I retrieved all scans and copied them into a designated folder behind the Ross Laboratory firewall. Images were transferred in a condensed format. I unzipped each file, saved a copy of the raw (condensed) CT images, and stored the viewable images on a folder labeled by the scan ID number. I visually inspected each image on the Slice-O-Matic software to ensure quality of acquisition, number of scans obtained, and proper image labeling.

#### *Data backup*

Raw (unanalyzed) images were burned onto compact disks and stored in the CT section of the black binder labeled “Senior Images.” A secondary backup was created at the same time and stored at my off-campus apartment. Scans were analyzed as described in the Data Analysis section of this protocol, and new tag files were created. Analyzed material was stored on the

local hard drive of the analysis computer, which was backed up daily by an automated system onto another hard drive stored in a different room and locked under a different key – available only to the principle investigator and our computer maintenance technician. When at least 50 new scans have been analyzed, 2 copies of the raw images and associated tag files were burned onto separate DVDs: one of them was for me to hold onto, and the other was an archival copy, stored separately. When the study was complete, the images were removed from the local analysis computer to free it up for future projects, and there still remained *at least 2 copies* of the complete data.

Database files containing the image analysis results were transferred to an Excel spreadsheet for compilation of all the data, and were subsequently transferred into the Senior Study Database in Access format. All data were consistently backed up by the automated system and archived every other week on DVDs as per the database protocol.

### *Data Analysis*

#### Mid-thigh images

While in Slice-O-Matic, all images from one subject's pre or post data acquisition were opened (identified by test ID number): File → File open → Shortcut to Senior CT → ID number. Since the Senior Study subjects have 4 contiguous 10mm images, and we only analyzed two of them, the middle two images were chosen by pressing F12 and examining the Z axis numbers of the individual images. Images are segmented using standard threshold values:

Adipose tissue: -200 to 0 HU

Low density muscle: 1 to 30 HU

High density muscle: 31 to 150 HU

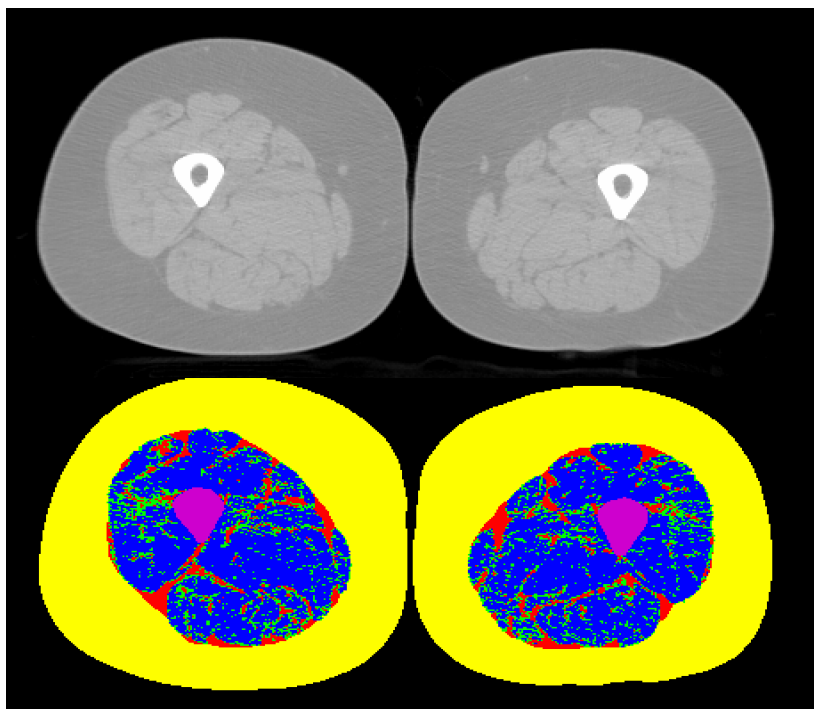
Bone: >150 HU

Raw segmentation is then touched up by the analyzer according to this protocol:

1. Edit the low density areas out of the femoral bone (label as bone) and the high density areas tagged as bone within the muscle (label as high density muscle).

2. Edit the high density areas (skin) out of the subcutaneous AT.
3. Change the tag for subcutaneous AT to differentiate it from the sub-fascial (intermuscular) AT.
4. See raw and analyzed thigh images that follow:

Example of mid-thigh image analysis:



### Liver Images

Of the liver images acquired (early in the study there were sometimes 4-8 images instead of just two), the one in which the spleen has the greatest volume is chosen for analysis. I attempted to match the appearance of pre and post images on each subject as well to ensure imaging of the same liver/spleen regions.

### Revising assessment of liver fat

In all of our previous studies, liver and spleen had been analyzed using sample “regions of interest” from the CT image, attempting to find representative areas of the liver or spleen from

which we could gather attenuation data. The regions of interest were often placed near the outer edge of the liver (perhaps so that they would correlate better with liver biopsy data) and the analyzer needed to be wary that the region of interest did not contain any areas of inhomogeneity, like vessels or fatty deposits. When I began analyzing the senior livers in this way, I noticed that my subjective placement of these regions of interest had a great impact on the attenuation outcomes. I attempted to develop a less subjective approach to my analysis, and arrived at a few questions that I felt needed to be answered.

1. What region of the liver or spleen best represents the whole organ?
2. Is that region relatively consistent throughout all subjects?
3. Does choosing a different vertical positioning of the scan also affect attenuation?

After tossing around a few ideas, Dr. Ross, Jennifer Kuk and I decided to perform an analysis of the Cooper CT scans, to which we had access in our laboratory, to answer some of those questions. Our work resulted in a published manuscript in the Journal of Applied Physiology (see section 7.2.0), providing evidence to support a few adjustments to the methodological approach to proper acquisition and analysis of CT liver data. Our work helped us to recommend a bony landmark (the T12-L1 intervertebral space) to target when acquiring images of the liver, minimizing radiation exposure while also increasing the likelihood of imaging the spleen simultaneously. We also found that while there are some regions of the liver which are inhomogeneous from the rest across a population, these regions do not differ widely from the whole. Thus, the most reliable, repeatable, and objective measure of liver attenuation was to sample the entire liver visible within an image instead of sampling specific regions of interest.

Following the protocol recommended in our methodology paper, we began obtaining liver images at the level of T12-L1. I used the entire visible liver and spleen for attenuation values on that image instead of choosing regions of interest. Here are a few tips for performing the analyses:

1. When tracing the liver and spleen on the images, avoid tagging clear to the edge. Leave a few millimeters of liver near the borders, since the borders often have uncharacteristically low attenuation values.
2. Avoid including major vessels as part of the liver.
3. If possible, have only one person do the analyses on pre and post images to avoid incorporating inter-analyzer error into change scores.

#### *7.1.8.8. Hyperinsulinemic Euglycemic Clamp*

The hyperinsulinemic euglycemic clamp (or “the clamp” as we like to call it) is the gold standard for quantifying insulin resistance. It measures the amount of glucose necessary to maintain normal glucose levels while compensating for a known infusion of insulin, and indicates the subject’s level of peripheral insulin resistance. In order to obtain reliable results in this test, the following things must be accounted for and controlled in each participant:

1. Acute physical activity – any exercise performed within 24-48 hours of the clamp may increase insulin sensitivity. We asked the participants to not engage in any exercise for 3-4 days prior to the initial clamp, and we scheduled the last exercise intervention session between 24-36 hours of the post clamp. The last 24 hours before the clamp was a rest day; they were not to do exercise of any kind. We also had them arrive at the Hotel Dieu Hospital as rested and relaxed as possible: we paid their cab fare when needed so they wouldn’t be driving, and asked them to not shower or brush their teeth. We encouraged them to just “roll out of bed” and get in the cab.
2. Nutritional state – depleted muscle glycogen stores increase insulin sensitivity. The participants fasted for 12 hours prior to the clamp, but to ensure complete restoration of muscle glycogen prior to the fast, we devised a meal plan for them to follow the night before with plenty of carbohydrate to “top them up.” The meal they recorded for the pre clamp was re-issued (we provided them with a photocopy of their dietary record) and they were asked to follow the same dietary pattern for the post clamp.

3. Anxiety and muscle activity – Immediately before and during the clamp, it is essential to minimize muscle contraction, which provides an alternative route for glucose disposal from blood than insulin mediated glucose disposal. When participants are nervous or fidgety during the test, glucose disposal is falsely elevated. I did anything I could to calm the nerves of the seniors before the clamp. I phoned each one the night before the clamp to reassure them that I would be there in the morning, offered a wake-up call, met each one personally at the entrance to the hospital, and remained with them through the “needles” and the beginning of the clamp. Although I was usually processing blood samples or doing other testing during the duration of the clamp, I checked in with the participants regularly to answer questions and keep them at ease.

Many tests are performed on the morning of the clamp, and I needed to be prepared ahead of time and ensure proper operation of equipment for it to run smoothly. Before testing began for the Senior Study, I made a checklist of things to prepare the night before each clamp to have with me in the morning:

1. The key to the Hotel Dieu Laboratory – we only had one key available to the students for the metabolic unit, and forgetting it meant alerting the hospital night security to come and open our door since we were there in the morning before regular hospital operating hours.
2. Hotel Dieu ID badge – the Hotel Dieu closes at 8:00 p.m. and doesn’t re-open until 6:00 a.m. My ID badge opened the electronic locks on the main entrance and was essential to getting the participant into the hospital at 5:15 a.m.
3. Anthropometrics data sheet – we needed the height measurement (same pre value as post) taken in the lab to calculate body surface area for determining the appropriate amount of insulin to infuse.
4. Clamp binder with phone numbers – in case the participant, nurse, or physician fails to arrive, contact numbers were needed for wake-up calls or cancellation notices.

5. Queen's University athletic shirt and shorts the right size – for the weigh-in and for ease in performing the other tests, I had to have a clean set of appropriately-sized “grays” with me.
6. Money for lunch – for more than half of the study, I had to buy the participant's lunch after the clamp. They needed to consume a solid meal and have blood glucose levels elevated before being discharged from the unit. In the last two years of testing, the café downstairs allowed me to run an account with them, which alleviated the need to have cash on hand for the clamps.

The following is the timeline I followed on the morning of the clamp:

- 5:05 Arrive at the Brock Street entrance of the Hotel Dieu Hospital
- 5:15 Meet the participant and escort to the clamp room
- 5:20 Instruct participant to change into shirt and shorts in the clamp room and meet back in the hall. Meanwhile, prepare the standing multi-frequency bio-impedance computer; enter essential data.
- 5:30 Perform bio-impedance (bioelectrical impedance) measures.
- 5:35 Instruct participant to return to clamp room, get into bed, and try to relax or sleep. Ensure the senior has sufficient blankets to maintain comfortable temperature. Retrieve more if necessary. In an adjacent room, prepare all of the clamp documentation, including the body surface area calculation using formulas and the weight from the bio-impedance scale. Print separate copies of the clamp data sheet (section 7.1.13., Appendix 21) for the physician and for the nurse. Pull a desk into the hall for the physician and place the data sheets on it. Arrange a writing table outside the clamp room for the nurse, and on it place the other copy of the datasheet; fill out the blood gases and lipid profile requisition forms (section 7.1.13., Appendix 22) and set them also on the nurses table.
- 5:55 Enter the clamp room and begin quietly calibrating and preparing the Deltatrac (used for obtaining basal metabolic rate (BMR) and clamp calorimetry) machine.

- 6:05 Take blood pressure manually and/or set up the BPtru blood pressure machine and take resting blood pressure. Record the mean measurements on the back of the Anthropometrics datasheet, which is the clamp morning data collection sheet (section 7.1.13., Appendix 11).
- 6:15 Plug in 2-4 heating pads to begin warming the participant's arms to bring out the veins for the nurses. Install the hood over the participant and begin measuring breathing gases for 30 minutes. Remain in the room, but quiet to ensure that the Deltatrac is working properly and that the participant does not fall asleep during the measurement. Set up the supine multi-frequency machine (Tanita prototype) and measure bio-impedance on the hand and foot. Record the readings from the screen by hand onto the datasheet.
- 6:45 Remove the hood, stop the Deltatrac, keep the printout, and do a backup of the electronic copy of the BMR reading. Introduce the participant to the nurse and aid her as she sets up equipment and finds the two veins for intravenous sites.
- 7:00 Retrieve the insulin from the refrigerator and place it on the physician's desk along with a needle and saline bag.
- 7:15 Turn on the temperature-controlled centrifuge and set it for a single cycle. If there is a Roche sample to be processed (see section 7.1.8.13.), prepare the tubes.
- 7:30 Clamp test begins. Make sure that the participant is comfortable, and set up a selected movie or set the radio station to meet the participant's preferences (the participant must be awake, yet relaxed throughout a three-hour test wherein he/she must be supine. Non-stimulating distractions are extremely helpful.) Begin spinning Roche samples, if necessary.
- 9:45 Recalibrate the Deltatrac. Prepare for 30 minute clamp calorimetry when the physician is certain that the participant is "clamped" and will continue to be so for the next 30 minutes. Without eliciting any movement or excessive talking, obtain a lunch request from the participant. Essentials of this meal include a large fruit juice, a piece of fruit, and a healthy, substantial main course (soup and sandwich). Install the hood and begin testing gases at the physician's request – around 10:00.

- 10:30 Have lunch ready to be served by the end of the clamp – never earlier than 10:30, and often later if participant wasn't "clamped" by 10:00. Remove the hood, congratulate the participant on successful completion of the test, and serve lunch.
- 10:50 The participant is not allowed to leave until at least 30 minutes after lunch is completed and blood glucose readings indicate normal for post-prandial state. While waiting, administer the SF-36 questionnaire (section 7.1.13., Appendix 23) to the participant.
- 11:30 Escort the participant to the main entrance. Re-affirm upcoming appointments for testing or for exercise session appointments if the clamp was the final test.

#### *7.1.8.9. Bioelectrical Impedance*

In keeping with our purpose as a body composition laboratory, we perform many different methods of assessing body fat and muscle. Bioelectrical impedance is a method that became commercially available in the mid 1980's, and some of Dr. Ross's own research as a student and early career was related to this measurement method. Because of his interest in bioelectrical impedance, and because of our ability to compare other methods with the "gold standard" of whole body multi-slice MRI, we routinely assess study participants with various types of bioelectrical impedance machines – some of them prototypes.

Bioelectrical impedance is a method of measuring body fat using current electrodes for applying a constant current through a human body and voltage electrodes for detecting a voltage drop caused by bioelectrical impedance of the human body. Some of these electrodes took the form of "foot to foot" pads which the subjects stood on, often while obtaining a standard weight measurement before the clamp. Other machines had "hand to hand" and "foot to foot" capabilities that extended measurements also to "hand to foot" measurements, most were performed in standing position, but another was supine with stick-on electrodes.

When the senior study began, each participant was tested by no fewer than four bioelectrical impedance machines. When we obtained two more machines from Tanita Corporation (Japan) and another stopped functioning, we reassessed the situation and phased out a couple of machines that were obtaining parallel measurements. Through all of this,

however, we have a wealth of bioelectrical impedance data on the senior participants that could be used for an interesting side project comparing bioelectrical impedance to other standards of body composition assessment.

The impedance measurements were obtained using the following protocol:

While the subject is changing into greys at the clamp:

Pull the scales out from underneath the desk.

Check each one to be sure it works. (Turn both on, press start)

Check with the subjects to see whether they have had anything to eat or drink.

Have participant take socks off and stand on Tanita machine with Japanese writing on it (this was a whole body assessment prototype). Subject holds the “guns” in the proper hands (L and R), arms straight out, no moving.

Press display; write results next to the corresponding number on the back of the Anthropometrics Data Collection Form (section 7.1.13., Appendix 11).

Turn on Tanita machine with English writing on it. Select Adult.

Type in height from Standing Height entry on Anthropometric Data Collection Form (Anthros sheet)

Wait for the “Stand On” arrow to flash.

Record the weight (kg) into the “Clamp Weight” space on the Anthros sheet

Staple the TBF-305 analyzer receipt onto the Anthros sheet as well.

Unplug and carry the multi-frequency equipment to the bedside chair.

Plug it in. Turn on the laptop.

Have the subject lie down on the bed with hands not touching the sides of his/her body

Cut the electrode pads in half. You'll need 8 per subject.

Put the pads on the dorsal surface of the feet and hands:

Feet – joint space of the ankle and a finger-width from the base of the toes

Hands – joint space of the wrist and a finger-width from the base of the fingers

Put the rest of the electrodes away and fold the flap over on the package so they don't dry out.

Click on the shortcut to multi-frequency

File, Open

Type last name, Enter

Attach the clips to the little black box (1 pair of leads to a terminal).

Test; see "z standard check" and make sure that numbers appear. If not, readjust and try again.

Type in "Arm-arm" and attach clips:

Red = proximal

Black = distal; "blood towards the heart, dirt at the fingertips"

Press Start

When numbers appear, press PrtSc (Print screen) on the laptop.

Go to Paint on the desktop.

Ctrl V to paste, select Yes.

Minimize Paint screen.

Repeat for "whole body" and "leg-leg."

Remove electrode pads and discard.

Record data onto the multi-frequency data sheet from each minimized Paint window.

Close each window without saving.

Similar instructions were followed for the newer machines, with some simplification of data management. For instance, the new standing multi-frequency machine required no hand-entering of impedance values; rather, data was stored in Excel spreadsheets. I helped Bill Pierce write a program that would convert the data from spreadsheets into a single database at the end of the study, which I then transferred into the Senior Study data, indexed by subject number.

#### *7.1.8.10. Basal Metabolic Rate and Clamp Calorimetry*

For nearly half of the data collection in the Senior Study, the machine that measures metabolic rate and clamp calorimetry was not operational, and I came to know the operator and

technician manuals for it quite well. In memory of those numerous hours of frustration, here are the instructions for operating the Deltatrac machine when it was measuring expired gases correctly:

Shortly after bio-impedance data have been collected, the subject should be lying in bed and preparing for BMR readings with the hood. Be sure that the subject has been lying undisturbed for at least 20 minutes.

Be sure that the Deltatrac is plugged in.

Check the gauge on the side (through the makeshift hole that Ken cut); be sure pressure is up.

Press the Cal button.

Choose 1 Gas.

Press Patient Data

You will need to provide: gender, DOB, height (cm), weight (kg)

Press 4 Save; "data accepted"

Press 4 again for Normal Screen

Pull out the hood (or canopy)

Instruct the subject to not talk but relax for 30 minutes. No sleeping!

Tuck the plastic in around pillow

Press Start

Ensure that the printer is generating a minute-by-minute hard copy

Monitor the progress, ensuring that the RER is within acceptable physiological levels

... Press Stop, End.

Turn on computer, attach cord to laptop (you'll likely have to press Stop, End again)

Go to Deltatrac on desktop

Press any key

F9 to start

Press 2 Snd data on Deltatrac

Select Y to edit header or summary.

Type in <subject\_lastname> <pre or post> <bmr>

Enter through until Esc = Exit; hit Esc.

On the C drive, open the Deltatrac folder, then tests.

Click on the old lotus file with the highest number or date on it .prn

Adjust the name so that it is left justified in the appropriate cell.

Check that all columns are there (30 columns or so)

Save file as <subject last name, first initial>, as the latest version of Excel, and in the appropriate folder (Seniors pre / post)

Check that the saved spreadsheet is intact where you put it.

Go back to the Tests folder and delete all of the recent tests sent.

Disconnect laptop from the Deltatrac

Clear all data on the Deltatrac

Label printout as BMR (or Clamp Cal) and file in binder back at the lab.

The clamp cal is done exactly like the BMR, but only when the subject has been completely clamped (usually more than 3 hours later). Before you put the subject under hood, however, obtain a lunch order for the participant that you will buy from the deli downstairs for lunch.

#### *7.1.8.11. Blood Pressure*

When the subject has been lying down for *at least* 15 minutes on the morning of the Clamp, pull out the blood pressure cuff and take a reading. Wait for 1 minute and take another reading. Record these measurements in the space provided on the Anthropometrics Data Collection Form.

Partway through the study, we had a new automated blood pressure machine made available to us. The instructions for this “BPtru” machine are as follows:

In addition to the manual readings, hook up the automatic blood pressure machine, and allow it to take 6 readings (2 minute spacing) and record the mean blood pressure. Explain the machine to the participant; ensure that the cuff is comfortably placed around the upper left arm,

with the lower edge of the cuff proximal to the antecubital area of the arm. Remain in the room with the subject through the first measurement, and then leave the room to reduce the “white coat syndrome” effect. Record the measurements on the Data Collection form.

#### *7.1.8.12. Blood Lipids / Blood Gases*

As mentioned earlier, requisition forms (section 7.1.13., Appendix 22) were prepared for the nurse before the clamp. During the pre-clamp fasting blood draw, a sample was taken in a special tube and sent to the blood analysis lab (CORELAB) at KGH for analysis of plasma lipids. A printout of the lipid profiles were sent to the Rapid Response Lab printer at the Hotel Dieu Hospital, where the technicians saved them for me (or later, one of the Proactive staff) to come by and pick up every few days. I took these printouts back to my office for data entry and subsequent filing.

To reaffirm that the venous sample site (the hand) was sufficiently heated to increase blood flow so that venous blood more closely approximated arterial blood, a sample was taken partway through the clamp for analysis of the blood gases. The sample was put on ice immediately and a courier was called to deliver the tube to the CORELAB as quickly as possible. The CORELAB technicians phoned us (usually within a half hour) to give the results, which I recorded on the clamp data sheet. If the oxygen content was lower in the sample (below 0.90), we would adjust the heating pads, wait at least 10 minutes, and then do another sample. If the oxygen content was high, we were confident that our glucose readings on the venous samples were not artificially low due to glucose disposal occurring upstream of the sample site.

#### *7.1.8.13. Hoffman-LaRoche Blood Samples*

In an effort to secure sufficient funding to carry out the study, Dr. Ross agreed to provide pre and post blood samples from the senior study to a pharmaceutical company, Hoffman-LaRoche. Involvement in the “Roche” study was purely voluntary, and some participants opted out (usually on principle), although the sample amount was rather minimal. The project coordinator or I explained the study to the participants, and a separate consent form (section

7.1.13., Appendix 24) was signed before the morning of the oral glucose tolerance test. Pre samples were usually taken the morning of the OGTT, and post samples were usually taken on the morning of the post clamp. All of the handling of these Roche samples was done by me (with some help from Diana Hall early on in the study); the sample processing was not to interfere with the nurses properly performing the clamp or OGTT. The following are instructions for the handling and processing of the Roche samples:

Samples must be placed immediately on ice and cooled before spinning. All steps of this protocol must be carried out in order and as quickly as possible, to ensure maximum sample quality and to prevent proteolysis. If samples must sit – always keep them sitting on ice.

1. FOR PRE SAMPLE ONLY: One 6ml tube must be gently mixed by inversion and frozen as soon as possible at  $-80^{\circ}\text{C}$  in the HDH Senior Study freezer. Label with pre/post test ID # and place in a zip-lock bag.
2. Place remaining 9x6ml tubes carefully in temperature-controlled centrifuge. Balance the rotor by placing samples of equal level opposite each other. Use the “blank” (water-filled tube from the rack at the side of the centrifuge) to balance the 9<sup>th</sup> tube. Spin at 1500g for 15min @  $4^{\circ}\text{C}$ .
3. Locate a pre-stocked bag of tubes in the drawer of Lance’s desk and label all tubes with the subject’s test ID #.
4. When the cycle is completed, draw off plasma layer from each 6mL sample tube using a transfer pipet– leave approx 2mm in each to ensure no carryover of cells. Transfer to 4 x15ml polypropylene tubes. Be certain all tubes contain the same sample amount to assist in balancing. Cap tightly and place these tubes in the centrifuge - balancing the rotor – and spin at 3000g for 30min @  $4^{\circ}\text{C}$ .
5. Label 5-6 cryotubes with subject’s assigned pre/post test ID#. When centrifuge finishes its spin, carefully remove tubes from the rotor, one at a time. Gently remove each tube to not disturb the layers.

6. Transfer plasma supernatant from all 4 tubes, with a pipette, to a large (50ml) conical tube, leaving any sediment behind (leave the bottom 2/3 of each tip of the conical tubes). This is now a pooled sample from all the original tubes. Cap, mix by gentle inversion, and transfer with a pipette to labeled cryotubes. Place these tubes together in a zip-lock bag and place in freezer at -80° C.
7. Record the name of the subject and the date in the sample key in Lance's desk.
8. All spills must be diluted with chlorine bleach (Javex) and wiped up immediately.

Twice during the study, I packaged and shipped the Roche samples to the headquarters in New Jersey. Funding from these samples made possible the purchase of a new -80° C freezer to replace our old one and helped immensely in providing wages for essential study personnel.

#### 7.1.9. Exercise Interventions

Participants randomized into any of the three exercise arms of the study underwent training specific to their given intervention. For all but a few of the participants, I delivered initial orientation of the equipment, gave them instructions on safety, and explained what was expected of them as exercisers in our laboratory. I did this introductory session personally to ensure that all were given uniform instruction. I also trained all exercise monitors to ensure that the guidelines were uniformly followed and enforced. My rationale in taking a personal role in this aspect of the study was not that I have superior knowledge of exercise implementation and form (on the contrary, the monitors that we employed were as capable or more so in that regard), but that if all participants were exposed to the same instruction and guidelines throughout duration of the study, the interventions would be as uniform as possible. Sections 7.1.9.1 and 7.1.9.2 describe the points of training provided the seniors as they began their specific exercise sessions.

Regardless of the exercise group, all senior participants were encouraged to wear appropriate clothing. Queen's issue shirt, shorts, and socks were available, but not required. Since these clothes were laundered for the participants and they were provided with a drying towel each time they came, most took advantage of this service. All were required to wear

appropriate shoes. Semi-private changing rooms with lockers and showers were available as they came into the research area of the Physical Education Centre, and we provided locks and keys for them to secure their belongings.

The seniors were given extraordinary latitude in making appointments for exercise sessions. For the first half of the study, we offered to monitor their exercise at their convenience any time from 7 a.m. to 7 p.m., 7 days a week. We found that the seniors tended to like to exercise in groups and do most of their sessions in the mornings, which cut down our monitoring costs significantly. Toward the end of the study, we encouraged incoming seniors to continue the tradition of exercising in small groups, which they adhered to gladly.

#### *7.1.9.1. Aerobic Exercise*

For each aerobic exercise session, we obtained a starting heart rate and then obtained a steady state exercise heart rate every 5 minutes thereafter. Participants were instructed to go to the anthropometrics room each time, where they would find a Polar heart rate monitor. These monitors consisted of a T31 transmitter, which was strapped to their chests, and an A1 wrist receiver, which they strapped to their wrists like a watch. After telling the exercise monitor the starting heart rate, participants would step onto one of three treadmills and begin 5 minutes of walking warm up. The five minute walking warm up was designed to elevate heart rate from a non-exercise rate to nearly the exercise range. Target exercise heart rate ranges were specific to each participant, calculated from the most recent  $VO_2$ max test, and written on the weekly exercise session record. Participants were encouraged to choose a speed and grade after the 5 minute warm up that would elevate their heart rates into the exercise range. Once within the range, participants could maintain or adjust walking/jogging speed and treadmill grade as desired every five minutes after telling the monitor the “steady state” heart rate for that exercise interval. All exercise heart rates and treadmill speed and grade associated with those heart rates were recorded by the exercise monitor onto the weekly exercise session record (section 7.1.13., Appendix 25).

As one might expect, there was some variance in perceived difficulty of the moderate exercise. Some exercisers needed more prodding than others to “pick up the pace” to elevate their heart rates sufficiently. Others needed to be reminded to not get too intense as their competitive natures drove them on to “improve” the calories burned each day or move on to a greater treadmill speed or grade. Most, however, required little coaching and gentle reminders were sufficient to have them continue to increase work rate gradually as their cardiorespiratory fitness improved. Despite the seemingly variable response, nearly all treadmill exercisers were able to maintain an exercise intensity that was high-moderate during the 30-minute treadmill sessions.

A five minute walking cool down at the end of each session was also performed, designed to return the exercise heart rate back to near-starting levels. Participants were encouraged, but not required to stretch upon completion of exercise. Participants washed and rinsed the transmitter and chest straps at the sink in the anthropometrics room and hung them out to dry in preparation for the next group of seniors.

#### *7.1.9.2. Resistance Exercise*

A five minute warm up consisting of treadmill walking or stationary cycling began each resistance exercise session. Participants were then accompanied by an exercise monitor down the stairs to the Queen’s exercise facilities to perform nine resistance exercises, mostly on Nautilus machines. The following are a list of exercises and the “proper techniques” encouraged for each one:

1. Chest Press – The initial fitting of the machine consisted of adjusting the seat height to allow for full arm extension. Seat height was recorded on the resistance exercise session record (section 7.1.13., Appendix 25) and maintained at that height throughout the intervention. Participants were taught to keep head, back, and shoulders against the seat, relax all unrelated muscles, and breathe out slowly during arm extension. Breathing in occurred during eccentric motion, as the hands returned to nearly chest level. Repetitions continued until volitional fatigue. Resistance weight was increased after 15

repetitions were performed with good form. A few of the subjects did not fit the Nautilus Chest Press machine, and performed a bench press on a nearby Universal machine.

2. Leg Extension – Initial fitting consisted of determining whether a spacer was needed to move the knee closer to the axis of rotation of the leg extension machine. Use of a spacer was recorded on the data sheet and maintained throughout the intervention. Participants were taught to maintain proper posture, breathing, and repetition rate as they had learned previously. Some seniors with kyphotic spinal columns had difficulty resting their heads against the straight seat back. A “neutral” head position was allowed as long as movement (especially neck flexing) did not occur concurrent to repetition motion, and a few seniors brought a rolled towel to support their necks in this position during exercise. Some seniors experienced knee pain with open circuit leg extension, and substituted leg extensions for leg press on a nearby Universal machine.
3. Shoulder Raise – Initial fitting consisted of adjusting the seat height so that the axis of rotation of the machine arms aligned with the shoulder axes. Seat height was recorded and maintained throughout the intervention. Participants were taught to keep the entire back and head against the seat back or in a neutral position while raising the elbows to shoulder height. Technique on this machine was difficult for some, and special attention was drawn toward only using elbows, not wrists or hand grips, to accomplish the exercise. Performing the proper breathing seemed counter-intuitive for most, and had to be coached well into the intervention. A few women were unable to perform this exercise with no weight added, and were taught to use 1 or 2lb dumbbells while performing a lateral arm raise until they could progress to the machine.
4. Leg Flexion – No fitting was required on this machine. While lying prone on the bench, participants were taught to curl their heels against the resistance of the machine for as great a range of motion as possible. Participants learned to keep hips pressed into the bench to avoid any lower back extension, to breathe properly, and to watch the weight rack for feedback on their range of motion.

5. Superpullover/Lat pulldown – Initial fitting on the superpullover machine entailed setting the seat height so that the axis of rotation of the arm bar was aligned with the shoulder joint. Seat height was recorded and used throughout intervention. Participants were taught to keep head and back straight against the seat and to not allow back or neck flexion during arm motion. Repetition rate and proper breathing were reinforced. Those who were uncomfortable using this machine (usually those with smaller frames) opted for a lat pulldown from a kneeling position at a nearby Universal machine. For the lat pulldown, participants were encouraged to lean back slightly and maintain back posture while pulling the hanging bar to just below their chins, performing a motion similar to a chin-up, with elbows out.
6. Triceps Extension – Seat adjustment was made and maintained so that when the elbow rested on the machine's elbow pad, it was equal to shoulder height. Participants were instructed to position hands in a "karate chop" position so as not to bend the wrist, and extend the arm in a slow-motion "chop" while breathing out. Repetition rate, breathing, and eliminating head movement were all reinforced.
7. Arm curls – Using one of our dumbbell weights, participants stood squarely, held the weight in one hand to the side, and then curled the weight upward toward the shoulder. Participants were taught to minimize body (shoulder or back) movement, to maintain the position of the upper arm, and to breathe out slowly during the concentric contraction. When a few men exceeded 20 repetitions on each arm with our heaviest dumbbells (25lbs), they opted for a Nautilus "preacher curl" machine to increase resistance.
8. Abdominal Crunches – On floor mats, participants performed one set of abdominal crunches to fatigue, adjusting the difficulty throughout the intervention by arm or leg positioning. Instruction was given and reinforced to minimize neck flexion. Proper breathing was emphasized.
9. Pushups – Participants performed one set of pushups to fatigue, adjusting the difficulty by placing the hands on a wall, a tabletop or bench, or the floor. Emphasis was placed on flexing the core to maintain a rigid body, completing nearly 90 degrees of motion at

the elbow, and breathing properly throughout. Many of the men and some of the women progressed to floor pushups before completion of the study.

The participants were encouraged, but not required, to stretch as a method for cooling down after their resistance exercises. All weights and repetitions were documented in the resistance exercise session record (section 7.1.13., Appendix 26). The seniors were encouraged to become self-sufficient in setting the seat heights and machines according to the specifications on their data sheets, but often received help with these tasks by the exercise monitor. Wherever possible, the exercise monitor provided encouragement to the seniors to push themselves to fatigue/failure while maintaining proper form on each exercise.

Similar to the aerobic exercisers, the ability to comply to exercise guidelines (to push to fatigue in weight lifting, for example) was variable between subjects. Because volitional fatigue is a subjective endpoint that often incorporates psychological barriers, the exercise monitors often needed to provide daily support and encouragement to some, whereas others were self-motivated. Our goal was for the resistance exercisers to perform repetitions to failure, so the exercise monitors tailored their interaction with the exercisers as needed to attain the desired outcome.

#### 7.1.10 Data Management

When I began this project, I could see immediately that the sheer volume of data collected would be unwieldy and difficult to manage in multiple Excel spreadsheets, as had been done in previous trials in our laboratory. This trial also contained more than double the participants of any other trial previously conducted, and thus required a new data management strategy. Truly, a study of this magnitude should have had a dedicated data manager, ideally not the project coordinator, principal investigator, statistical analyst, or the managing graduate student, whose vested interest in the study outcomes could be a source of bias to the end results. However, since we were on a limited budget and since this was a project intended to provide graduate students (and in particular, me) with hands-on experience while attending an

educational institution, I essentially took the role of data manager. With some pointers from a few experienced database users around campus, like Celine Zakos and Bill Pierce, I began designing a Senior Study database in Microsoft Access with the intent to incorporate data from the numerous Excel spreadsheets, DEXA output, and hand-entered variables I was accumulating.

One of my first steps in database management was to create a unique subject number for each participant, as described in Randomization: section 7.1.7. My purpose in selecting a subject number instead of a name was to be able to remove proper names entirely from any data analysis: for participant confidentiality and for ease in managing the data coming in from all sources. I also needed to assign a unique number, instead of proper names or the subject number, for pre and post imaging and all other clamp or freezer samples that would be sent out of our laboratory or for which easy identification of the participant might influence analysis. We decided that two testing ID numbers would be assigned each participant: one for pre testing, and one for post. This would facilitate blinded analysis of freezer samples and MRI or CT images. Only for data entry would these numbers be associated with a name, and then only as verification that data was being entered for the appropriate subject.

With these numbering systems in place, I created data tables for the various hand-entered data and linked them by subject number to the data from Excel spreadsheets and other database forms I imported into the Access database. This allowed me to create Access queries which would call up any variable I needed from all of the linked databases for any or all participants. I also learned how to program my statistical package (SAS 9.1) to tap right into an Access query so that I wouldn't have to import data every time I wanted to investigate relationships or run statistics. I created forms in Word and WordPerfect for results packages, pulling data directly out of the Access database to present exercise-induced changes in readable format for graduated participants.

Hand-entering data is often a source of error in studies. For all hand-entered data, I created a system of routine checks that were completed before ever using the values for analytical purposes. On my desk, I had a basket for hard copies of datasheets to be entered. Using forms I created in Access, I called up the appropriate data entry form, linked to a subform

that allowed me to scroll through subject names and all associated ID numbers, forcing me to verify that the data was being entered for the proper participant. I established data parameters on some of the important entries so that I would be notified if a possibly “incorrect” value had been entered. After each form had been filled, I checked the hard copy against what I had typed to check for errors. When I had entered the data from each hard copy, it was placed in a binder specific to testing (Anthropometrics, VO<sub>2</sub>max, Functional Fitness, Questionnaires, Medical Forms, etc), which contained all of the current participants’ data. These binders were stored on a bookshelf in my office, allowing me easy access to data from participants currently in the intervention phase. When a subject was completed, I removed the data for that participant from each of the binders, and, with another person (usually one of the exercise monitors), rechecked all of the hand-entered values before filing the hard copies away in the Senior Study filing cabinet. I created the Access data entry forms in a manner that allowed me to see pre, mid and post values along the same visual line while inspecting the data -- as one another method of data checking. I re-investigated all obviously non-physiological changes I observed. After these routine checks, I created the results packages for the seniors and their physicians (see the following section), a process that occasionally brought to light abnormal values because of their presentation in a comparative format. The final check of hand-entered values was when all data had been compiled, and statistics could be run on data normality to detect any outliers.

Data compiled during imaging analysis often requires calculations and manipulations that are most easily accomplished in Microsoft Excel. I managed all of the MRI data from a single Excel workbook, which was formatted such that each pre or post MRI was indexed by test ID number. A summary spreadsheet created the final database, linking important calculated tissue totals from the appropriate pre and post tests, and was imported into Access by subject ID number. The CT data were also compiled similarly. I had graduate students check formulas and perform random checks from as many angles as possible to ensure the integrity of the imaging data.

Electronic backup was performed routinely throughout the duration of the study, and stored on a hard drive of a computer that could only be accessed by the principal investigator or

our laboratory's computer manager. I also periodically burned the data onto DVDs and kept them in a data storage binder in the Senior Study file cabinet. I stored extra copies of these backup DVDs at my residence, away from the Queen's laboratory.

#### 7.1.11 Results Packages

Upon completion of their post testing schedule, participants were told that they would be receiving a results package (sometimes called a feedback package) by mail that contained some of the important results and interpretation of personal health improvements induced by exercise as measured by the study outcomes. Because it was easier to create these packages in groups instead of one at a time, I often did a batch of them every 3-4 months instead of giving them out immediately.

Early on, I put together a form that included some of the key health-related variables from the study, some explanation about desirable ranges, and encouragement to stay active. I did not include variables that required substantial analysis or would hold up the turnaround time on the feedback packages, like MRI and CT. I instead emphasized measures with a direct health or clinical message, like waist circumference, cardiorespiratory fitness, insulin resistance, and functional fitness. I included the original DEXA output forms from KGH, made a copy for the participant's physician, and kept a copy for the participant's laboratory file. For most of the study participants, I provided a CD that contained their whole body MRI images. The study coordinator/nutritionist helped me by including some nutritional and health pamphlets, and we put together a nice congratulatory paper, printed on nice paper that could be framed, acknowledging the efforts of each participant. We prefaced this package with a letter expressing gratitude to the participant for his/her involvement in the study. An example of a results package including a letter, summary of results, DEXA form, and congratulatory paper are found in section 7.1.13., Appendix 27. The physician was sent a copy of the summary of results and DEXA forms along with a preface letter encouraging referrals to the study. Examples of the four types of letters, specific to each intervention group, are found in section 7.1.13., Appendix 28.

#### 7.1.12. Statistical Analyses

In randomized controlled trials, intervention-induced changes are compared against the changes (or lack of changes) observed in a control group. An efficacy trial investigates the effect of one intervention versus another, investigating the specific benefits achieved when a protocol or treatment is strictly adhered to. In contrast, an effectiveness trial investigates how well an intervention is adhered to when it is given as a recommendation, and the ability to comply with that recommendation is measured. The Senior Study is designed as an efficacy trial, investigating the health benefits derived from strict adherence to different exercise modalities over a six month period. Under ideal circumstances, randomly assigned groups are produced which do not differ in any baseline variable, and treatment-induced changes are then compared between groups, within which all subjects will have adhered completely to their respective protocols. Ideal circumstances happen in theory and in non-human laboratory studies; in reality, deaths in families, work-related moves, technical errors in testing procedures, and even subjects' loss of interest thwart the model efficacy study. Some researchers choose to disregard subjects who do not comply with the protocol or cannot finish, which is arguably in-keeping with an efficacy design. Increasingly, however, an "intent-to-treat" analysis is now viewed as a desirable method of dealing with missing values in these cases. Under an intent-to-treat analysis, all subjects who were initially randomized into a group are still considered, either using a "last observation carried forward" procedure, or some other means of estimating missing values, assuming those values are missing at random. The dropout rate in the Senior Study was approximately 20%; those who dropped out were not found to be characterized differently than those who completed the study, and were considered "missing at random." Thus, we chose a multiple imputations procedure that estimated the missing values randomly, based on the multivariate normal distribution of the data within each gender-specific intervention group. Analysis of variance (ANOVA) was used to determine differences between means of the treatment groups at baseline. Treatment-related changes in outcomes were adjusted for baseline values in an analysis of covariance (ANCOVA). The ANCOVA model was extended to include gender and treatment-by-gender interaction to

determine whether the effects of treatment varied by gender. Tukey post hoc tests with adjustment for multiple comparisons were performed to determine the differences between interventions. *P* values of <0.05 were considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Performing the multiple imputation procedure was a work that took nearly a year to perfect and accomplish. Dr. Miu Lam, a biostatistician at Queen's University, helped me understand and perform the procedure, and wrote code for the more difficult portions of the analysis. Section 7.1.13., Appendix 29 contains a sample of the SAS code used to perform the multiple imputations modeling on changes in body weight, with variable names of "wk1wt," "wk24wt," and "Wtc," to describe the mean body weight in kilograms obtained during the first and last weeks and the difference between those two means, respectively. Section 7.1.13., Appendix 30 contains the multiple imputations output for changes in body weight, including an example of the missing data patterning analysis in the RE women, an example of one of the 10 imputation outputs, and the summary of the 10 multiple imputations with post hoc analyses using both Bonferroni and Tukey methods to determine significance between the groups. The control, resistance only, aerobic only, and combined resistance and aerobic groups were coded as 0,1,2, and 3, respectively.

#### 7.1.13. Procedural Appendices

## Appendix 1: Newspaper Advertisements

### **Exercise Study for Senior Men & Women**

Researchers at Queen's University are looking for overweight, inactive men and women, 60-80 years old, to volunteer for an exercise study looking at the effects of aging, body fat and physical activity on risk factors for heart disease and diabetes.

If you are interested in participating or would like more information, please contact Ann-Marie Kungl at (613) 533-6000 Ext. 75118.

## **Exercise Study for Senior Men & Women**



Researchers at Queen's University are looking for Men and Women between the ages of 60-80 years old who are not exercising regularly to volunteer for an exercise study.

**Here are some comments from our participants:**



"This program offers an enjoyable environment to help me achieve physical wellbeing and healthy eating"



"It's the best way to learn about these nutrition and exercise... to make your senior life healthier"



"I am most grateful to wonderful people for the opportunity to improve my fitness and health"

**If you are interested in participating please call Shelley Atkinson at 533-6000 Ext. 75118**

# Exercise Study for Senior Men & Women



Researchers at Queen's University are looking for Men and Women between the ages of 60-80 years old who are not exercising regularly, to volunteer for an exercise study.

**Here are some comments from our participants:**



"The participants benefit...  
Exercise research benefits...  
The staff is very encouraging.  
What more could you want?"



"As an arthritis sufferer I feel  
so much better after joining  
the program. My quality of  
life has greatly improved."



"The one-on-one supervision  
has helped to keep me  
motivated. I feel great!"



"The pleasant and encouraging  
environment has helped me to stay  
committed to my exercise program."

**If you are interested in participating please call Shelley Atkinson at 533-6000 Ext. 75118  
Call now; limited space available.**

# Exercise Study for Senior Men & Women



Researchers at Queen's University are looking for Men and Women between the ages of 60-80 years old who are not exercising regularly to volunteer for an exercise study.

**Here are some comments from our participants:**



"The participants benefit...  
Exercise research benefits...  
The staff is very encouraging.  
What more could you want?"



"The pleasant and  
encouraging atmosphere  
has helped me to stay  
committed to my  
exercise program."



"I love the atmosphere...  
What a great way to get  
in shape!"



"As an arthritis sufferer I feel  
so much better after joining  
the program. My quality of life  
has greatly improved."



"This program has  
helped me to improve  
my diet, health, and  
fitness. I recommend it!"



"I couldn't ask for a  
better program to keep  
me motivated."



"The one-on-one supervision  
has helped to keep me  
motivated. I feel great!"



"The staff is very helpful  
and encouraging."

**If you are interested in participating, please call Amanda McDougall at 533-6000 ext 75118.  
Last chance! Call now.**

## Appendix 2: Promotional Articles Written by Senior Participants

## GO FOR IT

I saw an ad in the Whig-Standard last spring: "Exercise Study for Senior Men & Women." Researchers at Queens University were looking for overweight, inactive men and women between the ages of 60-80 as volunteers. The purpose of the study was to look at the effects of aging, body fat and physical activity on risk factors for heart disease and diabetes.

At that time, I was just turning 60 and I fit the criteria. I gave them a call, then met with the researchers at the School of Physical and Health Education at Queen's University. They were very friendly and gave me extensive information about the study.

At the beginning and end of the program, all participants go through very important tests at Kingston General and Hotel Dieu hospitals. These 'before' and 'after' tests give researchers and you incredibly valuable information about your body and health.

During the study you are always under the supervision of nutritionists, doctors and grad students. You meet many fellow volunteers and the environment is really fun.

I completed my program last January. Those seven months were one of the best investments I have ever made for my health. Also, knowing that you are contributing to a very important study is a great feeling.

I strongly encourage everyone to volunteer for this study. Call Ann-Marie Kungl at (613) 533 6000, ext.75118 today. You will thank me later...

Bora HINCER

Published in *Kingston This Week*, 2003

I have recently completed my participation in an exercise study at Queen's designed especially for those of us who are over 60 and perhaps somewhat overweight, and I'd like to tell you about my experiences during the six months that I was enjoying the program. Yes, enjoying ... after my initial discoveries of how far and fast I could walk and how strong I wasn't, I was very pleasantly surprised at how quickly my strength, my endurance, and my general energy level improved. I was constantly encouraged by all the friendly Team members to push myself a little further, and I realized that I was constantly exceeding what I had previously thought were my limits. Usually I exercised in the company of other participants, and lots of lively discussions occurred between the huffing and panting, and some good friendships were made.

No specific diets are involved during the study, and you continue to eat and drink as you would normally, though gentle suggestions for improving one or other aspects of your intake are made when necessary. Despite increasing my strength and joie de vivre, I managed to lose some weight and could pull my belt in a couple of notches by the end of the program, though weight loss is not its primary purpose. The timing of one's exercise is very flexible, to allow for the work schedule of those like myself who are still working, and to fit in with the schedules of some busy retirees.

I had a lot of fun during the study and found it extremely interesting, providing me as it did with a lot of information about the general status of my health and metabolism (my glucose metabolism had improved by a reassuring 47% by the time I completed the program, for example). I'd like to recommend this study to any of you who are interested in improving your level of fitness and strength, and perhaps losing a little weight. If you enter, I can assure you that you'll learn a lot about yourself, and that you'll feel a lot better as a result. The challenge now is to keep exercising on a regular basis!

Peter Froud, FFR, FRCPC

For more information on this Exercise Study for Seniors, call 533-6000 ext 75118.

Published online at RAQ – *Retirees Association of Queen's*, 2004

### Appendix 3: Study Poster



# Exercise Study For Seniors

**We are looking for seniors who would like to  
begin a FREE exercise program.**

- Enjoy the companionship of others while they make healthy lifestyle changes with you
- Exercise with professional supervision -- every time
- Receive guidance from professionals on how to eat healthier foods

To be eligible, you should be

**Between 60-80 years**

**Not exercising regularly**

**A non-diabetic, non-smoker**

For information, contact Dr. Ross's Lab at Queen's

**533-6000 ext. 75118**

#### Appendix 4: Promotional Article by Pat Galasso

# A Question of Good Health From Levity to Longevity

*By Pat Galasso*

**T**hose of us who attended the presentation by Dr. Bob Ross, Ph.D., Professor of Physical and Health education at Queen's, and cross-appointed in the Department of Medicine (Division of Endocrinology and Metabolism), were both entertained and educated. We are beholden to the volunteers who run the Learn and Linger program for scheduling this important presentation on Wednesday, January 21. The room was packed.

With humour and conviction, Dr. Ross portrayed a picture of our age group. The majority of us, it seems, are exercising less, or are simply less active, and are adding to our fat while losing muscle mass. He also pointed out that there has been a substantial increase in degenerative disease in our age group.

In a review of the literature on overweight and obesity, Dr. Ross cited a study of thousands of subjects in Denmark which showed that waist circumference was a strong, independent predictor of disease and death. Simply wrapping a tape measure around our waists (level with the top of our hip bones) can be much more informative than stepping onto a bathroom scale! Having a waist circumference of greater than 88 and 102 centimeters for women and men, respectively, is considered obese and can dramatically increase our chances of contracting degenerative disease and/or dying prematurely. The message to seniors is quite clear. Based on the evidence, and our position on the lean to obese scale, we would be wise to play the odds and do something now to diminish our middles.

Dr. Ross also showed cross-sections of MRI slides of the thigh of a 25-year-old and a senior. In the younger person, the muscles were a solid shade of colour indicating solid muscle, whereas with the senior, the muscles were highly marbled with fat. This means that obese people don't just carry their fat subcutaneously, but that fat is distributed throughout their bodies within the muscles and surrounding their organs.

As founding Dean of Human Kinetics at the University of Windsor, now retired, it was my role to evaluate faculty performance. I can state unequivocally that the applied nature and superb quality of Dr. Ross' work has always appealed to me. Through this he is attempting to benefit society in general.

In order to address the impact of obesity and how to deal with it, Dr. Ross has acquired major grants, along with his colleagues, and with the help of grad students, he is attempting to determine the best way to reduce waist circumference measures, and by implication to improve health and increase longevity.

To succeed, this major research project requires subjects. You could not learn more about your health indicators than to be involved in this study. Tell your friends about it, and please call 533-6000 #75118, and speak to Ann-Marie.

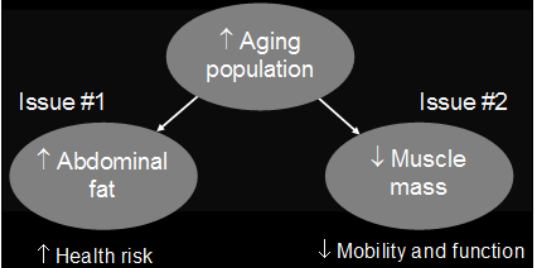
Text published in *Vista*, March 2004

## Appendix 5: PowerPoint Presentation Used for Orientation Meetings

## Prevention and treatment of abdominal obesity and related insulin resistance in senior men and women



## What is the issue?



## The challenge

Develop a lifestyle-based intervention that reduces abdominal fat while maintaining or improving muscle mass and function.

### DIET

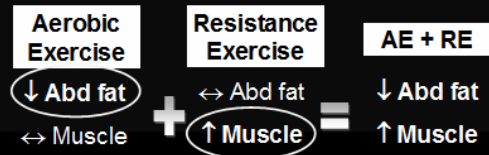
↓ Abd fat mass  
↓ Muscle mass

### EXERCISE

↓ Abd fat mass  
↔ Muscle mass

## The challenge

Which type of exercise is most beneficial for an abdominally obese senior population?



## Objectives

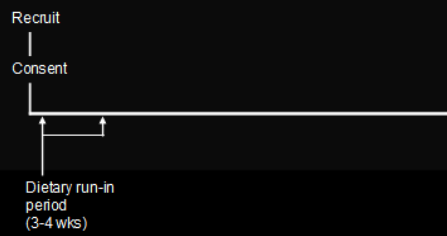
To determine the separate and combined effects of aerobic and resistance exercise on the following:

- Abdominal fat stores
- Skeletal muscle mass
- Insulin resistance

## Study design



## Study protocol

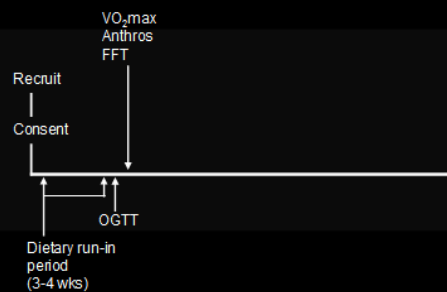


## Dietary Control

### All participants:

- Maintain current (stable) calorie intake
- Record food eaten each day
- 30% calories from fat, protein intake controlled
- No caloric restriction

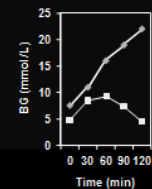
## Study protocol



## OGTT

### Metabolic Research Laboratory @ HDH

- Overnight fast
- Orange drink – (75g glucose)
- Blood sugar tested every 30 minutes for 2 hours



## VO<sub>2</sub>max

### Queens Physiology Laboratory

- Treadmill exercise to fatigue
- Physician supervised



## Anthropometrics

### Queens Physiology Laboratory

- Skinfolds
- Circumferences



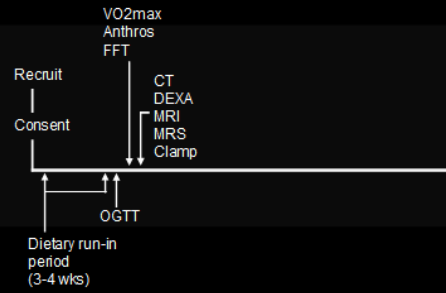
## Functional Fitness Test

Queens Physiology Laboratory

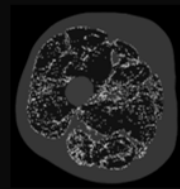
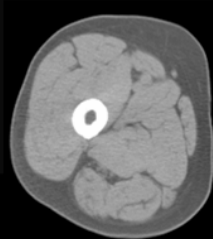
- 6 physical tests
- Designed for seniors by Rikli et al.



## Study protocol



## CT Measurement of Skeletal Muscle Lipid Levels



- Adipose Tissue (<0 HU)
- Low Density Muscle (0-30 HU)
- High Density Muscle (30-100 HU)

## DEXA

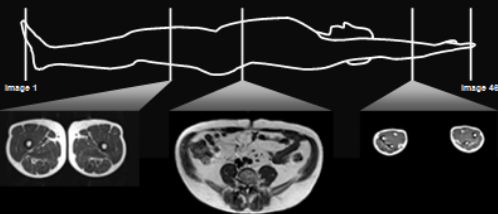


DXA Results Summary:

Region	Fat (g)	Lean+BMC (g)	% Fat
L Arm	1781.3	4183.2	29.9
R Arm	2045.7	4487.9	31.3
Trunk	19480.8	35845.3	35.2
L Leg	4788.3	10913.8	30.5
R Leg	5110.0	11403.3	30.9
Subtotal	33206.2	66833.6	33.2
Head	1203.4	4609.2	20.7
Total	34409.6	71442.8	32.5

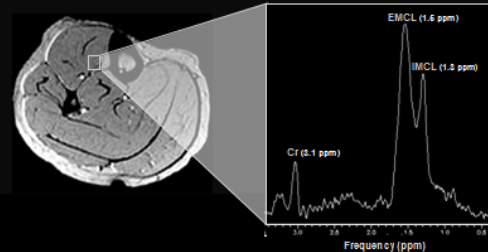
## Magnetic Resonance Imaging

Kingston General Hospital

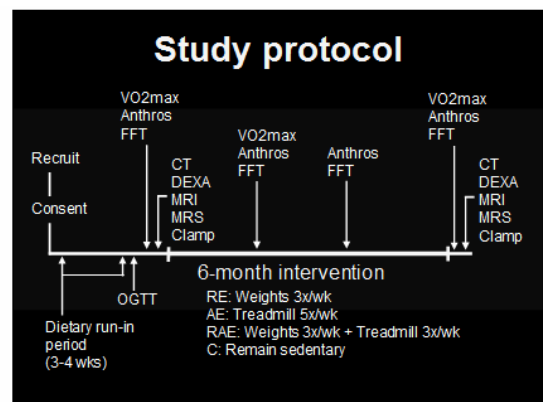
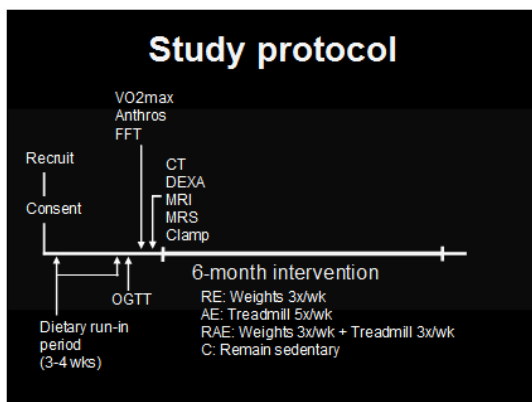
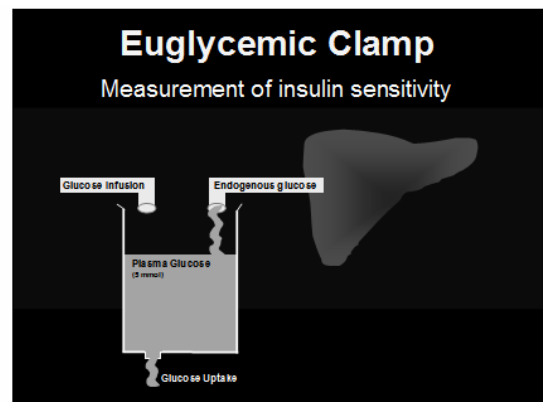
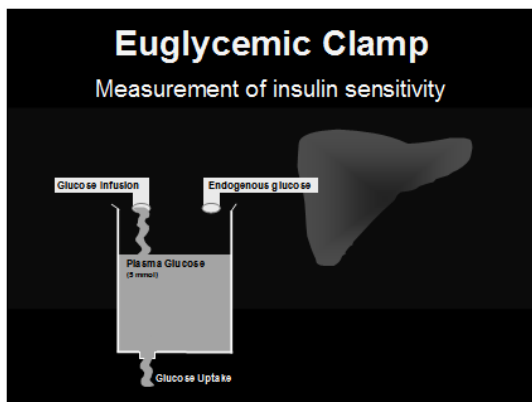
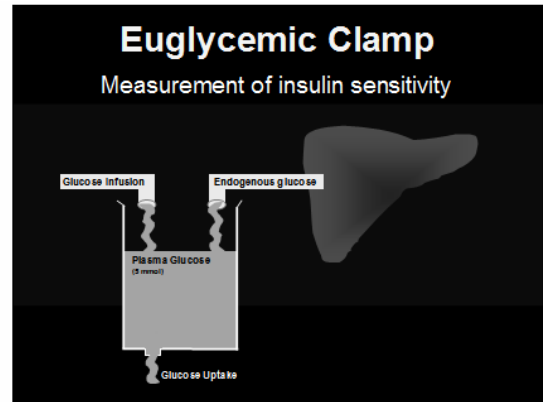
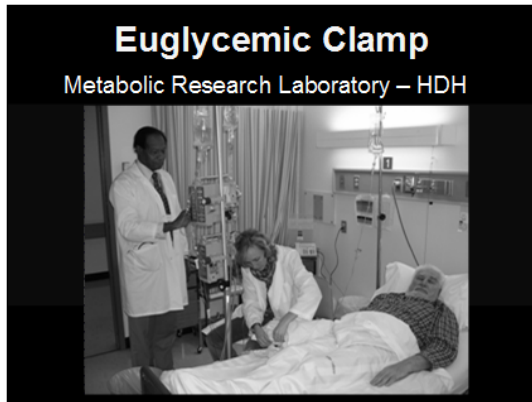


## MR Spectroscopy

Kingston General Hospital



Boesch et al....



### Data collection ongoing



### Data collection ongoing



### Clinical implications

The results from this study will provide evidence for developing an improved therapeutic strategy for the treatment and prevention of abdominal obesity and insulin resistance in older men and women.

### A team effort...



## Appendix 6: Orientation Meeting Information Sheet

## Queens Exercise Study for Seniors Information Sheet

Please complete the following:

Name: _____	
Phone number: _____	Email: _____
Mailing address: _____ _____	
Age: _____	Date of Birth: _____
Are you taking a calcium supplement? No _____ Yes _____	
Are you on hormone replacement therapy? No _____ Yes _____	
Are you taking other medications? No _____ Yes _____	
If yes, list all medications _____ _____ _____	
Are you diabetic? No _____ Yes _____	
Do you smoke? No _____ Yes _____	
How many alcoholic beverages do you consume each week? _____	

After hearing the presentation, please indicate your preference:

\_\_\_\_\_ I will make an appointment with my physician to complete the medical form and start as soon as possible

\_\_\_\_\_ I would like to begin, but after this date \_\_\_\_\_

\_\_\_\_\_ I will not participate in this study at this time

– For Office Use Only –

Height: _____ cm	Weight: _____ kg
Waist Circumference: _____ cm	

## Appendix 7: Informed Consent

## **CONSENT TO VOLUNTEER FOR PARTICIPATION IN A STUDY**

**TITLE:      Prevention and treatment of abdominal obesity and related  
                 insulin resistance in elderly men and women**

### **PRINCIPAL INVESTIGATOR:**

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Queen's University  
School of Physical and Health Education/  
Medicine, Division of Endocrinology and  
Metabolism  
Kingston, Ontario, K7L 3N6  
533-6583**

### **CO-INVESTIGATORS:**

**Chris Boesch, M.D., Ph.D.  
University of Berne  
Switzerland**

**Robert Hudson, M.D., Ph.D., FRCPC  
Kingston General Hospital  
Medicine, Division of Endocrinology and Metabolism  
Kingston, Ontario, K7L 3N6  
533-2973**

You are invited to participate in a research study on the influence of aging and exercise on abdominal fat and insulin resistance. The following brief is intended to provide you with the details you should be aware of prior to your consent as a participant in this study. Please read the following information carefully and feel free to ask any question that you may have.

## **BACKGROUND INFORMATION**

Many elderly people have problems keeping their blood glucose (sugar) levels normal, a condition referred to as “insulin resistance” by scientists and medical doctors. Although the reasons associating aging with insulin resistance are unclear, the increase in fat in the abdominal region is at least in part responsible for the increased insulin resistance. A reduction in physical activity with aging may also contribute to an increase in insulin resistance.

Recent studies have shown a relationship between muscle lipid (fat) content and insulin resistance in young healthy individuals and persons with diabetes. This is important as the amount of fat within the muscle increases with aging. Thus, muscle fat may partially explain why insulin resistance increases with age. However, at this time it is unknown whether or not muscle fat content is related to insulin resistance with aging.

Although muscle fat content is associated with insulin resistance, we also know that muscle fat content is increased in individuals who exercise on a regular basis. This is important because individuals who exercise on a regular basis are very insulin sensitive (opposite to insulin resistance). Thus, it appears that an increase in muscle fat content does not always suggest a person will become insulin resistant. An important question to ask then is whether the muscle fat in insulin resistant (e.g., sedentary elderly) and insulin sensitive (e.g., physically active elderly) individuals follows the same pattern. We will also be looking at whether the normal insulin sensitivity seen in physically active elderly persons is due to changes in skeletal muscle fat content.

Exercise is thought to be a good thing to do for reducing both abdominal fat and insulin resistance. However, whether aerobic (e.g., walking) or resistance-type exercise (e.g., weight lifting) is best for reducing either is unknown. Further, whether the two forms of exercise combined (aerobic and resistance exercise) is better than either one alone for reducing abdominal fat and insulin resistance is unknown. This is especially true for older persons.

Therefore, you are invited to participate in a study to assess the relationships between exercise, abdominal fat, muscle fat, and insulin resistance. We hope that the results of this study will provide a better understanding of the reasons for the age-related increase in insulin resistance. In addition, we hope to determine whether regular exercise, and more importantly what type of exercise, can prevent the insulin resistance common to the aging process. As insulin resistance is a major predictor of diabetes and cardiovascular disease, these results may have important implications for developing ways to prevent and treat diabetes and cardiovascular disease in elderly persons.

## **EXPLANATION OF PROCEDURES**

### **Pre-participation screening**

You will be required to have a medical exam prior to participation in this study. The examination will be performed by your family physician. In addition to the medical examination, you will have a fasting blood test to measure your blood sugar levels. This procedure is explained in further detail on page seven (7) of this form.

### **Study Protocol**

The study will be approximately 7 months in duration. The exercise part of the study will last 6 months. The 6-month exercise period will be preceded by a 3-4 week weight maintenance period -- thus the duration of the study will be about 7 months in total. By volunteering to participate in this study, your name will be selected by chance and placed into one of the following four groups: (1) Control - no exercise, (2) Aerobic (walking) exercise, (3) Resistance (weights) exercise, (4) Aerobic and Resistance exercise.

**Control Group:** For the entire study the men and women in this group will consume a diet that will maintain bodyweight. Thus there will be no weight loss or exercise.

**Aerobic Exercise Group:** As a participant in the aerobic exercise group you will be asked to perform walking type exercise on a motorized treadmill for 30 minutes, 5 times per week, at about 65% of your cardiovascular fitness level (e.g., brisk walking) for the duration of the 6 month treatment

period. During each exercise session we will measure your heart rate every 5 minutes using an automated heart rate monitor. All of your exercise sessions will be by appointment and performed under supervision within our laboratory at Queen's.

**Resistance Exercise Group:** As a participant in this group you will be asked to perform a series of 10 exercises, 3 times per week, for the duration of the 6 month treatment period. Eight of the exercises will be performed using Nautilus strength training equipment and 2 using your own body weight (e.g., sit-ups). All resistance exercise sessions will be supervised by a qualified undergraduate or graduate level student and performed within Dr. Ross' laboratory at Queen's.

**Aerobic and Resistance Exercise Program Combined:** As a participant in this group, you will perform an exercise regimen that combines resistance and aerobic exercise. The resistance exercise program will be the same as that described for the resistance exercise only group. In addition, the aerobic exercise will be performed at the same intensity as the aerobic only group (~65% of your cardiovascular fitness for 30 minutes), but is reduced to 3 days of the week. Most exercisers should be able to perform both an aerobic and a resistance session in a single laboratory visit, so the total (6) exercise sessions can be performed on 3 days per week at Queen's.

**Nutrition:** All study participants will follow a similar dietary pattern. A nutritionist will explain to you the role of nutrition in this study. A session will take place at the beginning of the study, with several additional sessions planned throughout to help you follow the dietary plan. If someone else shops for your food or prepares your meals, or if you share those tasks with someone else, that person is invited to meet with the nutritionist as well. You will be required to record the food you eat each day for the duration of the study. All of your meetings with the nutritionist will be in Dr. Ross's laboratory within the Physical Education building at Queen's.

At the beginning of the study, using the diet records that you complete, the number of calories required to maintain your body weight will be determined. During the study we will ask you to maintain this caloric intake. In other words, eat an amount of food that would normally maintain your body weight. Thus any weight loss you experience will be the result of an increase in exercise.

## **Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a method for imaging or creating pictures of body structures or organs. MRI gives images in slices comparable to those produced by x-ray tomography (e.g., CT scan). One of the primary advantages of MRI is that it does not employ x-rays or other forms of radiation. Instead, a large magnet, a radio transmitter/receiver and a computer are used to gather chemical information from the body, and to produce images or pictures of internal anatomy. No harmful effects have been associated with MRI under existing conditions of use. It is important that you fill out the enclosed MRI questionnaire to determine if there is any reason why you should not have the MRI exam.

As mentioned, the MRI procedure is very similar to a scanner examination. You will be placed on a table and moved smoothly into the scanner. A loud-speaker within the magnet makes it possible for you to keep in constant contact with the staff. At all times the operator can see and hear you and if you need help or have questions, you can be removed from the machine if necessary. The whole procedure takes about 35 minutes and will be performed by appointment at Kingston General Hospital.

## **Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) works the same way that MRI does. You will be positioned in the magnet as in the MRI test. The difference is that MRS does not provide pictures of the body. Instead, the radio signal emitted from the body is used to provide information about where the fat is positioned within your muscle. In other words, MRI provides pictures of muscle and fat, which tell us about the quantity of muscle and fat. Information obtained using MRS tells us something about the quality of muscle. As with MRI, the MRS procedure will be performed at Kingston General Hospital and will take about 30 minutes to complete.

## **Computerized Tomography (CT)**

Computerized tomography or CT is another method that will be used to obtain information about the quality of your muscle and your liver. Unlike MRI, CT provides pictures of the muscle and liver that can be used to determine the amount of fat in your liver and muscle. Specifically, two CT images of your mid-thigh will be obtained to measure the amount of fat in

the muscle; one CT image of the liver will be obtained to determine the amount of fat in the liver. You will be asked to lie on an exam table while the CT scan is being performed. The entire CT procedure will take about 10 minutes.

### **Dual Energy X-Ray Absorptiometry (DEXA)**

DEXA measures whole body fat, bone quality, and skeletal muscle. For this test you lie on your back on a table. The scanner moves above you measuring the transmission of X-rays from a source under the table. During this procedure you are asked to lie still for approximately 10 minutes. The radiation exposure involved with this test is approximately equivalent to one percent of a chest X-ray. This measurement will take place by appointment and be performed within the Department of Radiology at Kingston General Hospital.

### **Anthropometry (Skinfolds and Circumferences)**

Many circumference measurements will be taken at numerous sites on your body. These measures can be used to derive estimates of body composition. In addition, through the use of skinfold calipers, skinfold thickness will be measured at 8 different sites on your body. The anthropometric measurements require about one hour to complete and will be obtained at the School of Physical and Health Education, Queen's University.

### **Bioelectrical Impedance**

This is a very simple and safe procedure requiring no more than 5 minutes to complete. While you lie on your back, 2 electrodes will be placed on the surface of your right hand and foot. Two of the electrodes will introduce an alternating current that you can't feel into the body, while the other 2 record the resistance. The results are used to determine body composition. The bioelectrical impedance measurements will be obtained at the Hotel Dieu Hospital.

### **Assessment of Cardiovascular Fitness**

We will measure your cardiovascular fitness (endurance) using a treadmill procedure. The test will begin at a level you can easily accomplish

and will be advanced in stages, depending on your capacity to do so. We may stop the test at any time because of signs of fatigue or you may stop the test because of personal feelings of fatigue or discomfort.

The treadmill test involves risks comparable to any strenuous exercise situation. They include very rare instances of abnormal blood pressure, fainting, disorders of the heartbeat, and heart attack. Every effort will be made to minimize your risk by preliminary medical examination and observation during the test. A graduate student will conduct your fitness test in the presence of a physician. You will perform the exercise test 3 times: once at the beginning, once after one month, and once at the end of the exercise training period.

### **Assessment of Muscular Strength**

Improvement in muscular strength will be assessed before and at weeks 8, 16 and 24 using a 3-repetition maximum (3RM) test. The 3RM is defined as the maximal resistance that could be moved through the full range of motion for 3 repetitions.

### **Laboratory measurements (blood glucose (sugar) and lipid (fat) tests)**

The measurement of how much sugar and fat are in your blood will be done at Hotel Dieu Hospital. To determine your ability to manage blood sugar you will be asked to perform two (2) separate tests. The first test, an Oral Glucose Tolerance Test or OGTT, will be performed after an overnight fast. You will be asked to arrive at the hospital at about 8am after an overnight fast (no eating after 7pm the night before). The first step of this test will involve a venipuncture with a needle and the removal of about 30 ml (3 tablespoons) of blood from a vein in your arm. The only risk from this procedure is possible local pain and bruising at the time of the blood test. In addition, you will be asked to drink a fluid that contains 75 grams of sugar (like an orange drink). At 30-minute intervals for 2 hours after drinking the sugar solution, a small amount of blood will be taken from a vein in your arm for the purpose of measuring the amount of sugar in the blood.

The second test will also be performed after an overnight fast, and, after having not exercised on the prior 3 days. This procedure will also be performed at Hotel Dieu Hospital. Having arrived at the hospital you will be asked to lie comfortably on a bed for about 4 hours. Catheters (needles) will

be placed in a vein on the top of one hand and in a vein in your arm. A catheter in the arm vein will be used to give glucose (sugar) and insulin at a rate designed to keep your blood sugar level normal for 3 hours. Every 5-10 minutes during this procedure a small amount of blood will be taken from a vein in your hand to measure blood sugar to ensure that it remains normal. A physician will monitor this procedure at all times.

The purpose of these tests is to determine your ability to maintain normal blood sugar levels (insulin sensitivity). Reduced sensitivity to insulin is a complication of aging and may be associated with diabetes mellitus, high blood pressure, and other health problems. These tests should not have any lasting side effects.

### **Summary of Appointments and Time Requirements**

For the testing you will be required to make a 1-hour appointment at the Queen's University Physical Education Centre to complete the anthropometry and functional fitness tests, and another ½-hour appointment for the cardiovascular fitness test. We will arrange five appointments for you at Kingston General and Hotel Dieu Hospitals: one 2½-hour appointment for the oral glucose tolerance test (Hotel Dieu Hospital); one 6-hour appointment for the bioelectrical impedance, insulin sensitivity, and blood lipid/cholesterol tests (Hotel Dieu Hospital); one 1½-hour appointment to complete the MRI and MRS (Kingston General Hospital); one 10-minute CT test (Hotel Dieu Hospital); and one 15-minute appointment for the DEXA test (Kingston General Hospital). All of these appointments will be scheduled at a time that is convenient for you. Further, each of these tests (excepting the oral glucose tolerance test) will be performed twice, once at the beginning and once at the end of the treatment period.

### **Risks and Benefits**

You will gain no direct benefit through participation in this study. Participation may involve some risks. The known risks are:

- 1) Insertion of a catheter in your arm or hand vein may cause bruising, bleeding, soreness or infection.
- 2) Computerized Tomography (CT). Participation in this research study will involve a small radiation exposure (1.0 RAD or 2.0 RAD) from

the CT scan to a small region of your thighs and chest (liver). For comparison, a radiation worker is allowed 5 RADS of whole body exposure per year.

- 3) The effective dose (the term used to describe your exposure to radiation) that you will receive during the Dual Energy X-ray Absorptiometry (DEXA) exam is approximately 5 microsieverts. The average background radiation that you are exposed to on a daily basis is estimated to be approximately 10 microsieverts. Thus the DEXA exam adds approximately half the daily background radiation.

For CT and DEXA, there is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects or cancer. However, the risk associated with the amount of radiation exposure you will receive from these procedures is considered to be very low and comparable to other everyday risks.

- 4) MRI or MRS has certain conditions which would exclude you from participating in this study. These include cardiac pacer, aneurysm clip, cochlear implant, intra-uterine device (IUD), shrapnel, neurostimulators or other metal devices. Metal objects present in the body could be moved by the large magnet involved in the MRI, and such movement could cause serious injury. Fear of closed spaces is also a reason you would be excluded from the study. No serious biological effects have been reported from being in a magnet. If you experience a fear of the confined space while in the magnet, you can terminate the study. Trained personnel are always in attendance during these studies.
- 5) The risk of receiving insulin (as in the test at Hotel Dieu Hospital in which your sensitivity to insulin is measured) is the development of hypoglycemia (blood sugar which is too low). Because we give you glucose (sugar) throughout the test, and, your blood sugar levels are measured every 5 to 10 minutes, the likelihood of your having a low blood sugar is very low. The symptoms of low blood sugar include increased sweating, fast heart rate, feeling shaky and/or hungry. In very rare cases when your blood sugar levels fall to low, seizures or death may occur.
- 6) The exercise test may cause muscle soreness or fatigue. In any

individual there is a minute risk of a heart attack or death from the exercise test. A trained paramedic or medical doctor will be present. If you develop chest pain the test will be stopped immediately.

You should inform the investigators if you have participated in any other research study during the previous year. This will help to ensure that you have not been exposed to a procedure in another study that may influence your ability or eligibility to participate in this one. You should understand that this study is a research study and may not be of direct benefit to you. If requested, a report will be generated for your medical record, which will include any information important for your medical care.

## **CONFIDENTIALITY**

All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times. Your information will be kept in locked files and will be available only to Dr. Robert Ross and those working within his laboratory. Your identity will not be revealed in any description or publication.

In the event you that you are injured as a result of the study procedures, medical care will be provided to you until resolution of the medical problem. By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities.

Financial remuneration will not be provided to you for participation in this study.

## **VOLUNTARY CONSENT**

I have been given an opportunity to ask any questions concerning the procedures. All of my questions regarding the research project have been satisfactorily answered. I understand that my test results are considered confidential and will never be released in a form that is traceable to me, with the exception of my family physician or me. I do understand that I am free to deny consent if I so desire, and may withdraw from the study at any time without prejudicing current or future medical care.

Should I have any questions about the study, I know that I can contact any of the following: Dr. Robert Ross (533-6583), Dr. Robert Hudson (533-2973), Dr. Janice Deakin, Head, School of Physical and Health Education (533-6601), Dr. Donald Brunet, Head, Department of Medicine (533-6327), or Dr. Albert Clark, Chair of the Ethics Review Board at Queen's (533-6081). A copy of this consent form will be provided me for my records. My signature below means that I freely agreed to participate in this study.

---

**Date:**

---

**Volunteer's Signature**

---

**Witness' Signature**

## **STATEMENT OF INVESTIGATOR**

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

**Principal Investigator's Signature**

**Date**

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## Appendix 8: Medical Questionnaire

## School of Physical and Health Education



### MEDICAL QUESTIONNAIRE FOR RESEARCH STUDY

#### PREVENTION AND TREATMENT OF ABDOMINAL OBESITY AND RELATED INSULIN RESISTANCE IN ELDERLY MEN AND WOMEN

**To the study participant:** Please answer all questions in sections 1 and 2 of this form. Have your family doctor fill out section 3.

**To the physician:** Please fill out section 3 of this form (pages 4-6). Completing this form may not require a medical re-evaluation of your patient. If the results of recent tests are readily available that might prove useful to study personnel while dealing with the participant, please include that information in this questionnaire.

Please note that we will pay all costs for completing this questionnaire. Please bill your patients directly and we will reimburse them accordingly.

**SECTION 1: PERSONAL DATA (please print)**

Name: \_\_\_\_\_

Date of Birth: \_\_\_\_\_

Date: \_\_\_\_\_

**SECTION 2: MEDICAL HISTORY**

	<b>Yes</b>	<b>No</b>
A. Has your doctor ever said you have heart trouble?	_____	_____
B. Do you get pain, pressure, or tightness in your chest?	_____	_____
C. Do you often feel faint or experience dizziness?	_____	_____
D. Has your doctor ever told you that you have high blood pressure?	_____	_____
E. Is there a good reason, not mentioned above, why you should avoid exercise?	_____	_____

F. Do you have, or have you ever had, problems with any of the following?

	<b>Yes</b>	<b>No</b>
i. Heart or blood vessels	_____	_____
ii. Nerves or brain	_____	_____
iii. Breathing or lungs	_____	_____
iv. Hormones, thyroid, or diabetes	_____	_____
v. Muscles, joints, or bones	_____	_____
vi. Other (please list)		

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G. Please list any serious injuries suffered, or surgeries you have had.

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H. If you have had surgery, was any metal (e.g., pins or screws) left in your body?

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I. Are you presently taking any medications? If yes, please list.

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J. Are you presently undergoing physiotherapy, or any other sort of treatment?

If yes, please list.

---

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### **SECTION 3: MEDICAL REFERRAL**

**Physician:** The applicant is considering participation in a research study that is investigating the effects of exercise modality on changes in body composition (e.g., abdominal fat), cardiovascular fitness, glucose tolerance and insulin resistance. As a participant in this study, your patient would undergo a cardiovascular fitness appraisal (see explanation on page 7) and a number of other tests to assess body composition and metabolic health risk. We will forward any test results to you at your patient's request.

A brief describing the details of the study is appended to the back of the Medical Questionnaire. Should you have any questions regarding the participation of your patient in this project, please contact Robert Ross Ph.D., School of Physical and Health Education, Queen's University (533-6583).

#### **I. Review of Systems – please include diagnoses**

- a) Cardiovascular \_\_\_\_\_
- b) Respiratory \_\_\_\_\_
- c) Neurological \_\_\_\_\_
- d) Gastrointestinal \_\_\_\_\_
- e) Genitourinary \_\_\_\_\_
- f) Endocrine \_\_\_\_\_
- g) Musculoskeletal \_\_\_\_\_
- h) Skin \_\_\_\_\_
- i) Gynecological \_\_\_\_\_

#### **II. Physical Examination**

Blood Pressure: \_\_\_\_\_ Pulse: \_\_\_\_\_

Cardiovascular: \_\_\_\_\_

Respiratory: \_\_\_\_\_

Head and Neck: \_\_\_\_\_

MSK: \_\_\_\_\_

Abdomen: \_\_\_\_\_

Neurological: \_\_\_\_\_

12-lead ECG results: **(not mandatory)**

\_\_\_\_\_

**III. Laboratory findings (not mandatory)**      Date of Test(s): \_\_\_\_\_

Hb \_\_\_\_\_ WBC \_\_\_\_\_ Plts \_\_\_\_\_

Total Cholesterol \_\_\_\_\_ HDL \_\_\_\_\_ Chol:HDL ratio \_\_\_\_\_

LDL \_\_\_\_\_ Triglycerides \_\_\_\_\_ Uric Acid \_\_\_\_\_

TSH \_\_\_\_\_ Glucose \_\_\_\_\_ fasting ☐ random ☐

75 g OGTT @ 120 min \_\_\_\_\_

**IV. Additional abnormalities of which you are aware** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**V. Current medications and doses**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**VI. On the basis of your knowledge and medical evaluation of the applicant, you would recommend (mark the appropriate answer):**

- ☐ Participation in a fitness appraisal supervised by a physical education graduate, or
- ☐ Participation in a fitness appraisal only when a physician or paramedic is present, or
- ☐ Participation in a fitness appraisal is not recommended

**Note:** An explanation of the fitness appraisal protocol, as well as absolute and relative contraindications to exercise testing, is provided on page 7 of this form.

Physician's Name: \_\_\_\_\_

Physician's Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Phone Number: \_\_\_\_\_

Address:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Thank you very much for your help.**

**We hope that this study and its results will be beneficial to you and your patient.**

## **Appraisal of Cardiovascular Fitness (VO<sub>2</sub>max test)**

Cardiovascular fitness is assessed using a maximal oxygen uptake (VO<sub>2</sub>max) test, which is routinely employed within the laboratory of the study investigators. The treadmill walking test begins at a level the study participant can easily accomplish (comfortable walking pace with no incline) and is slowly increased in intensity (by increasing treadmill incline) until the participant reaches volitional fatigue. We may stop the test at any time because of signs of fatigue or the subject may stop the test because of personal feelings of fatigue or discomfort.

The maximal oxygen uptake test involves risks comparable to a very strenuous exercise situation. Every effort is made to minimize the risk by preliminary medical examination and close observation during the test by physical education graduate students and a physician.

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## **American College of Sports Medicine Contraindications to Exercise Testing**

### **Absolute Contraindications**

1. A recent change in the resting ECG suggesting infarction or other acute cardiac events
2. Recent complicated myocardial infarction
3. Unstable angina
4. Uncontrolled ventricular dysrhythmia
5. Uncontrolled atrial dysrhythmia that compromises cardiac function
6. Third-degree A-V block
7. Acute congestive heart failure
8. Severe aortic stenosis
9. Suspected or known dissecting aneurysm
10. Active or suspected myocarditis or pericarditis
11. Thrombophlebitis or intracardiac thrombi
12. Recent systemic or pulmonary embolus
13. Acute infection
14. Significant emotion distress (psychosis)

### **Relative Contraindications**

1. Resting diastolic blood pressure >120 mm Hg or systolic blood pressure >200 mm Hg.
2. Moderate valvular heart disease
3. Known electrolyte abnormalities (hypokalemia, hypomagnesemia)
4. Fixed-rate pacemaker (rarely used)
5. Frequent or complex ventricular ectopy
6. Ventricular aneurysm
7. Cardiomyopathy, including hypertrophic cardiomyopathy

8. Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxoedema)
9. Chronic infectious disease (e.g., mononucleosis, hepatitis, AIDS)
10. Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
11. Advanced or complicated pregnancy

## Appendix 9: Daily Dietary Record

Name: \_\_\_\_\_  
 Date: APRIL 01, 2006

Target kcal	Max. fat(g)

	Source <small>(SEE KEY)</small>	Amount	Food	Calories	Fat (g)
Breakfast	X	3/4 C.	LIFE-CEREAL	120	1.5
	X	1/2 C	SKIM MILK	40	<1
	FF	2 CUPS	MY COFFEE	80	3
Breakfast Subtotals:				240	4.5
Lunch	T-47	1	HAMBURGER	260	9
	T-47	1 SM. ORDER	FRIES	210	10
	T-9	8 OZ	COKE.	114	0
Lunch Subtotals:				584	19
Dinner	T-28	1 CUP	RIGATONI (WITH SCS + MEAT)	382	15
	FF	1 CUP	GARDEN SALAD	30	0
	X	1 TBSP	SALAD DRESS	30	0
	T-29	1/2	CHOC CAKE	388	17
Dinner Subtotals:				830	32
Snacks					
Snacks Subtotals:					

Please include source book and page  
 or reference number (eg. T-5 = T-factor, page 5)  
 T = T-factor  
 P = Photocopied book  
 \* = Food label  
 ? = Best guess

Totals: A 1654 B 55.5

Fat calories: (B) x 9 kcal/g fat 499.5 C

% kcal from fat (C/A) X 100 = 30.20%

Canada's Food Guide Checklist:

Grains: 1 2 3 4 5 6 7 8 9 10 11 12  
 F&V: 1 2 3 4 5 6 7 8 9 10  
 MEK: 1 2 3 4  
 Meat: 1 2 3

## Appendix 10: Goals for Nutrition Sessions

## **Senior Study Nutrition Package Goals**

### **Package 1: Canada's Food Guide to Healthy Eating**

#### **Goals:**

1. Provide an overview of Canada's Food Guide and Guidelines for Healthy Eating.
2. Educate participants about the importance of variety, balanced meals and moderation.
3. Help participants to recognize their own eating habits and to see healthy alternatives.

### **Package 2: Hidden Fat**

#### **Goals:**

1. Recognize the higher fat food choices in each food group and be aware of hidden fat.
2. Identify healthy, lower fat options of various foods.
3. Include hidden fat sources on the diet records.

### **Package 3: Types of Fat**

#### **Goals:**

1. Recognize fat as an essential nutrient
2. Introduce the different types of fats and learn about which foods they are found in.
3. Understand how the different types of fats affect heart health, targeting the reduction of saturated and trans fat.
4. Clarify the 'cholesterol' issue:
  - recognize the difference between blood cholesterol and cholesterol found in food.
  - realize that different kinds of dietary fats have different effects on blood cholesterol
5. Introduce trans fatty acids

### **Session 2: Understanding Food Labels**

#### **Goals:**

1. Educate participants on the regulations governing food labels in Canada.
2. Increase participants understanding of food labels by teaching them to find nutrition information in the "Nutrition Facts Table" and the ingredient listing and use this information to make healthy food choices.
3. Provide recommended daily allowances for various nutrients: cholesterol, sodium, fibre, and protein
4. Introduce nutrition claims on food packages and help participants recognize misleading claims.

### **Package 5: Eating Out**

#### **Goals:**

1. Recognize breakfast as an important meal to start the day.
2. Provide healthy snacks ideas.
3. Learn that fast foods tend to be high in fat and salt, and low in fiber.
4. Educate participants on how to make healthy choices when eating out.

### **Package 6: Meat & Alternatives**

#### **Goals:**

1. Participants should choose 2-3 servings from the meat and alternative food group each day.
2. Understand that meat and alternatives provide many essential nutrients, including protein.
3. Understand that red meat can be high in saturated fat; by choosing leaner meats and using low-fat cooking methods, red meat can fit into a healthy diet.

4. Provide practical suggestions for buying and preparing lean meat.
5. Encourage participants to choose poultry, fish and meat alternatives more often.

**Package 7: Fiber****Goals:**

1. Educate participants on the importance of fiber in the diet.
2. Introduce the two types of fiber, their effects on health and the different foods they are found in.
3. Encourage participants to consume 25-35 grams of fiber per day; provide ideas on how to achieve this as well as ways to decrease the discomfort that is usually associated with increased fiber intake.

**Package 8: Fruit & Vegetables****Goals:**

1. Educate participants on the importance of consuming fruit and vegetables.
2. Encourage participants to consume 5-10 servings of fruit and vegetables daily, and to provide practical suggestions on how to achieve this.
3. Introduce different kinds of fruit and vegetables and to provide ways of eating them as a snack or part of a meal.

**Package 9: Calcium****Goals:**

1. Recognize calcium as an important part of a healthy diet; in particular, its importance in keeping bones strong and healthy.
2. Understand what osteoporosis is and the role that calcium plays in the prevention of this condition.
3. Introduce different foods that contain calcium and urge participants to make calcium-rich choices more often.

## Appendix 11: Anthropometric Data Collection Form

### Seniors Anthropometric Data Collection Form

Name: \_\_\_\_\_ Test: PRE Mid8 Mid16 POST

Gender: M F Date: \_\_\_\_\_ Student: \_\_\_\_\_

<b>Anthro Weight:</b>	_____ kg	Arm Length:	_____ cm
Standing Height:	_____ cm	Sitting Height:	_____ cm
Acromion Height:	_____ cm	Knee Height:	_____ cm

<b>Skinfolds (mm)</b>	1	2	3	mean
Subscapular	_____	_____	_____	_____
Tricep	_____	_____	_____	_____
Bicep	_____	_____	_____	_____
Mid-Axillary	_____	_____	_____	_____
Iliac Crest	_____	_____	_____	_____
Abdomen	_____	_____	_____	_____
Thigh	_____	_____	_____	_____
Calf	_____	_____	_____	_____

#### Circumference Measures (cm):

Hip:        1        2        mean  
 \_\_\_\_\_

		1	2	mean
Waist (standing)	Last Rib:	_____	_____	_____
	Iliac Crest:	_____	_____	_____
Waist (supine)	Last Rib:	_____	_____	_____
	Iliac Crest:	_____	_____	_____

		1	2	mean		1	2	mean
Bicep:	R	_____	_____	_____	L	_____	_____	_____
Forearm:	R	_____	_____	_____	L	_____	_____	_____
Thigh: Proximal	R	_____	_____	_____	L	_____	_____	_____
	Medial	R	_____	_____	_____	L	_____	_____
Distal	R	_____	_____	_____	L	_____	_____	_____
Calf:	R	_____	_____	_____	L	_____	_____	_____

# BIOIMPEDANCE

## Clamp Morning Data Collection

Subject Name: \_\_\_\_\_ Test ID: \_\_\_\_\_

Gender: M F Today's Date: \_\_\_\_\_

DOB: \_\_\_\_\_

Age: \_\_\_\_\_ Height: \_\_\_\_\_ cm

Blood Pressure: 1. \_\_\_\_\_ / \_\_\_\_\_ mmHg

2. \_\_\_\_\_ / \_\_\_\_\_ mmHg

### Bio-Impedance Measurements

Tanita Segmental (BC-418)

Weight \_\_\_\_\_ %Fat \_\_\_\_\_ TBW \_\_\_\_\_

Whole Body Impedance \_\_\_\_\_

RL \_\_\_\_\_ LL \_\_\_\_\_ RA \_\_\_\_\_ LA \_\_\_\_\_

Supine Multifrequency

Whole Body

	Z	Phase		
4 Hz			Rinf	
8 Hz			Ro/Re	
16 Hz			Ri	
32 Hz			Beta	
64 Hz			Fc	
128 Hz			R	
256 Hz			X	
512 Hz				

## Appendix 12: Functional Fitness Test Data Sheet

## Functional Fitness Data Collection Form

Subject Name: \_\_\_\_\_

Gender:        M        F                      Age: \_\_\_\_\_

Date: \_\_\_\_\_ Time: \_\_\_\_\_ Tester: \_\_\_\_\_  
(day/month/year)

<b>Test:</b>	<b>Pre</b>	<b>8 wks</b>
	<b>16 wks</b>	<b>Post</b>

### 1. 30-sec chair stand

Have subject try one stand, rest, and then perform one 30-second trial.

Number of stands: \_\_\_\_\_

### 2. Arm curl

Use subject's dominant arm (*circle one*):    Right        Left

Explain full range of motion and position of wrist in up and down position. Have subject practice one or two curls, rest, and then perform one 30-second trial.

Number of controlled curls: \_\_\_\_\_

### 3. 2-Minute Step Test

Mark midpoint between ASIS and patella. Put a piece of tape on wall adjacent to subject as a guide for the knee height when stepping (no running).

Number of times the right knee reaches the marker: \_\_\_\_\_

### 4. Chair sit-and-reach

Explain leg positioning and remind subject to perform the test slowly and without bending the extended leg. Perform two tests for practice, and then record two actual trials. *Circle the best score.*

Trial 1: \_\_\_\_\_ (cm)                      Trial 2: \_\_\_\_\_ (cm)

### 5. Back Scratch

Have the subject try either elbow up and choose the better one (*circle*):    Right    Left

Give the subject two practice stretches and then record measurements from two actual trials. *Circle the best score.*

Trial 1: \_\_\_\_\_ (cm)                      Trial 2: \_\_\_\_\_ (cm)

### 6. 8 ft up-and-go

Explain that the subject should not run, and give one practice trial.

*Circle the score* of the better of two trials.

Trial 1: \_\_\_\_\_ (sec)                      Trial 2: \_\_\_\_\_ (sec)

### Appendix 13: Heart Rate Record for Graded Maximal Exercise Test

**Maximal Oxygen Consumption Test -- Seniors Study**

PRE    MID    POST

Participant Name: \_\_\_\_\_

Date: \_\_\_\_\_

Participant ID: Senior \_\_\_\_\_

Weight (kg): \_\_\_\_\_

Height (cm): \_\_\_\_\_

Speed (mph): \_\_\_\_\_

DOB: \_\_\_\_\_

Tester: \_\_\_\_\_

Age-predicted HR<sub>max</sub>: \_\_\_\_\_

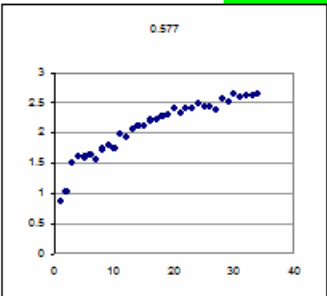
Time (min)	Grade (%)	HR (bpm)
00:00	0	
00:20		
00:40		
01:00		
01:20		
01:40		
02:00		
02:20		
02:40		
03:00	2	
03:20		
03:40		
04:00		
04:20		
04:40		
05:00	3	
05:20		
05:40		
06:00		
06:20		
06:40		
07:00	4	
07:20		
07:40		
08:00		
08:20		
08:40		
09:00	5	
09:20		
09:40		
10:00		
10:20		
10:40		
11:00	6	
11:20		
11:40		

Time (min)	Grade (%)	HR (bpm)
12:00		
12:20		
12:40		
13:00	7	
13:20		
13:40		
14:00		
14:20		
14:40		
15:00	8	
15:20		
15:40		
16:00		
16:20		
16:40		
17:00	9	
17:20		
17:40		
18:00		
18:20		
18:40		
19:00	10	
19:20		
19:40		
20:00		
20:20		
20:40		
21:00	11	
21:20		
21:40		
22:00		
22:20		
22:40		
23:00	12	
23:20		
23:40		

#### Appendix 14: VO<sub>2</sub>max Summary Data Sheet

\*\*\* Results will not be valid until column lengths are adjusted for each new test.\*\*\*

CIHR Seniors

Name:	Senior Participant			Grad student:	Peter&Kate			Physician:	Kathie		
DOB:	23-Jan-1946										
Time	VO2	VO2/kg	VCO2	RQ	VE	VEO2	HR	kcal	RESULTS		
0:00:20	0.577	5.8	0.515	0.9	22.3	39	102	2.885	Age	60.2	years
0:00:40	0.866	8.7	0.794	0.93	27.6	33	107	4.33	Weight	99.5	kg
0:01:00	1.036	10.4	1.047	1.07	32.8	33	115	5.18	Speed	3.5	mph
0:01:20	1.511	15.2	1.303	0.86	38	25	117	7.555	Max Elev	6	%
0:01:40	1.603	16.1	1.456	0.91	41.4	26	122	8.015	Max RQ	1.2	
0:02:00	1.595	16	1.505	0.94	42.7	27	125	7.975	VO2 max	2.64767	L/min
0:02:20	1.648	16.6	1.558	0.95	42.5	26	129	8.24	per kg	26.6333	ml/kg/min
0:02:40	1.562	15.7	1.498	0.96	44.6	28	130	7.81	Max HR	174	bpm
0:03:00	1.73	17.4	1.678	0.97	41.7	24	132	8.65	Predicted	166	bpm
0:03:20	1.801	18.1	1.871	1.04	52.4	29	136	9.005	Target HR		
0:03:40	1.734	17.4	1.83	1.06	47.7	28	139	8.67	60%	130	bpm
0:04:00	1.988	20	2.114	1.06	57.8	29	142	9.94	75%	145	bpm
0:04:20	1.926	19.4	2.043	1.06	51.6	27	143	9.63	HR/VO2		
0:04:40	2.057	20.7	2.167	1.05	57.3	28	145	10.285	Slope	37.3741	
0:05:00	2.121	21.3	2.358	1.11	64.7	30	148	10.605	Intercept	70.8548	
0:05:20	2.107	21.2	2.374	1.13	65.8	31	149	10.535	kcal/HR		
0:05:40	2.205	22.2	2.534	1.15	72.2	33	151	11.025	Slope	0.12847	
0:06:00	2.224	22.4	2.511	1.13	67.2	30	154	11.12	Intercept	-8.69133	
0:06:20	2.285	23	2.597	1.14	74.6	33	155	11.425	Yes=1, No=0		
0:06:40	2.309	23.2	2.656	1.15	75.1	33	157	11.545	MAX EXER CRITERIA		
0:07:00	2.406	24.2	2.738	1.14	76.3	32	158	12.03	1 VO2 plateau with increase		
0:07:20	2.317	23.3	2.679	1.16	78.9	34	158	11.585	in workload	1	
0:07:40	2.406	24.2	2.78	1.16	82.4	34	159	12.03	2 RER greater than 1.1		
0:08:00	2.399	24.1	2.741	1.14	80.6	33	162	11.995		1	
0:08:20	2.496	25.1	2.915	1.17	90.2	36	162	12.48	3 Max HR exceeds age estimate		
0:08:40	2.441	24.5	2.861	1.17	87.8	36	164	12.205	85%Pred	141.0	1
0:09:00	2.443	24.6	2.819	1.15	86.6	35	165	12.215	# of Criteria Met:	3	
0:09:20	2.386	24	2.813	1.2	86.1	36	166	11.93			
0:09:40	2.565	25.8	2.964	1.16	94	37	168	12.825			
0:10:00	2.522	25.3	2.942	1.17	91.4	36	169	12.61			
0:10:20	2.654	26.7	3.025	1.14	95.2	36	169	13.27			
0:10:40	2.606	26.2	3.082	1.2	99.6	38	171	13.03			
0:11:00	2.617	26.3	3.058	1.17	99.4	38	171	13.085			
0:11:20	2.632	26.5	3.126	1.19	103.4	39	173	13.16			
0:11:40	2.657	26.7	3.139	1.18	104.4	39	174	13.285			

## Appendix 15: Whole Body MRI Acquisition Protocol

## **Whole Body MRI Acquisition Protocol**

Ross et al. 1992 and 1996

### **Summary**

The purpose of this protocol is to acquire T1-weighted images the entire length of the body (with 4 cm slice gaps between slices). These images will be analyzed to determine total body fat and muscle content.

### **Protocol**

#### Specifications:

Axial multi-slice spin-echo TR/TE = 210ms/17ms

FOV = 48cm (LR) x 36cm (AP) (i.e. 48cm FOV with rectangular FOV at 75%)

7 axial slices of 10mm thickness and 40mm slice gap (i.e. 50mm center to center)

0.5 or 1.0 NEX

1. Place subject in the prone position feet first and landmark at approximately L4-L5.
2. Acquire localizers:
  - a. Saggitals (to find L4-L5)
  - b. Coronals (to find head of femur)
3. Acquire 7 axial T1W SE images from L4-L5 down (towards feet) with the breath hold T1W sequence. Breath hold will be approximately 0.26 seconds at 0.5 NEX.
4. Reposition the patient couch and acquire 7 T1W axial slices starting at the femoral head going towards the feet.
5. Reposition the patient couch such that the next 7 T1W axial slices can continue to be acquired with a 4cm slice gap.
6. Repeat step 5 until the entire length of the legs are acquired. (1/2 FOV if possible at extremities)
7. Reposition patient prone and head first with arms over the head and landmark at approximately L4-L5.
8. Acquire localizers:
  - a. Saggitals (to find L4-L5 again)
  - b. Coronoals (to find head of right humerus)
9. Acquire 7 axial T1W SE images from L4-L5 upwards (toward head) with the breath hold T1W sequence.
10. Reposition patient couch and acquire 7 more T1W SE images continuing (towards the head) with a 4cm slice gap with the breath hold T1W sequence.
11. Reposition patient couch and acquire 7 T1W SE images starting at the humeral head (going towards the fingers) with a 4cm slice gap.
12. Reposition the patient couch such that the next 7 T1W axial slices can continue to be acquired with a 4 cm slice gap.
13. Repeat step 12 until the entire length of the arms is acquired.

### Protocol (Abdomen)

T1-weighted, spin-echo pulse sequence  
 Each image = 10 mm thickness, 40 mm spaces  
 TR = 210 ms; TE = 17 ms; 1/2 NEX  
 FOV = 48 cm X 36 cm (Rectangular)  
 Matrix = 256 X 256  
 Each acquisition = 7 images  
 Time = 26 seconds (breath hold)

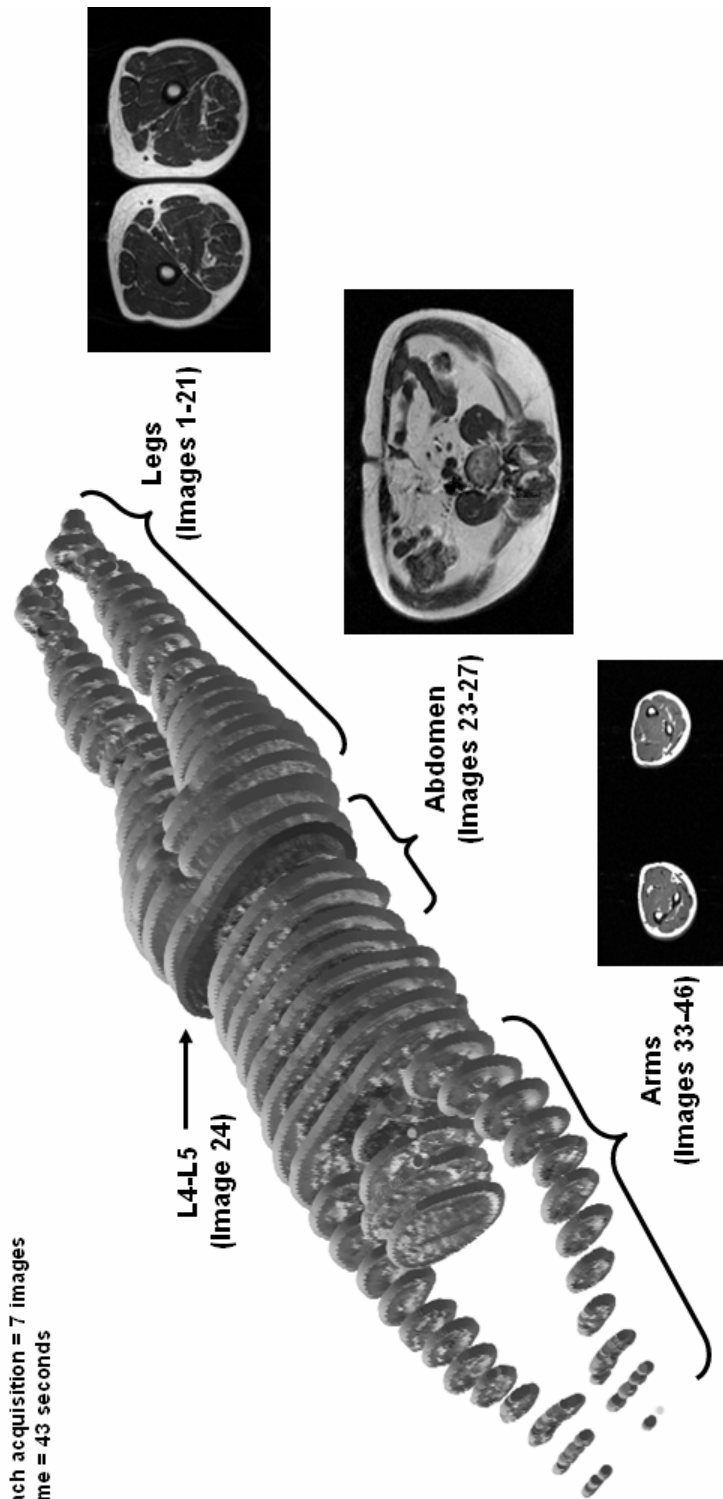
### Protocol (Appendicular)

T1-weighted, spin-echo pulse sequence  
 Each image = 10 mm thickness, 40 mm spaces  
 TR = 210 ms; TE = 17 ms; 1 NEX  
 FOV = 48 cm X 36 cm (Rectangular FOV) or 48 cm X 24 cm (1/2 FOV)  
 Matrix = 256 X 256  
 Each acquisition = 7 images  
 Time = 43 seconds

### Sequence of Series to Acquire Images

1. Sagittal scout to locate L4-L5 & Right Femoral Head
2. L4-L5 down (abdomen protocol)
3. Femoral Head down (appendicular protocol, rectangular FOV)
4. 35 cm below Femoral Head down (appendicular protocol, 1/2 FOV)
5. 70 cm below Femoral Head down (appendicular protocol, 1/2 FOV)
6. Sagittal scout to locate L4-L5
7. Coronal scout to locate Right Humeral Head
8. L4-L5 up (abdomen protocol)
9. 35 cm above L4-L5 up (appendicular protocol, rectangular FOV)
10. Humeral head up (appendicular protocol, rectangular FOV)
11. 35 cm above humeral head up (appendicular protocol, 1/2 FOV)

\* For each series of images data is acquired over 310 mm  
 (155 cm above isocentre of magnet, 155 cm below isocentre)



## Appendix 16: MRI Script File

```

# -----#
# --- script file for          test.scp          --#
# --- created: 28 Jun 2002 09:18                --#
# -----#

# -----#
# --- patient name and directory                --#
# --- (if not present here, they can be entered in the program) --#
# -----#
Read: path      "\\Lance\Lance\Queens PhD\CIHR Seniors\MRI\Scans\479"
# -----#
# --- list of files, slices, offsets and flips  ---#
# --- Read: image [$]name.ext [i=val] [f=val] [t=val] ---#
# ---#
# --- the "$" sign will be replaced by the patient name ---#
# ---#
# --- the number after the "i=" is the slice number in the file ---#
# --- (by default, all the slices in the file will be read) ---#
# --- "i=3" will read the third slice in the file ---#
# --- "i=3-7" will read from the third to the seventh ---#
# --- "i=7-3" will read from the seventh to the third ---#
# --- "i=all" will read all the slices in the file ---#
# ---#
# --- the character after the "f=" is the slice flip ---#
# --- (by default, no flip is done on the file) ---#
# --- "0" no flip of the file ---#
# --- "|" horizontal flip (left->right, right->left) ---#
# --- "-" vecrtical flip (bottom->top, top->bottom) ---#
# --- "+" both flip (180 deg rotation) ---#
# ---#
# --- the number after the "t=" is the slice offset ---#
# --- (by default, the "t" value comes from the file header) ---#
# --- "+val" will add "val" to each t of the file ---#
# --- "-val" will subtract "val" to each t of the file ---#
# --- "val" will replace the t value by "val" ---#
# -----#

Read: patient    "ST1\"

Read: image "$PATH$PATIENT03661116" i=all p=01 g=01
Read: image "$PATH$PATIENT03661103" i=all p=01 g=01
Read: image "$PATH$PATIENT03661090" i=all p=01 g=01
Read: image "$PATH$PATIENT03661077" i=all p=01 g=01
Read: image "$PATH$PATIENT03661064" i=all p=01 g=01
Read: image "$PATH$PATIENT03661051" i=all p=01 g=01
Read: image "$PATH$PATIENT03661038" i=all p=01 g=01

Read: image "$PATH$PATIENT03661025" i=all p=01 g=01
Read: image "$PATH$PATIENT03661010" i=all p=01 g=01
Read: image "$PATH$PATIENT03660995" i=all p=01 g=01
Read: image "$PATH$PATIENT03660980" i=all p=01 g=01

```

Images proceed from inferior to superior, arranged sequentially....

## Appendix 17: MRI Script Record

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MRI Script Record

Test ID:

Name:  
Date:

Script File

SE1: (scout)  
SE2: (L4-5↓)  
SE3: (FH↓)  
SE4: (35cm below FH [knee])  
SE5: (70cm below FH [toes])  
SE6: (scout) L4-5:  
SE7: (scout) FH:  
SE8: (L4-5↑) L4-5:  
SE9: 35cm above L4-5) HH:  
SE10: (HH↑)  
SE11: (35cm above HH [fingers]  
SE12:  
SE13:  
SE14:  
SE15:

In 35cm above L4-5, use:  
<400 = 1 image → 45  
400-450 = 2 images → 46  
>450 = 3 images → 47

Partial Volume Adjustments

Line 21

L4-5:  
FH:

Line 31, 32, or 33

L4-5:  
HH:

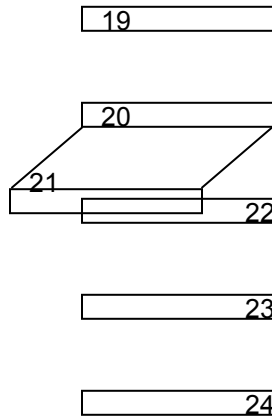
## Appendix 18: MRI Partial Volume Anomalies Guide

## Partial Volume Adjustments: Anomalies

### Overlapping Images in Order

#### Line 21

L4-5: S 9  
FH: I 97



In MRI summary spreadsheet, change image thickness on the respective partial volume (subtract amount of overlap from 1.0 cm) and delete truncated cone portion (from “+” sign onward) of volume equation.

#### Line 21:

$$PV\ 21 = B24 * 0.6 + ((SUM(B24:B25) + SQRT(B24 * B25)) / 3) * 1.3$$

#### Line 31:

$$PV\ 31 = B34 * 0.5 + ((SUM(B34:B35) + SQRT(B34 * B35)) / 3) * 2$$

#### Line 32:

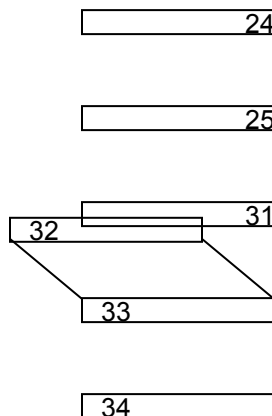
$$PV\ 32 = B35 * 0.6 + ((SUM(B35:B36) + SQRT(B35 * B36)) / 3) * 2$$

#### Line 33:

$$PV\ 33 = B36 * 0.5 + ((SUM(B36:B37) + SQRT(B36 * B37)) / 3) * 2$$

#### Line 31

L4-5: I 7  
HH: S 348



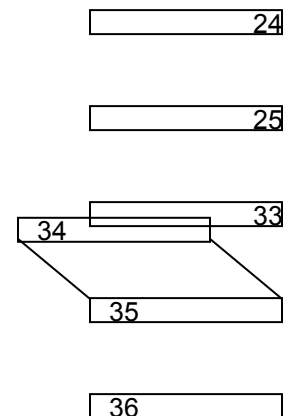
#### Line 32

L4-5: I 37  
HH: S 369



#### Line 33

L4-5:  
HH:

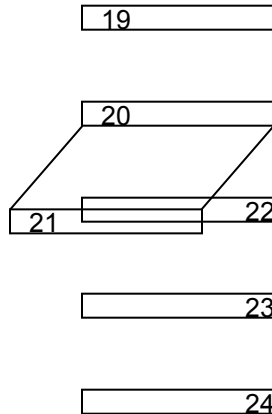


## Overlapping Images Out of Order

### Line 21

L4-5: I 41

FH: I 138



In MRI summary spreadsheet, enter zeros for area 22 *and* partial volume 22. Adjust the spacing for partial volume 21 so that it reflects the distance between images 21 and 23.

Area 22 = 0

PV 22 = 0

PV 21 =  $B24 * 1 + ((SUM(B24:B26) + SQRT(B24 * B26)) / 3) * 3.7$

Apply the same rules to cases where image 22 appears completely before image 21.

## Appendix 19: MRI Tissue Area and Whole Body Volume Calculations

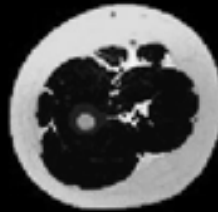
## 1. Area (cm<sup>2</sup>)



Grey Level Image



B. Edge Detection

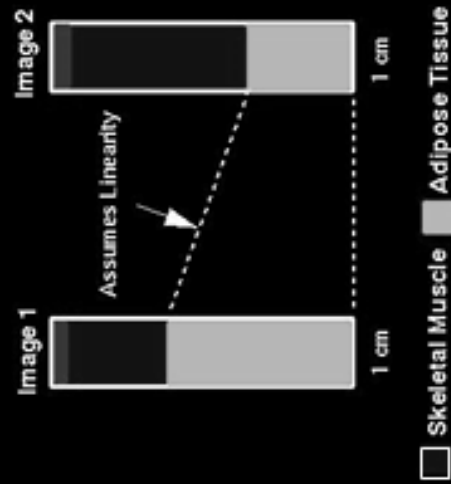


$$\text{Voxel Size} = \frac{\text{FOV}}{\text{Matrix}} \times \text{Image Thickness}$$

FOV = 480 x 480 mm  
Matrix = 256 x 256  
Image Thickness = 1 cm  
Voxel size = 1.88 mm<sup>3</sup>

- - Skeletal Muscle (115 cm<sup>2</sup>)
- - Subcutaneous AT (117 cm<sup>2</sup>)
- - Interstitial AT (11 cm<sup>2</sup>)
- - Bone (6 cm<sup>2</sup>)

## 2. Volume (cm<sup>3</sup>, liters) and Mass (kg)



Equation 1

$$\text{Volume} = \sum_{i=1}^N A_i t + h/3 \sum_{i=2}^N (A_{i-1} + A_i + \sqrt{(A_{i-1} A_i)})$$

Equation 2


$$\text{Volume} = \sum_{i=1}^N (A_i + A_{i+1}) / 2 \times h$$

Equation 3

$$\text{Mass (kg)} = \text{Volume} \times \text{Tissue Density}$$

Muscle = 1.04 kg/L  
Adipose Tissue = 0.92 kg/L

## Appendix 20: CT Requisition Form

TIME RECEIVED IN DEPT. <b>7:00pm</b>				<b>The Religious Hospitallers of Saint Joseph of the Hotel Dieu of Kingston</b>				<b>Requisition for Consultation with Department of Radiology</b>					
DATE OF EXAMINATION <b>Jan. 12/2005</b>		OUTPATIENT <b>✓</b>		EMERG Ch #		INPATIENT room #							
PORT.	STRETCH	WHEEL CHAIR	WALK	CARRY	ISOLATION YES NO	W.C.B.	D.V.A.	OTHER					
SURNAME <b>Davidson</b>				FIRST <b>Lance</b>				MR. MRS. MS.					
ADDRESS <b>M</b>				CITY		PROVINCE		POSTAL CODE					
DATE OF BIRTH		SEX <b>M</b>		HOME PHONE NO.		WORK PHONE NO.							
ATTENDING PHYSICIAN				<b>ID # 999</b>									
CHIP				SUBSCRIBER'S INITIALS / RELATIONSHIP									
INJURY DATE		S.I.N.		EMPLOYER'S NAME & ADDRESS / WORK CLAIM NO.									
PARTS TO BE EXAMINED					CLINICAL HISTORY / Diagnosis								
1. <b>Thigh</b>													
2. <b>Liver/spleen</b>													
3.													
4.													
5.					LMP:								
C.T. INSTRUCTIONS (FOR RADIOLOGY USE ONLY)					PREVIOUS X-RAYS		WHERE?						
					YES	NO							
with C+		without C+		with & without C+		WHEN?		WHAT?					
I.V. Contrast					NUCLEAR MEDICINE		Radionuclide + Amount:						
Oral Contrast:					Esophocat		Barium		Comments:				
C.T. Protocol:					Date & Time Given:		Initials:						

**1/12/05 hmk** **Dr. Ross Senior Study**

## Appendix 21: Clamp Data Sheet

Name Senior Participant

BMI: 27.12 kg/m<sup>2</sup>

Today's Date: 8-Sep-03

DOB 27-Nov-40

BSA: 1.670

Study: Seniors

Age 62.8 yrs

BSA \*20/250ml NaCl = 33.40

Clamp: Pre

Ht 156.7 cm

Units of Insulin = 33

Doctor: Hudson

Wgt 68.6 kg

Line:

Nurse: Tammy

CR#:

Student: Lance

Visit#:

Real Time	# of Min	Extra samples	Glucose			D20 Rate ml/hr	Glucose mg/min	Glucose mg/kg/min	Blood Gas	Comments
			A.A. mmol/L	Elite	Repeat					
	0	Insulin								
	5									
	10									
	15									
	20									
	25									
	30	Insulin								
	35									
	40									
	45									
	50									
	55									
	60	Insulin								
	65									
	70									
	75									
	80									
	85									
	90	Insulin								
	95									
	100									
	105									
	110									
	115									
	120	Insulin								
	125									
	130									
	135									
	140									
	145									

Real Time	# of Min	Extra samples	Glucose			D20 Rate ml/hr	Glucose mg/min	Glucose mg/kg/min	Blood Gas	Comments
			A.A. mmol/l	Elite	Repeat					
	150	Insulin								
	155									
	160									
	165									
	170									
	175									
	180	Insulin								
	185									
	190									
	195									
	200									
	205									
	210	Insulin								
	215									
	220									
	225									
	230									
	235									
	240	Insulin								
	245									
	250									
	255									
	260									
	265									
	270	Insulin								
	275									
	280									
	285									
	290									
	295									

Average Glucose Level:

± mmol/L

Disposal Summary :

± mg/kg/min

± mmol/kg/min

Blood Gas Results:

Time	pH	pO2	pCO2	HCO3	O2 Sat	H+

## Appendix 22: Blood Gases and Lipid Profile Requisition Forms

CORE LABORATORY SERVICES STUDY REQUISITION

Dr. Robert Ross 2005

DATE:	Addressograph
TIME COLLECTED: BY: TIME RECEIVED: BY:	ROSS, CODE _____
ACCESSION #	Physician: Dr. R. Hudson

☐ Syringe for Blood Gases

Sample type: arterialized

LABORATORY INSTRUCTIONS:

1. Accession in LIS as Labo-L/, visit NR-L/, Doctor: unknown ( 0)
2. Name: ROSS, CODE(number as above) ~~eg~~ ROSS, CODE999
3. Order BGAS in normal fashion.
4. In s-com indicate "Phone results to 544-3400 ext 3372 (Tammy Zeb)"
5. Attach report to requisition and file.

Questions: Please see JOYCE.

LEAVE REQUISITION FOR JOYCE

Dr. Robert Ross 2005

# CORE LABORATORY SERVICES STUDY REQUISITION

Dr. Robert Ross 2005

DATE:	Addressograph
TIME COLLECTED: BY: TIME RECEIVED: BY:	ROSS, CODE _____
ACCESSION #	Physician: Dr. R. Hudson

☐ 1 SST for Lipids (Triglycerides, Cholesterol, HDL, LDL, ~~Chol~~HDL ratio)

Fasting: Yes NO

Lab Assistants to call 544-3400 ext 3372 (Tamm) leave a message indicating that the blood has arrived on the above patient.

\*\*\*\*\*

## LABORATORY INSTRUCTIONS:

1. Accession in LIS as Labs-L/, visit NR-L/, Doctor: unknown ( 0)
2. Name: ROSS, CODE(number as above) eg ROSS, CODE999
3. In o-com indicate "Send results to RRL printer"
4. Order Lipids (-S), eg, normal fashion.
5. When report prints, put comment into computer that the printing was done, file report with the lab requisition.

Questions: Please see JOYCE.  
LEAVE REQUISITION FOR JOYCE  
Dr. Robert Ross 2005

Appendix 23: Medical Outcomes Survey -- SF-36

## Medical Outcomes Survey (MOS)

Name: \_\_\_\_\_

Date: \_\_\_\_\_

**Instructions:** This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by **circling** the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. In General, would you say your health is:

- |   |           |
|---|-----------|
| 1 | Excellent |
| 2 | Very Good |
| 3 | Good      |
| 4 | Fair      |
| 5 | Poor      |

2. Compared to **one year ago**, how would you rate your health in general now?

- |   |                                       |
|---|---------------------------------------|
| 1 | Much better now than one year ago     |
| 2 | Somewhat better now than one year ago |
| 3 | About the same as one year ago.       |
| 4 | Somewhat worse now than one year ago  |
| 5 | Much worse now than one year ago      |

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<b>Activities</b> Circle one number on each line	<b>Yes, limited a lot</b>	<b>Yes, limited a little</b>	<b>No, not limited at all</b>
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities **as a result of your physical health?**

<i>Circle one number on each line</i>	<b>Yes</b>	<b>No</b>
a. Cut down on the <b>amount of time</b> you spent on work or other activities	1	2
b. <b>Accomplished less</b> than you would like	1	2
c. Were limited in the <b>kind</b> of work or other activities	1	2
d. Had <b>difficulty</b> performing the work or other activities (for example it took extra effort).	1	2

5. During **the past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems**, (Such as feeling depressed or anxious)?

<i>Circle one number on each line</i>	<b>Yes</b>	<b>No</b>
a. Cut down the <b>amount of time</b> you spent on work or other activities	1	2
b. <b>Accomplished less</b> than you would like	1	2
c. Didn't do work or other activities as <b>carefully</b> as usual	1	2

6. During **the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- |   |             |
|---|-------------|
| 1 | Not at all  |
| 2 | Slightly    |
| 3 | Moderately  |
| 4 | Quite a bit |
| 5 | Extremely   |

7. How much **bodily** pain have you had during the **past 4 weeks**?

- |   |             |
|---|-------------|
| 1 | None        |
| 2 | Very Mild   |
| 3 | Mild        |
| 4 | Moderate    |
| 5 | Severe      |
| 6 | Very severe |

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (Including both work outside the home and inside the home and housework)?

- 1 Not at all
- 2 A little bit
- 3 Moderately
- 4 Quite a bit
- 5 Extremely

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much time during the **past few weeks**:

<i>Circle one number on each line</i>	<b>All of the time</b>	<b>Most of the time</b>	<b>A good bit of the time</b>	<b>Some of the time</b>	<b>A little of the time</b>	<b>None of the time</b>
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Did you feel calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the **past 4 weeks** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 All of the time
- 2 Most of the time
- 3 Some of the time
- 4 A little of the time
- 5 None of the time

11. How true or false is each of the following sentences for you?

<i>Circle on number on each line</i>	<b>Definitely True</b>	<b>Mostly True</b>	<b>Don't Know</b>	<b>Mostly False</b>	<b>Definitely False</b>
a. I seem to get sick a little easier than most people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

## Appendix 24: Informed Consent for Hoffmann-LaRoche Study

## **CONSENT TO VOLUNTEER FOR PARTICIPATION IN A STUDY**

**TITLE: Prevention and treatment of abdominal obesity and related  
insulin resistance in elderly men and women  
(*Clinical Research Study*)**

### **PRINCIPAL INVESTIGATOR:**

**Robert M.J. Ross, Ph.D.  
Queen's University  
School of Physical and Health Education/ Medicine, Division of  
Endocrinology and Metabolism  
Kingston, Ontario, K7L 3N6  
533-6583**

### **CO-INVESTIGATORS:**

**Chris Boesch, M.D., Ph.D.  
University of Berne  
Switzerland**

**Robert Hudson, M.D., Ph.D., FRCPC  
Kingston General Hospital  
Medicine, Division of Endocrinology and Metabolism  
Kingston, Ontario, K7L 3N6  
533-2973**

## **PURPOSE OF THE STUDY**

You are being asked to join, by your own choice, a clinical research study that is part of the exercise study for which you have agreed to participate. Participation in this second study is NOT obligatory and you are free to deny participation without compromising participation in the exercise and obesity reduction study.

So that you can decide whether or not you want to take part in this second study, you should understand its possible risks and benefits enough to make an informed decision. Before you decide whether or not to take part, you should read this information carefully. Ask as many questions as you like until you are completely satisfied that you understand the answers.

The purpose of this study is to look at the relationships between various blood factors including proteins, lipids (fats), hormones, or biological molecules of interest, to visceral adiposity, insulin resistance, and obesity related problems. The DNA in your blood will be used to look for blood factors related to disease or lack thereof.

## **STUDY PROCEDURES**

If you decide to participate in this study, one 60mL blood sample will be collected from a vein in your arm. This will be done once at the beginning, and once at the end of the study (6 months later). This blood sample will be sent to Roche Pharmaceutical for analysis.

## **RISKS AND BENEFITS SIDE EFFECTS**

You will gain no direct benefit through participation in this study. Participation may involve some risks. There is the risk of slight pain or bruising when your blood is drawn for tests in this study. You may feel some brief discomfort from the needle in your arm. There is a small risk of bruising, bleeding, or swelling where the needle enters the body. Rarely, fainting or a local infection may occur.

## **CONFIDENTIALITY OF RECORDS**

You have a right to privacy, and all information that is collected for this study is confidential as much as possible by law. To protect your privacy, you will be identified only by your patient number in the study.

Your information may be analyzed in any country worldwide by Roche Pharmaceutical or other companies acting on behalf of Roche Pharmaceutical. Roche Pharmaceutical may then send the study results to Health Authorities worldwide, and report results at medical meetings and in medical magazines, so that other doctors can find out about the results of the study. If you leave the study, information already collected about you will still be used.

Roche Pharmaceutical may need to re-analyze the data from this study at a later date, and may need to carry out extra tests on samples collected during the study or perform further statistical tests on the data. In addition, it is possible that in the future Roche Pharmaceutical may need to collect additional data from your medical chart/records in order to put the already collected data in the proper medical context. The approval of the appropriate Institutional Review Board or Ethical Committee will be sought prior to collecting any additional information.

Representatives from Roche Pharmaceutical, Health Authorities, and your local Ethical Committee may be allowed to look at your medical records so that they can make sure that the information collected is correct. If this happens, it may be possible for them to identify you.

Study results will only be looked at for groups (eg patients who have the same disease characteristics), and not for any individual patient. If the study results show anything that could affect how your condition is managed, this will only be known after many more studies are done. This is why it is important for you to understand and agree that Roche Pharmaceutical will not be giving you or your Doctor the results of the test(s) done on your sample(s). The results will not have any effect on your own treatment.

## **NEW DISCOVERIES**

It is possible that results from this study may lead to discoveries and inventions (eg patents) or other commercial benefits. The rights to these will all belong to Roche Pharmaceutical.

## **SAMPLE STORAGE AND USE**

Your blood sample will be stored for a maximum of 15 years after the end of this study as part of a sample bank, and may be made available only for future research in the field of obesity. This research may include extra tests on your sample and analysis of information about you that was collected as part of the exercise and obesity study. The research may take several years to complete, but if successful, may lead to earlier diagnosis and better treatment of obesity and related diseases. The blood samples will be destroyed no later than 15 years after the end of this study.

## **MEDICAL TREATMENTS FOR INJURIES**

You will not have to pay for any clinic visits or for any of the tests required by the study. If you develop a problem related to the study, which requires medical attention, you will be examined by your physician and medical care will be given. Roche Pharmaceutical will pay for the cost of medical treatment for any injury that is a direct result of the study procedures when they have been performed as it states in the study protocol. No other compensation will be offered.

In the event you that you are injured as a result of the study procedures, medical care will be provided to you until resolution of the medical problem. By signing this consent form, you do not waive your legal rights nor release the investigator(s) and sponsors from their legal and professional responsibilities.

Financial remuneration will not be provided to you for participation in this study.

## **VOLUNTARY CONSENT**

An opportunity has been provided to you to ask any question concerning the procedures. All your questions regarding the research project have been satisfactorily answered. Your test results are considered confidential and will never be released in a form that is traceable with the exception of your family physician or yourself. You are free to deny consent if you so desire, and may withdraw from the study at any time without prejudicing current or future medical care.

Should you have any questions about the study you are encouraged to contact any of the following: Dr. Robert Ross (533-6583), Dr. Robert Hudson (533-2973), Dr. Janice Deakin, Head, School of Physical and Health Education (533-6601), Dr. John McCans, Head, Department of Medicine (533-6327), or Dr. Albert Clark, Chair of the Ethics Review Board at Queen's (533-6081). A copy of this consent form will be provided to you for your records. The signature below means that you freely agree to participate in this study.

---

**Date**

---

**Volunteer's Signature**

---

**Witness's Signature**

## **STATEMENT OF INVESTIGATOR**

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

---

**Principal Investigators Signature**

---

**Date**

## Appendix 25: Aerobic Exercise Session Record

THR: \_\_\_\_\_ bpm

Name: \_\_\_\_\_ Week # \_\_\_\_\_

Date	HR	Spd	Elev	HR	Spd	Elev	HR	Spd	Elev	HR	Spd	Elev	HR	Spd	Elev	HR	Spd	Elev
kcal																		
Time																		
0																		
5																		
10																		
15																		
20																		
25																		
30																		
35																		
40																		
45																		
50																		

Wt-kg \_\_\_\_\_

WC \_\_\_\_\_

Remember to ask for weekly waist circumference!

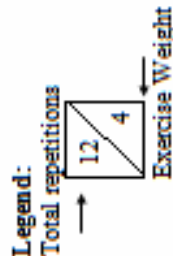
Comments

## Appendix 26: Resistance Exercise Session Record

## RESISTANCE TRAINING PROGRAM

### Technique:

Select a weight with which you can obtain *total momentary failure* between 8 and 12 repetitions.  
 One repetition should take approximately 7 seconds.  
 POSITIVE – 2 seconds lifting / PAUSE – 1 second hold / NEGATIVE – 4 seconds lowering.  
 Perform each repetition smoothly and with good form.



Name: \_\_\_\_\_ Group: R RA

Exercise	Seat Pos.	Week ____		Week ____		Week ____		Week ____		RECORD EXERCISE WEIGHTS AND TOTAL REPS FOR EACH EXERCISE (See Legend)
		M/D		M/D		M/D		M/D		
Minutes of warm-up										
Chest Press										
Leg Extension										
Shoulder Raise										
Leg Flexion										
Super Pullover										
Triceps Extension										
Biceps Curl										
Sit-ups	C									
	F									
Pushups	W									
	B									
Minutes of stretching										
Administrator Initials										

Administrator:  
 deviations from  
 protocols should  
 be recorded on  
 the back with  
 each note  
 referenced by a  
 number in the  
 appropriate box  
 or column.

## Appendix 27: Results Package for Participants



School of Kinesiology and Health  
Studies  
Queen's University  
Kingston Ontario Canada

Dear Jane,

Thank you for participating in the Queen's Senior Exercise Study. Without your diligent efforts and commitment, this project would never be possible. The information that we obtained from you and your fellow participants during testing will enable us to help other Seniors become more healthy and reduce the risk of developing diabetes.

We hope that your involvement in this project has brought you to a new sense of awareness of your health and inspired you to continue with more healthy habits throughout your life. Enclosed is a summary of the results of most of the tests you underwent in our lab. They are accompanied by brief explanations of the importance of each outcome, but please contact us if you want further information or find any of your results difficult to understand.

Brought on by popular demand and purely for interest's sake, we have included a CD which contains a presentation of the cross-sectional images of your whole body obtained by magnetic resonance imaging (MRI) technology at the conclusion of the study. If you would like an explanation or further help with this CD, please contact Lance.

Once again we thank you for being part of our lives as you participated in the Senior Exercise Study. We hope that the coming years will bring you and your loved ones health and happiness. Please keep in touch. We would love to hear from you!

Sincerely,

Shelley Atkinson  
Queens phone: 533-6000 ext 75118  
Home phone: 544-7340  
E-mail: [atkins@post.queensu.ca](mailto:atkins@post.queensu.ca)

Lance Davidson  
Queen's phone: 533-6000 ext 75118  
Home phone: 542-7434  
E-mail: [1led@qlink.queensu.ca](mailto:1led@qlink.queensu.ca)

Test Results  
for

*Jane Doe*

a graduate of the

Queen's University  
Senior Exercise Study  
in the Ross Laboratory

Completed  
*October 2004*

The following is a description of the variables that were measured during the Queen's Senior Exercise Study. A brief explanation of the importance of each test is included with your final test results, as well as normative and change data where applicable. We hope that you will find this summary useful and informative.

## Body Composition

The composition of your body, particularly the ratio of fat to lean tissue (muscle, bone), has a marked impact on your health and capacity for mobility and function into later years. Excess body fat is associated with many different risk factors, including high blood pressure, heart disease, diabetes, stroke and cancer. The general population tends to gain weight at a rate of about a pound per year from age 30 to 50 (for men) and age 30 to 60 (for women), stabilize for a few years, and then begin a gradual decline in weight. Unfortunately, this weight loss for people in their later years is owed to degeneration of muscle mass and bone, not reduction of fat. Because weight loss in the senior population usually reflects a reduction of the very tissues that keep them mobile and living independently, indexes of body fatness and muscle composition are more useful in determining health risk than simply measuring body weight.

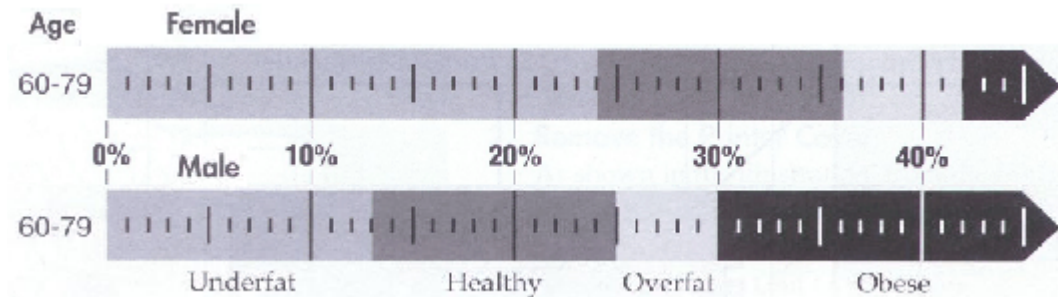
During this study, your body composition was measured in a variety of ways, including bioelectrical impedance (BIA), anthropometry (circumferences and skinfolds), dual-energy x-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI). Of these measurement methods, MRI is the most accurate for quantifying differences in fat and muscle, but because the other methods are more widely used, standards for comparison are more readily available. Following are your body composition outcomes with tables for comparison against a health or population standard.

### **Bioelectrical Impedance**

Impedance reflects the body's inherent resistance to an electrical current. Muscle acts as a conductor of the electrical current; adipose tissue acts as a resistor. Using the impedance values we collected from you in the study, your body fat percent (or the percentage of your body that is fat versus muscle, bone, fat-free tissue or water) was estimated.

Your body fat percentage at the beginning of the study was 38.4%. At the conclusion of the study, it was 37.8%.

The following are guidelines for determining health risk by body fat percentage in males and females in your age range.



Another helpful tool in determining health risk is to see your percentile ranking among your fellow seniors. Since no percentile rankings currently exist for Canadian seniors, these are data from a Swiss population:

		Percentile Rankings						
Gender	Age	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
Men	55-64	12.0	13.8	17.7	22.8	26.4	29.1	30.6
	54-74	14.6	17.2	19.8	24.2	27.6	30.7	32.6
	75-84	15.5	18.0	21.1	25.2	28.0	30.3	31.2
Women	55-64	21.4	24.4	28.3	32.5	36.0	39.4	40.5
	54-74	24.4	27.3	31.4	36.0	39.9	42.4	44.4
	75-84	25.9	29.1	32.8	36.9	40.4	44.2	45.2

### Anthropometry

Although excessive body fat is a health hazard, the distribution of body fat is perhaps even more important. Fat storage in the trunk region is more of a health risk than fat distributed on the limbs. One of the more meaningful measurements that can be collected with anthropometry is waist circumference taken at the level of the iliac crest. We recommend working toward a waist circumference of less than 80 cm, since measurements

greater than this are associated with increased health risk (a waist circumference greater than 88cm (in women) and 100 cm (in men) is associated with a substantial increase in risk). You began the study with a waist circumference of 94 cm. Your final waist circumference, measured at the level of the iliac crest, was 88 centimeters(cm).

### **Dual-Energy X-Ray Absorptiometry (DEXA)**

DEXA uses two X-ray beams that differ in intensity. The extent to which the two beams are diffracted by bone and soft tissue allows for differentiation of muscle and fat as well as bone mineral density (BMD). Your body fat percentage as determined by DEXA was 36.5% before you began the study; after, it was 34.9%. Often in research literature, DEXA is considered a standard by which bioelectrical impedance and anthropometric measures are verified. You may use your DEXA body fat percentage score in the tables on the previous page to reaffirm your current health risk and determine your ranking in a representative senior population.

The most common use of DEXA is for determining bone mineral density in screening for the development of osteoporosis. Bones naturally become thinner as you grow older, because existing bone is broken down faster than new bone is made. As this occurs, bones lose minerals (such as calcium), and their structure is compromised, making them weaker. This bone thinning, called osteopenia, can develop into a condition called osteoporosis, and most commonly occurs in post-menopausal women. Diagnosis of osteoporosis is done by comparing your bone mineral density to population values. Having a z-score that is -2.5 or lower (2.5 standard deviations below the population mean of young adults) is cause for concern and medical consultation.

There are currently no population means determined for men. Because most screening is performed specifically on the areas of the body where bone loss is first apparent (hip and lower spine), and this whole body bone density test represents mineral density throughout your body as a whole, you may wish to seek out further and more specific diagnostic testing if your score approaches higher risk. A copy of your results for the DEXA test is appended to this document.

# Metabolic Variables

## Insulin Sensitivity

Insulin is a hormone produced by the body in the pancreas. It is mainly important for the storage of glucose and prevents excessive glucose levels in the blood. Chronic overeating and lack of exercise can tax insulin's ability to regulate blood glucose levels, and eventually leads to hyperinsulinemia, a risk factor in the development of Type II (non-insulin dependent or adult onset) diabetes mellitus and cardiovascular disease. In Type II diabetes, the body's cells become progressively less sensitive to insulin, causing higher levels of insulin and glucose in the blood. By practicing moderation in diet and developing good exercise habits, you can improve the effectiveness of insulin in your body and take steps to prevent the onset of Type II diabetes. The Oral Glucose Tolerance Test and the Euglycemic Clamp are used to evaluate your insulin sensitivity.

### Oral Glucose Tolerance Test (OGTT)

To evaluate your tolerance to a glucose load, you were given an orange drink (75g glucose) after 12 hours of fasting. Your blood glucose was measured every half hour. A fasting glucose (See 0 min in table below) of 5.6 mmol/L or greater has recently been used by the American Diabetes Association as an indication of impaired glucose tolerance. Of perhaps greater clinical importance is the 2-hour plasma glucose level (See 120 min below), which, if found to be greater than 11.1 mmol/L, is diagnostic for Type II diabetes.

The results of your OGTT are summarized below in mmol/L:

Time	0 min	30 min	60 min	90 min	120 min
Glucose	5.3	9.8	9.7	8.9	6.1

### The Hyperinsulinemic Euglycemic Clamp

"The clamp," as we call it for short, measures how effectively insulin helps the muscles take glucose out of the blood. As mentioned earlier, high blood sugars put you at risk for disease. In this test, we infuse a measured dose of insulin (hence the name Hyperinsulinemic) into your blood and then infuse

glucose until your blood glucose stabilizes at a normal level (Euglycemic). The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/kg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/kg/min or lower) suggest that the body is resistant to insulin action. Levels between 4.1 and 7.4 mg/kg/min are indetermined and might point at "impaired glucose tolerance", considered an early form of insulin resistance. It is thought that weight loss and exercise can help to increase your insulin sensitivity, thereby decreasing your risk of developing Type II diabetes.

Your insulin sensitivity at the beginning of the study as indexed by your glucose disposal rate was 6.01 mg/kg/min. After the study, your glucose disposal was 10.71 mg/kg/min.

### **Blood Lipids**

Excess cholesterol in the blood is a risk factor for atherosclerosis and heart disease. Cholesterol found in the body can come from either the diet or organ production (mainly the liver). The total amount of cholesterol in the blood is not as important as the type of cholesterol with regard to health risk. High density lipoprotein (HDL) is known as the "good cholesterol" because it removes cholesterol from the blood. In contrast, low density lipoprotein (LDL) is "bad cholesterol" because it generates deposits on blood vessel walls. For this reason, it is beneficial to have high levels of HDL and low levels of LDL cholesterol in the blood. Modest reductions in blood cholesterol can be accomplished by lowering the intake of animal fats in your diet.

<b>Fractions (mmol/L)</b>	<b>Recommended Ranges</b>	<b>Your results before the study</b>	<b>Your results at the end of the study</b>
HDL	> 0.9	1.45	1.55
LDL	< 3.4	3.5	3.7
Total cholesterol	< 5.2	6.2	6.1
Triglycerides	0.55-3.30	2.66	1.76

# Fitness and Functionality

A physically inactive lifestyle can be a primary cause of frailty in older years, and has shown to be on a par with chronic disease as a cause of disability. Studies show that increased physical activity, even when begun later in life, results in improved physical fitness and functional capacity. During this study, you performed at least two maximal exercise tests. Your capacity to utilize oxygen to continue exercise during the last few moments of these tests was an objective measure of your fitness.

At the beginning of the study, your maximal oxygen consumption was 30.3 milliliters per kilogram of body mass per minute. This corresponds to a fitness level of very good in your age group. Your final test was 37.4 mL/kg/min, corresponding to a fitness level of *excellent* in your age group, or equal to an average 27 year old!

You also performed a series of 6 functional tests designed to assess your ability to perform basic "independent living" activities. The following is a table expressing your results and percentile ranking compared to others your age.

	<b>Beginning Score</b>	<b>Percentile Ranking</b>	<b>Ending Score</b>	<b>Percentile Ranking</b>
<b>Chair Stand</b> (stands)	12	<b>30<sup>th</sup></b>	20	<b>90<sup>th</sup></b>
<b>Arm Curl</b> (repetitions)	14	<b>35<sup>th</sup></b>	20	<b>80<sup>th</sup></b>
<b>2-Min Step</b> (steps)	82	<b>35<sup>th</sup></b>	126	<b>95<sup>th</sup></b>
<b>Chair Sit-&amp;-Reach</b> (inches beyond toes)	-2.16	<b>15<sup>th</sup></b>	2.16	<b>50<sup>th</sup></b>
<b>Back Scratch</b> (inches fingers overlap)	2.7	<b>85<sup>th</sup></b>	4.05	<b>90<sup>th</sup></b>
<b>8-Foot Up-&amp;-Go</b> (seconds)	5.28	<b>50<sup>th</sup></b>	4.22	<b>80<sup>th</sup></b>

**KINGSTON GENERAL HOSPITAL**  
**76 STUART ST.**  
**KINGSTON, ONTARIO K7L 2V7**

Telephone: 613-549-6666

Fax: 613-548-2413

Name:  
 Patient ID:  
 DOB: February 16, 1945

Sex: Female  
 Ethnicity: White

Height: 156.5 cm  
 Weight: 70.6 kg  
 Age: 60

**Scan Information:**

Scan Date: April 13, 2005 ID:  
 Scan Type: a Whole Body  
 Analysis: April 15, 2005 11:22 Version 11.2.1  
 Whole Body Fan Beam  
 Operator: DV  
 Model: Delphi A (S/N 70530)  
 Comment:

**DXA Results Summary:**

Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	146.33	1536.5	2357.8	2504.1	4040.6	38.0
R Arm	160.38	1625.2	2307.5	2467.9	4093.1	39.7
Trunk	605.21	11865.4	22505.1	23110.3	34975.7	33.9
L Leg	375.07	4990.1	6363.4	6738.4	11728.5	42.5
R Leg	392.70	5024.9	6350.5	6743.2	11768.1	42.7
Subtotal	1679.69	25042.1	39884.2	41563.9	66606.0	37.6
Head	470.99	877.0	3001.4	3472.3	4349.4	20.2
<b>Total</b>	<b>2150.68</b>	<b>25919.2</b>	<b>42885.6</b>	<b>45036.2</b>	<b>70955.4</b>	<b>36.5</b>

TBAR2649



**KINGSTON GENERAL HOSPITAL**  
76 STUART ST.  
KINGSTON, ONTARIO K7L 2V7

Telephone: 613-549-6666

Fax: 613-548-2413

Name: [REDACTED]  
Patient ID: [REDACTED]  
DOB: February 16, 1945

Sex: Female  
Ethnicity: White

Height: 156.5 cm  
Weight: 70.6 kg  
Age: 60

Referring Physician: ROSS



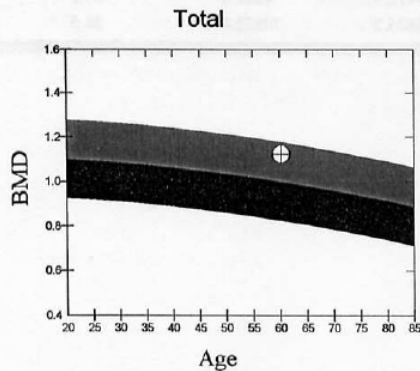
**Scan Information:**

Scan Date: April 13, 2005 ID: [REDACTED]  
Scan Type: a Whole Body  
Analysis: April 15, 2005 11:22 Version 11.2.1  
Whole Body Fan Beam  
Operator: DV  
Model: Delphi A (S/N 70530)  
Comment:

**DXA Results Summary:**

Region	Area (cm <sup>2</sup> )	BMC (g)	BMD (g/cm <sup>2</sup> )	T - Score	Z - Score
L Arm	202.66	146.33	0.722		
R Arm	217.22	160.38	0.738		
L Ribs	94.05	64.62	0.687		
R Ribs	136.15	89.65	0.658		
T Spine	148.35	130.74	0.881		
L Spine	44.07	54.98	1.248		
Pelvis	182.20	265.22	1.456		
L Leg	331.34	375.07	1.132		
R Leg	342.35	392.70	1.147		
Subtotal	1698.39	1679.69	0.989		
Head	216.04	470.99	2.180		
<b>Total</b>	<b>1914.43</b>	<b>2150.68</b>	<b>1.123</b>	<b>0.2</b>	<b>1.4</b>

Total BMD CV 1.0%



Reference curve and scores matched to White Female

Source: Hologic

**Physician's Comment:**

**HOLOGIC**

**KINGSTON GENERAL HOSPITAL**  
**76 STUART ST.**  
**KINGSTON, ONTARIO K7L 2V7**

Telephone: 613-549-6666

Fax: 613-548-2413

Name:   
 Patient ID:   
 DOB: February 16, 1945

Sex: Female  
 Ethnicity: White

Height: 156.5 cm  
 Weight: 69.0 kg  
 Age: 60

**Scan Information:**

Scan Date: October 26, 2005 ID:   
 Scan Type: a Whole Body  
 Analysis: October 26, 2005 08:32 Version 11.2.1  
 Whole Body Fan Beam  
 Operator: bm  
 Model: Delphi A (S/N 70530)  
 Comment:

**DXA Results Summary:**

Region	BMC (g)	Fat (g)	Lean (g)	Lean+BMC (g)	Total Mass (g)	% Fat
L Arm	153.83	1751.4	2562.4	2716.2	4467.6	39.2
R Arm	172.65	1580.3	2690.0	2862.7	4443.0	35.6
Trunk	589.29	11082.8	22997.3	23586.6	34669.4	32.0
L Leg	382.62	4459.1	6066.9	6449.5	10908.6	40.9
R Leg	392.00	4520.0	5899.5	6291.5	10811.5	41.8
Subtotal	1690.39	23393.6	40216.2	41906.6	65300.2	35.8
Head	458.18	829.7	2862.0	3320.2	4149.9	20.0
<b>Total</b>	<b>2148.57</b>	<b>24223.4</b>	<b>43078.2</b>	<b>45226.8</b>	<b>69450.1</b>	<b>34.9</b>

TBAR2649



**KINGSTON GENERAL HOSPITAL**  
76 STUART ST.  
KINGSTON, ONTARIO K7L 2V7

Telephone: 613-549-6666

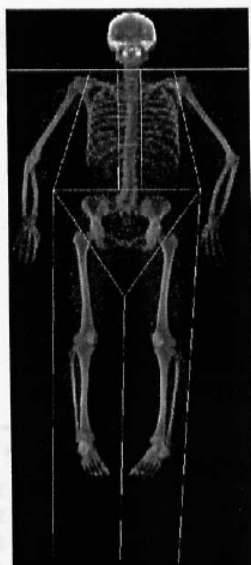
Fax: 613-548-2413

Name: [REDACTED]  
Patient ID: [REDACTED]  
DOB: February 16, 1945

Sex: Female  
Ethnicity: White

Height: 156.5 cm  
Weight: 69.0 kg  
Age: 60

Referring Physician: ROSS



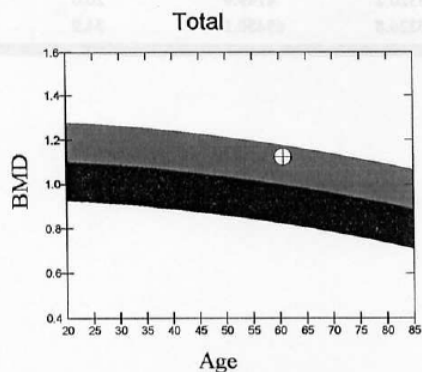
**Scan Information:**

Scan Date: October 26, 2005 ID: [REDACTED]  
Scan Type: a Whole Body  
Analysis: October 26, 2005 08:32 Version 11.2.1  
Whole Body Fan Beam  
Operator: bm  
Model: Delphi A (S/N 70530)  
Comment:

**DXA Results Summary:**

Region	Area (cm <sup>2</sup> )	BMC (g)	BMD (g/cm <sup>3</sup> )	T-Score	Z-Score
L Arm	211.71	153.83	0.727		
R Arm	230.60	172.65	0.749		
L Ribs	93.66	59.82	0.639		
R Ribs	110.18	72.67	0.660		
T Spine	133.40	123.28	0.924		
L Spine	60.99	71.14	1.166		
Pelvis	180.23	262.38	1.456		
L Leg	340.39	382.62	1.124		
R Leg	339.99	392.00	1.153		
Subtotal	1701.14	1690.39	0.994		
Head	212.50	458.18	2.156		
<b>Total</b>	<b>1913.64</b>	<b>2148.57</b>	<b>1.123</b>	<b>0.2</b>	<b>1.4</b>

Total BMD CV 1.0%



Reference curve and scores matched to White Female

Source: Hologic

**Physician's Comment:**

**HOLOGIC**

# *Congratulations*

Jane Doe

On your successful completion of the  
Queen's University Senior Exercise Study

October 2005

*Thank you very much for your participation!*

---

Shelley Atkinson, Research Coordinator

---

Lance Davidson, Doctoral Candidate

## Appendix 28: Results Package Letters for Physicians

Dr. David Hemmings  
464 Princess Street  
Kingston, Ontario  
K7L 1C2

August 13, 2004

Dear Dr. Hemmings:

Thank you for supporting your patient, John Doe, in becoming involved in our Senior Exercise Study at Queens University. John's experience with us has not only made him more aware of his health, but has contributed to a dataset which we hope will further current knowledge regarding the prevention and treatment of obesity and related co-morbidities.

John was randomized into the *control* group of this intervention trial, which required him to *not* change his previous level of physical activity over a 24-week period so that his data could be compared with other seniors randomized into exercise groups. Throughout the study, he maintained a healthy, isocaloric diet with the help of a nutritionist. He successfully completed the trial and has been encouraged to begin an exercise routine so that he may enjoy the health benefits of a physically active lifestyle.

Enclosed is a copy of the results summary given to John upon his completion of the study. In addition, we have included a copy of the results from dual energy x-ray absorptiometry (DEXA) scans performed for the purpose of collecting body composition data. We hope that this information will be useful to you as his primary caregiver.

Your support as a physician and encouragement to become physically fit were essential to John's involvement in our study, and we are grateful for the contribution he has made. If you encounter other seniors under your care who meet the basic criteria for this study and would benefit from becoming physically active, please pass along our contact information. We welcome new participants!

If you have additional questions or comments, please contact Dr. Robert Ross at (613)533-6583 or me at the number below.

Thank you,

Lance E. Davidson  
Doctoral Candidate  
Queens University  
(613)533-6000 ext75118

Dr. Colleen Webster  
312 - 797 Princess Street  
Kingston, Ontario  
K7L 1G1

August 13, 2004

Dear Dr. Webster:

Thank you for supporting your patient, Jane Doe, in becoming involved in our Senior Exercise Study at Queens University. Jane's experience with us has not only made her more aware of her health, but has contributed to a dataset which we hope will further current knowledge regarding the prevention and treatment of obesity and related co-morbidities.

Jane was randomized into the *resistance* exercise group, which required her to complete a circuit of nine resistance exercises in our Queen's laboratory three times per week for approximately 24 weeks. Throughout the intervention, she maintained a healthy, isocaloric diet with the help of a nutritionist. She successfully completed the exercise training and should continue to see health benefits as she strives to maintain a physically active lifestyle.

Enclosed is a copy of the results summary given to Jane upon her completion of the study. In addition, we have included a copy of the results from dual energy x-ray absorptiometry (DEXA) scans performed for the purpose of collecting body composition data. We hope that this information will be useful to you as her primary caregiver.

Your support as a physician and encouragement to become physically fit were essential to Jane's involvement in our study, and we are grateful for the contribution she has made. If you encounter other seniors under your care who meet the basic criteria for this study and would benefit from becoming physically active, please pass along our contact information. We welcome new participants!

If you have additional questions or comments, please contact Dr. Robert Ross at (613)533-6583 or me at the number below.

Thank you,

Lance E. Davidson  
Doctoral Candidate  
Queens University  
(613)533-6000 ext75118

Dr. Trevor Thompson  
945 Gardiners Rd  
Kingston, Ontario  
K7M 7H4

August 13, 2004

Dear Dr. Thompson:

Thank you for supporting your patient, Jane Doe, in becoming involved in our Senior Exercise Study at Queen's University. Jane's experience with us has not only made her more aware of her health, but has contributed to a dataset which we hope will further current knowledge regarding the prevention and treatment of obesity and related co-morbidities.

Jane was randomized into the *aerobic only* exercise group, which required her to perform moderate (about 60-75% of her maximal heart rate for 30-40 min) treadmill exercise in our laboratory at Queen's five times per week for approximately 24 weeks. Throughout the study, she maintained a healthy, isocaloric diet with the help of a nutritionist. She successfully completed the exercise training and should see health benefits as she strives to maintain a physically active lifestyle.

Enclosed is a copy of the results summary given to Jane upon her completion of the study. In addition, we have included a copy of the results from dual energy x-ray absorptiometry (DEXA) scans performed for the purpose of collecting body composition data. We hope that this information will be useful to you as her primary caregiver.

Your support as a physician and encouragement to become physically fit were essential to Jane's involvement in our study, and we are grateful for the contribution she has made. If you encounter other seniors under your care who meet the basic criteria for this study and would benefit from becoming physically active, please pass along our contact information. We welcome new participants!

If you have additional questions or comments, please contact Dr. Robert Ross at (613)533-6583 or me at the number below.

Thank you,

Lance E. Davidson  
Doctoral Candidate  
Queen's University  
(613)533-6000 extension 75118

Dr. William Beck  
125 Lakeview Ave.  
Kingston, Ontario  
K7M 3T6

August 13, 2004

Dear Dr. Beck:

Thank you for supporting your patient, John Doe, in becoming involved in our Senior Exercise Study at Queens University. John's experience with us has not only made him more aware of his health, but has contributed to a dataset which we hope will further current knowledge regarding the prevention and treatment of obesity and related co-morbidities.

John was randomized into the *aerobic and resistance* exercise group, which required him to do moderate (about 60-75% of his maximal heart rate for 30-40 min) treadmill exercise as well as complete a circuit of nine resistance exercises in our Queen's laboratory three times per week for approximately 24 weeks. Throughout the intervention, he maintained a healthy, isocaloric diet with the help of a nutritionist. He successfully completed the exercise training and should continue to see health benefits as he strives to maintain a physically active lifestyle.

Enclosed is a copy of the results summary given to John upon his completion of the study. In addition, we have included a copy of the results from dual energy x-ray absorptiometry (DEXA) scans performed for the purpose of collecting body composition data. We hope that this information will be useful to you as his primary caregiver.

Your support as a physician and encouragement to become physically fit were essential to John's involvement in our study, and we are grateful for the contribution he has made. If you encounter other seniors under your care who meet the basic criteria for this study and would benefit from becoming physically active, please pass along our contact information. We welcome new participants!

If you have additional questions or comments, please contact Dr. Robert Ross at (613)533-6583 or me at the number below.

Thank you,

Lance E. Davidson  
Doctoral Candidate  
Queen's University  
(613)533-6000 extension 75118

## Appendix 29: SAS Code for Intent-to-Treat Analysis

```

PROC IMPORT OUT= WORK.Seniors
            DATATABLE= "Subject Characteristics"
            DBMS=ACCESS REPLACE;
            DATABASE="C:\Documents and Settings\Administrator\My
Documents\Queen's PhD\Senior Study\Seniors Data.mdb";
            SCANMEMO=YES;
            USEDATE=NO;
            SCANTIME=YES;
RUN;

DATA Seniors;
SET Seniors;

*DELETE NEWLY-DIAGNOSED DIABETICS;
  IF ID = 3 THEN DELETE;
  IF ID = 29 THEN DELETE;
  IF ID = 57 THEN DELETE;
  IF ID = 72 THEN DELETE;
  IF ID = 114 THEN DELETE;
  IF ID = 116 THEN DELETE;

*DELETE "Non-randomized";
  IF ID = 63 THEN DELETE;
  IF ID = 80 THEN DELETE;
  IF ID = 109 THEN DELETE;
  IF ID = 140 THEN DELETE;
  IF ID = 32 THEN DELETE;
  IF ID = 58 THEN DELETE;
  IF ID = 112 THEN DELETE;

*SEX and GROUP codes;
  Sexnum = 9;
  IF Sex = 'F' THEN Sexnum = 0;
  IF Sex = 'M' THEN Sexnum = 1;
  GRPnum = 9;
  IF GROUP = 'C' THEN GRPNUM = 0;
  IF GROUP = 'RE' THEN GRPNUM = 1;
  IF GROUP = 'AE' THEN GRPNUM = 2;
  IF GROUP = 'RAE' THEN GRPNUM = 3;

*create body weight change variable;
  Wtc = wk24wt - wk1wt;
RUN;

PROC SORT DATA=Seniors; *Sort by randomized group;
BY Grpnum Sexnum;
RUN;

PROC mi data=Seniors seed=1305417 nimpute=10 out=seniors_mi;
BY Grpnum Sexnum;
VAR wk24wt wk1wt;
RUN;

DATA grpsex31; set seniors; /* Grpnum=3 and Sexnum=1 has 14
  observations with complete data -- excluded in MI */
IF grpnum=3 and sexnum=1; /* Make 10 copies indexed by _Imputation_
  of these 14 observations */

```

```

DO _Imputation_ = 1 to 10;
OUTPUT; END;
RUN;

DATA seniors_mi; set seniors_mi grpsex31; /* combine the imputed data
      with the complete portion of the data */
RUN;

DATA seniors_mi; set seniors_mi;
      * Need to recreate the change for the imputed data;
      Wtc = wk24wt - wk1wt;
RUN;

PROC SORT DATA=seniors_mi; by _Imputation_;
RUN;

      /* Perform 10 ANCOVA for the 10 imputed data sets */
PROC mixed data=seniors_mi; *ANCOVA - controlling for baseline;
BY _Imputation_;
CLASS GRPnum;
MODEL Wtc = GRPnum wk1wt / solution covb;
LSmeans grpnum / adjust=tukey diff;
ODS OUTPUT lsmeans=grp_lsm diffs=grp_diffs;
RUN;

      /*LSmeans with imputed data*/
PROC MIanalyze parms=grp_lsm; by sexnum;
CLASS GRPnum;
MODELEFFECTS GRPnum;
RUN;

      /*Summary of pairwise differences*/
DATA grp_diff; set grp_diffs; /* data set with pairwise LSmean
      differences and SE */
Vari = StdErr*StdErr;
KEEP _Imputation_ GRPNUM _GRPNUM Estimate DF Vari;
RUN;

PROC MEANS DATA=grp_diff n mean var; /* summarize 10 imputations --
      means (variances) of the LSmean differences */
CLASS grpnum _grpnum;
VAR estimate df vari;
OUTPUT OUT=grp_diff2 n=m mean=est edf vi var=estv;
      /* est average parameter estimate (pairwise lsmean difference) */
      /* vi average within imputation variance */
      /* estv between imputation variance */
RUN;

DATA grp_diff2; set grp_diff2;
IF _type_=3; /* Only the pairwise mean differences kept in data set */
t = vi + (1 + 1/m)*estv;
statistic = est/sqrt(t); /* Test statistic for pairwise comparison */
q_stat = sqrt(2)*statistic; /* Tukey's studentized range statistic */
r = ((1+1/m)*estv)/vi; /* relative variance incr due to nonresponse */
vmdf = (m - 1)*(1+1/r)**2;
lambda = (r + 2/(vmdf+3))/(r+1); /* fraction of missing information */
gamma = (1 + 1/m)*estv/t; /* degrees of freedom */

```

```

v0df = (1 - gamma)*edf*(edf+1)/(edf+3);
vmdf1 = 1/(1/vmdf + 1/v0df); /* adjusted degrees of freedom in case r
    is small and vmdf is large */
pvalue1 = min(1, (1 - cdf('T', abs(statistic), vmdf1))*2*6);
    /* 2-tailed bonferroni adjusted for 6 comparisons*/
pvalue2 = 1- probmc("range", abs(q_stat), ., vmdf1, 4);
    /* Tukey's adjusted p-values */
KEEP grpnum _grpnum m est edf vi estv t statistic r vmdf lambda v0df
    vmdf1 pvalue1 pvalue2;
RUN;

PROC PRINT DATA=grp_diff2;
RUN;

```

## Appendix 30: Multiple Imputations Output for Changes in Body Weight

----- GRPnum=1 Sexnum=0 -----

## The MI Procedure

## Model Information

Data Set	WORK.SENIORS
Method	MCMC
Multiple Imputation Chain	Single Chain
Initial Estimates for MCMC	EM Posterior Mode
Start	Starting Value
Prior	Jeffreys
Number of Imputations	10
Number of Burn-in Iterations	200
Number of Iterations	100
Seed for random number generator	1261520860

## Missing Data Patterns

Group	wk24wt	wk1wt	Freq	Percent	-----Group Means-----	
					wk24wt	wk1wt
1	X	X	20	95.24	77.670000	78.725000
2	.	X	1	4.76	.	83.200000

## EM (Posterior Mode) Estimates

_TYPE_	_NAME_	wk24wt	wk1wt
MEAN		77.891438	78.938095
COV	wk24wt	88.393511	82.939321
COV	wk1wt	82.939321	79.814563

## Multiple Imputation Variance Information

Variable	-----Variance-----			DF
	Between	Within	Total	
wk24wt	0.005303	5.047340	5.053173	18.24

## Multiple Imputation Variance Information

Variable	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
wk24wt	0.001156	0.001155	0.999885

----- GRPnum=1 Sexnum=0 -----

## The MI Procedure

## Multiple Imputation Parameter Estimates

Variable	Mean	Std Error	95% Confidence Limits		DF
wk24wt	77.884010	2.247926	73.16574	82.60228	18.24

## Multiple Imputation Parameter Estimates

Variable	Minimum	Maximum	t for H0:		
			Mu0	Mean=Mu0	Pr >  t
wk24wt	77.746028	77.991931	0	34.65	<.0001

----- Imputation Number=1 -----

## The Mixed Procedure

## Solution for Fixed Effects

Effect	GRPnum	Estimate	Standard Error	DF	t Value	Pr >  t
Intercept		-2.5695	1.0999	131	-2.34	0.0210
GRPnum	0	2.7134	0.4712	131	5.76	<.0001
GRPnum	1	1.6011	0.4409	131	3.63	0.0004
GRPnum	2	-0.4336	0.4378	131	-0.99	0.3239
GRPnum	3	0	.	.	.	.
wk1wt		0.002187	0.01242	131	0.18	0.8605

## Covariance Matrix for Fixed Effects

Row	Effect	GRPnum	Col1	Col2	Col3	Col4	Col5	Col6
1	Intercept		1.2098	-0.07883	-0.08708	-0.09757		-0.01309
2	GRPnum	0	-0.07883	0.2220	0.09872	0.09853		-0.00023
3	GRPnum	1	-0.08708	0.09872	0.1944	0.09852		-0.00013
4	GRPnum	2	-0.09757	0.09853	0.09852	0.1917		-0.00001
5	GRPnum	3						
6	wk1wt		-0.01309	-0.00023	-0.00013	-0.00001		0.000154

## Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
GRPnum	3	131	19.66	<.0001
wk1wt	1	131	0.03	0.8605

## Least Squares Means

Effect	GRPnum	Estimate	Standard Error	DF	t Value	Pr >  t
GRPnum	0	0.3307	0.3511	131	0.94	0.3480
GRPnum	1	-0.7815	0.3095	131	-2.53	0.0128
GRPnum	2	-2.8162	0.3053	131	-9.22	<.0001
GRPnum	3	-2.3826	0.3139	131	-7.59	<.0001

----- Imputation Number=1 -----

## The Mixed Procedure

## Differences of Least Squares Means

Effect	GRPnum	_GRPnum	Estimate	Standard Error	DF	t Value	Pr >  t	Adjustment	Adj P
GRPnum	0	1	1.1123	0.4680	131	2.38	0.0189	Tukey-Kramer	0.0866
GRPnum	0	2	3.1469	0.4655	131	6.76	<.0001	Tukey-Kramer	<.0001
GRPnum	0	3	2.7134	0.4712	131	5.76	<.0001	Tukey-Kramer	<.0001
GRPnum	1	2	2.0347	0.4348	131	4.68	<.0001	Tukey-Kramer	<.0001
GRPnum	1	3	1.6011	0.4409	131	3.63	0.0004	Tukey-Kramer	0.0023
GRPnum	2	3	-0.4336	0.4378	131	-0.99	0.3239	Tukey-Kramer	0.7552

## The MIANALYZE Procedure

## Model Information

PARMS Data Set WORK.GRP\_LSM  
 Number of Imputations 10

## Multiple Imputation Variance Information

Parameter	GRPnum	-----Variance-----			DF
		Between	Within	Total	
GRPnum	0	0.005803	0.130747	0.137130	4153.4
GRPnum	1.000000	0.029603	0.101595	0.134158	152.77
GRPnum	2.000000	0.006022	0.098872	0.105497	2282.6
GRPnum	3.000000	0.005060	0.104532	0.110098	3521.6

## Multiple Imputation Variance Information

Parameter	GRPnum	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
GRPnum	0	0.048823	0.047009	0.995321
GRPnum	1.000000	0.320518	0.252445	0.975377
GRPnum	2.000000	0.066999	0.063612	0.993679
GRPnum	3.000000	0.053245	0.051092	0.994917

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	Estimate	Std Error	95% Confidence Limits		DF
GRPnum	0	0.280685	0.370311	-0.44532	1.00669	4153.4

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	Minimum	Maximum
GRPnum	0	0.185363	0.387468

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	t for H0:		
		Theta0	Parameter=Theta0	Pr >  t
GRPnum	0	0	0.76	0.4485

## The MIANALYZE Procedure

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	Estimate	Std Error	95% Confidence Limits		DF
GRPnum	1.000000	-0.644884	0.366275	-1.36850	0.07874	152.77
GRPnum	2.000000	-2.752293	0.324802	-3.38923	-2.11535	2282.6
GRPnum	3.000000	-2.324532	0.331810	-2.97509	-1.67397	3521.6

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	Minimum	Maximum
GRPnum	1.000000	-0.970474	-0.438463
GRPnum	2.000000	-2.875482	-2.640898
GRPnum	3.000000	-2.446468	-2.219368

## Multiple Imputation Parameter Estimates

Parameter	GRPnum	Theta0	t for H0:	
			Parameter=Theta0	Pr >  t
GRPnum	1.000000	0	-1.76	0.0803
GRPnum	2.000000	0	-8.47	<.0001
GRPnum	3.000000	0	-7.01	<.0001

## The MEANS Procedure

GRPnum	_GRPnum	N	Variable	N	Mean	Variance
0	1	10	Estimate	10	0.9255684	0.0468495
			DF	10	131.0000000	0
			Vari	10	0.2322449	0.000562820
	2	10	Estimate	10	3.0329782	0.0101547
			DF	10	131.0000000	0
			Vari	10	0.2297699	0.000550888
	3	10	Estimate	10	2.6052162	0.0100214
			DF	10	131.0000000	0
			Vari	10	0.2354520	0.000578472
1	2	10	Estimate	10	2.1074098	0.0408193
			DF	10	131.0000000	0
			Vari	10	0.2005170	0.000419546
	3	10	Estimate	10	1.6796478	0.0295065
			DF	10	131.0000000	0
			Vari	10	0.2061843	0.000443597
2	3	10	Estimate	10	-0.4277620	0.0088933
			DF	10	131.0000000	0
			Vari	10	0.2033151	0.000431337

Obs	GRPnum	_GRPnum	m	est	edf	vi	estv	t	statistic
1	0	1	10	0.9256	131	0.23224	0.046850	0.28378	1.73747
2	0	2	10	3.0330	131	0.22977	0.010155	0.24094	6.17895
3	0	3	10	2.6052	131	0.23545	0.010021	0.24648	5.24755
4	1	2	10	2.1074	131	0.20052	0.040819	0.24542	4.25398
5	1	3	10	1.6796	131	0.20618	0.029506	0.23864	3.43831
6	2	3	10	-0.4278	131	0.20332	0.008893	0.21310	-0.92664

Obs	r	vmdf	lambda	v0df	vmdf1	pvalue1	pvalue2
1	0.22190	272.90	0.18753	105.610	76.144	0.51808	0.31173
2	0.04861	4187.36	0.04682	123.062	119.549	0.00000	0.00000
3	0.04682	4499.36	0.04515	123.273	119.986	0.00000	0.00000
4	0.22393	268.87	0.18897	105.435	75.736	0.00036	0.00034
5	0.15742	486.53	0.13954	111.494	90.707	0.00532	0.00483
6	0.04812	4270.58	0.04635	123.121	119.671	2.13586	0.79064

#### 7.2.0. Associated Appendix: Liver Fat Methodology Paper



## Protocol for measurement of liver fat by computed tomography

Lance E. Davidson,<sup>1</sup> Jennifer L. Kuk,<sup>1</sup> Timothy S. Church,<sup>3</sup> and Robert Ross<sup>1,2</sup>

<sup>1</sup>School of Physical and Health Education and <sup>2</sup>Division of Endocrinology and Metabolism, Department of Medicine, Queen's University, Kingston, Ontario, Canada; and <sup>3</sup>Centers for Integrated Health Research, The Cooper Institute, Dallas, Texas

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Davidson, Lance E., Jennifer L. Kuk, Timothy S. Church, and Robert Ross. Protocol for measurement of liver fat by computed tomography. *J Appl Physiol* 100: 864–868, 2006. First published November 17, 2005; doi:10.1152/jappphysiol.00986.2005.—To develop a protocol for measurement of liver fat using computed tomography (CT), we conducted a preliminary study with 118 men and 76 women to determine a readily identifiable vertebral landmark at which the CT image displayed both liver and spleen. Analysis of five landmarks revealed that the CT image obtained at the T<sub>12</sub>–L<sub>1</sub> level simultaneously displayed the liver and spleen in 90% of the men and women. The T<sub>12</sub>–L<sub>1</sub> protocol was cross-validated on a sample of 130 men and 113 women. In this sample, we also assessed the regional characteristics of liver and spleen tissue attenuation at the T<sub>12</sub>–L<sub>1</sub> level by subdividing each image into quartiles from anterior to posterior, each of which were further divided into medial and lateral regions. A similar analysis was performed on images located 12 mm above and below T<sub>12</sub>–L<sub>1</sub>. The T<sub>12</sub>–L<sub>1</sub> image displayed both liver and spleen in 92% (403 of 437) of the combined study sample. There was a significant ( $P < 0.005$ ) stepwise increase in attenuation values [Hounsfield units (HU)] from the inferior to superior image. Although some significant ( $P < 0.05$ ) differences were observed between the eight regions by comparison to the whole liver or spleen, the average magnitude of the difference was  $<2.0$  HU for liver and  $<3.5$  HU for spleen. Acquisition of a single CT image at the T<sub>12</sub>–L<sub>1</sub> level is a practical and reliable method for routine measurement of liver fat in research and clinical settings.

liver attenuation; spleen; fatty liver; hepatic steatosis

EMERGING EVIDENCE SUGGESTS that excess deposition of lipid in the liver may act as an “ectopic” site of fat distribution that independently predicts insulin resistance (18) and dyslipidemia (1, 11). The prevalence of excess liver fat or “fatty liver” approximates 34% in the general population (17) and 48% in obese cohorts (2). These observations underscore the importance of liver fat measurement in studies that seek to understand the health implications of complex obesity phenotypes. Although liver biopsy is often considered the gold standard for measurement of liver fat, it can be painful (5) and has notable mortality risk (6). Proton magnetic resonance spectroscopy is noninvasive and offers researchers a reliable tool for measuring liver fat in vivo. However, application of magnetic resonance spectroscopy requires exceptional technical expertise and is restricted to liver fat measures in specified regions of interest. Radiological imaging techniques such as computed tomography (CT) are obtained routinely in clinical settings, are easily interpreted without need for sophisticated image-analysis software, and provide estimates of liver fat that correlate well with needle biopsy, especially in subjects with increased liver fat (16). On the other hand, CT employs ionizing radiation, and

thus protocols need to be developed that measure the tissues of interest and limit exposure.

The identification of liver fat by CT as a predictor of health risk was first described by Banerji et al. (1) and Goto et al. (7) in 1995. The CT method employed realizes that the lower the mean liver attenuation or CT number in Hounsfield units (HU), the lower the tissue density and hence the greater the fat content. Therefore, liver density (e.g., attenuation in HUs) is inversely related to liver fat and thus is a surrogate for it (15). However, although extremely low HU values have been measured in livers infiltrated with fat, an overlap exists between normal and abnormal liver HU values (13). Therefore, the absolute liver density determined by CT may not be sensitive for predicting abnormal liver fat content. Because a constant relationship exists between liver and spleen attenuation in individuals with normal livers, the ratio of mean liver to spleen attenuation values is used as an index of liver fat, as originally described by Piekarski et al. (14) in 1980. Obtaining a CT image that contains both liver and spleen presents a challenge; variations exist not only in the vertical positioning of the spleen relative to the liver but also in positioning of both organs within the abdominal cavity. A multi-image approach is not feasible because of excess exposure (8). This implicates a single CT image approach; however, a single-image protocol at the level of the abdomen that routinely identifies the liver and spleen has yet to be firmly established. Furthermore, once obtained, it is important to determine whether the distribution of fat throughout the liver is uniform: an observation with direct implications for those that determine liver fat by measuring only small portions or regions of interest of the liver on the CT image (e.g., biopsy, magnetic resonance spectroscopy, and CT).

The aim of this study was twofold: first, to determine an optimal location for simultaneous imaging of both liver and spleen, and second, to document liver and spleen attenuation characteristics and determine whether variation exists, and if so, whether it is of a magnitude that should alter the protocol employed to measure liver fat.

### METHODS

**Subject testing.** Subjects were men and women who underwent a medical examination at the Cooper Institute in Dallas, TX, between 1995 and 2001. Although race data for all subjects was unavailable, ~98% of attendees at the Cooper Institute during this time were Caucasian. None of the subjects were smokers or had a history of diabetes mellitus, cardiovascular disease, stroke, or cancer. All gave informed consent before participation in the examination according to the ethical guidelines of The Cooper Institute Institutional Review Board. Medical examinations included an abdominal CT scan, comprising 40 contiguous images with 6-mm thickness, from at least T<sub>11</sub>

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Table 1. Presentation of liver and spleen on five CT images obtained at selected vertebral landmarks

Vertebral Landmark	Men (n = 118)			Women (n = 76)		
	Liver	Spleen	%*	Liver	Spleen	%*
T <sub>11</sub> -T <sub>12</sub>	118	102	86	76	43	57
T <sub>12</sub>	118	114	97	76	64	84
T <sub>12</sub> -L <sub>1</sub>	118	106	90	76	67	88
L <sub>1</sub>	118	95	81	76	56	74
L <sub>1</sub> -L <sub>2</sub>	118	73	62	76	35	46

n, No. of subjects; CT, computed tomography. \*Percentage of subjects in whom both liver and spleen were seen on the same image.

through L<sub>5</sub>, including all or most of the liver. CT images were obtained using an electron-beam CT scanner (Imatron, General Electric, Milwaukee, WI). The image-acquisition protocol used 130 kV and 630 mA with a 48-cm field of view and a 512 × 512 matrix. The full abdominal scan results in a patient radiation exposure of ~640 mrem. Body weight and height were measured using a standard physician's scale and stadiometer, and body mass index (BMI) was calculated using the weight in kilograms divided by the height in meters squared. Waist circumference was measured at the level of the umbilicus using a plastic tape measure.

**Determination of optimal image location.** A preliminary investigation was undertaken to determine the location of an easily identifiable, single axial image that would most frequently provide simultaneous visualization of liver and spleen. Axial images at the intervertebral spaces and the midpoints of the vertebral bodies within the region of T<sub>11</sub>-T<sub>12</sub> and L<sub>1</sub>-L<sub>2</sub> were visually inspected for the presence or absence of liver and spleen in a sample of 118 male and 76 female subjects (Table 1).

**Cross-validation of optimal image location.** Our initial analysis revealed that the image at T<sub>12</sub>-L<sub>1</sub> provided optimal results for our sample of men and women (see RESULTS). We cross-validated our initial observation using the T<sub>12</sub>-L<sub>1</sub> intervertebral space as a landmark for imaging liver and spleen in a second sample of 130 men and 113 women. Acknowledging the possibility for slight deviations in identifying the T<sub>12</sub>-L<sub>1</sub> intervertebral space, we analyzed the CT image 12 mm superior and 12 mm inferior to T<sub>12</sub>-L<sub>1</sub> to observe whether "missing" slightly above or below the target landmark had an effect on the frequency of successfully imaging both liver and spleen.

**Effect of image level on liver and spleen attenuation.** On the cross-validation sample of 130 men and 113 women, the three images identified at T<sub>12</sub>-L<sub>1</sub>, 12 mm superior, and 12 mm inferior were analyzed for liver and spleen attenuation characteristics using specialized image-analysis software (Tomovision, Montreal, Canada). Lines

were manually drawn around the perimeter of the liver and spleen on each image to calculate the mean HU value for each organ. Mean HU values were obtained at each level to compare the differences in attenuation that might occur with subtle differences in locating T<sub>12</sub>-L<sub>1</sub>.

**Regional variation in tissue attenuation.** We sought to further investigate liver and spleen tissue attenuation characteristics by dividing the liver and spleen at the T<sub>12</sub>-L<sub>1</sub> level into quartiles from anterior to posterior, and then subdividing each of the quartiles into medial and lateral regions, as depicted in Fig. 1. Our primary purpose in subdividing the images into these eight regions was to map regional variation in liver and spleen attenuation so that a recommendation could be made as to whether one region or another better represented the whole, and thus it be a better-suited location for placement of a region of interest when assessing liver fat by CT. The images 12 mm superior and 12 mm inferior to T<sub>12</sub>-L<sub>1</sub> were analyzed in a similar fashion to determine whether attenuation patterning differed in regions slightly above or below the targeted image.

**Reliability in image analysis.** Two analyzers performed blinded assessments of the mean liver and spleen attenuation in 48 subjects (24 men and 24 women), chosen randomly from the 243 subjects used in the cross-validation analysis. The subjects varied widely in age [46.5 yr (SD 7.3)], body mass index [26.8 kg/m<sup>2</sup> (SD 5.2)], and waist circumference [89.1 cm (SD 17.0)] in a manner similar to the original sample. Interobserver coefficients of variation for liver and spleen attenuation (HU) were 2.9% (1.6 HU) and 4.8% (2.3 HU), respectively.

**Statistical analyses.** Data are presented as means (SD). Independent *t*-tests were used to assess gender differences. Univariate general linear modeling with repeated measures was used to determine the effect of landmarking on mean liver and spleen attenuation and to determine regional variation in organ attenuation compared with the whole. Bonferroni adjustment was used post hoc to correct for the multiple comparisons. Logistic regression was used to determine whether variance in anthropometric measures could explain potential differences in optimal image location. All statistical procedures were performed using SPSS version 12.0 (SPSS, Chicago, IL).

## RESULTS

**Optimal image location.** Our preliminary investigation sought to determine a level most likely to contain a cross section of both liver and spleen in 118 men and 76 women [age: men 52.9 yr (SD 9.0); women 59.9 yr (SD 10.6), BMI: men 27.8 kg/m<sup>2</sup> (3.3); women 24.5 kg/m<sup>2</sup> (SD 4.9)]. Frequency of appearance of liver and spleen at each of the selected vertebral landmarks is summarized in Table 1. The liver, being a much larger organ than the spleen, is seen at each of the

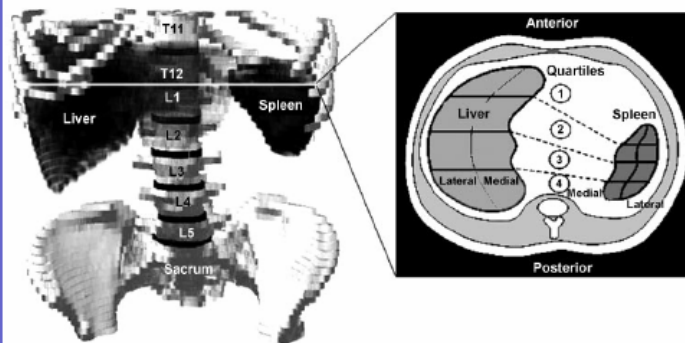

 Fig. 1. Identification of 8 regions in liver and spleen at T<sub>12</sub>-L<sub>1</sub>.

Table 2. Characteristics of cross-validation sample subjects

	Men (n = 130)		Women (n = 113)	
	Mean (SD)	Range	Mean (SD)	Range
Age, yr	51.3 (8.4)	22.0–76.0	40.9 (4.2)*	27.0–46.0
Weight, kg	88.0 (12.3)	60.7–124.3	65.1 (12.4)*	45.2–108.2
BMI, kg/m <sup>2</sup>	26.8 (3.2)	21.5–37.5	23.6 (4.3)*	18.6–38.1
Waist circumference, cm	94.8 (9.9)	74.0–123.0	74.5 (10.0)*	61.0–103.0
Visceral adipose tissue (L <sub>4</sub> –L <sub>5</sub> ), cm <sup>2</sup>	147.4 (63.7)	20.0–388.0	61.2 (40.8)*	8.0–182.0
Mean liver attenuation, HU	61.2 (9.6)	29.0–78.2	60.5 (5.3)	46.4–73.6
Liver-to-spleen ratio	1.24 (0.16)	0.73–1.79	1.19 (0.13)*	0.88–1.79

n, No. of subjects; BMI, body mass index; HU, Hounsfield units. \*Significantly different from men,  $P < 0.05$ .

vertebral landmarks in all 194 subjects. The lower appearance rate of the spleen at a given landmark reflects its smaller size and variable location between subjects. A higher percent score indicates an increase in likelihood that both liver and spleen are visible at a given landmark.

The two landmarks with the highest percentage of liver and spleen appearance were the midpoint of T<sub>12</sub> and the T<sub>12</sub>–L<sub>1</sub> intervertebral space. Because appearance rates were comparable in men and women at both sites, and because an intervertebral space is more readily identified than the midpoint of a vertebral body, the T<sub>12</sub>–L<sub>1</sub> intervertebral space was selected as the landmark for subsequent analyses.

**Cross-validation of optimal image location.** A separate sample of 130 men and 113 women, for which scans of the entire liver were available, was selected from a larger database. There was a relatively wide range of age and obesity in the sample selected, and the men differed from the women for most variables (Table 2).

Similar to the preliminary sample, liver was present in all three images for all cross-validation subjects. Both liver and spleen were visible at the T<sub>12</sub>–L<sub>1</sub> intervertebral space in 94% (122 of 130) of men and 96% (108 of 113) of women. For the image 12 mm superior to T<sub>12</sub>–L<sub>1</sub>, liver and spleen were observed in 94% of subjects independent of sex; the image 12 mm inferior contained both liver and spleen in 88 and 92% of men and women, respectively. Consideration of the influence of age, BMI, and visceral adiposity on the identification of the optimal image location revealed that BMI was the only variable with an independent influence ( $P < 0.05$ ) on the subtle differences observed in men and women. A BMI  $>25.0$  kg/m<sup>2</sup> in our cross-validation sample resulted in a reduction of simultaneous liver and spleen imaging from 98 to 91% in men and from 97 to 91% in women at the T<sub>12</sub>–L<sub>1</sub> landmark. For all subjects combined ( $n = 437$ ), liver and spleen were visible for 403 (or 92%) at the T<sub>12</sub>–L<sub>1</sub> level.

**Effect of image level on liver and spleen attenuation.** Mean attenuation values (e.g., HU) from liver and spleen derived from the three images analyzed in the cross-validation sample were compared to observe any differences that may be a function of obtaining an image slightly above or below the T<sub>12</sub>–L<sub>1</sub> level. A consistent, stepwise increase in tissue density of both liver and spleen was evident from the image 12 mm inferior to T<sub>12</sub>–L<sub>1</sub>, and then from T<sub>12</sub>–L<sub>1</sub> to the image 12 mm superior (Fig. 2). The increases from level to level were statistically significant ( $P < 0.001$ ) independent of sex, and they were an average magnitude of 1.5 HU (2.5%) in liver and 2.0 HU (3.9%) in spleen.

**Regional variation in tissue attenuation.** Characteristics of tissue attenuation throughout liver and spleen were assessed by subdividing the T<sub>12</sub>–L<sub>1</sub> image into eight regions (See Fig. 1) and then comparing each region to the HU of the entire liver or spleen image. Mean attenuation values for medial and lateral quartiles of liver and spleen at T<sub>12</sub>–L<sub>1</sub> are shown in Fig. 3.

The first quartiles (or anterior regions) of both liver and spleen consistently displayed attenuation values that were significantly lower than the whole on each image. In men, the medial liver regions of the second and third quartiles had increased HU values by comparison to the whole, whereas the lateral regions did not. In women, the liver attenuation was higher in both medial and lateral portions of the third and fourth quartiles, indicating a general increase in attenuation from anterior to posterior liver. In both men and women, the medial spleen was associated with decreased attenuation compared with the lateral regions. The average absolute difference of regional attenuation scores from whole liver and spleen was 1.8 HU (2.9%) and 3.4 HU (6.6%), respectively.

For the images 12 mm above and below the T<sub>12</sub>–L<sub>1</sub> level, with few exceptions, the pattern of attenuation for the respective regions mirrored those of T<sub>12</sub>–L<sub>1</sub> in relation to the whole (data not shown).

## DISCUSSION

The primary finding was that a single CT-measured image obtained at the level of the T<sub>12</sub>–L<sub>1</sub> intervertebral space identified the liver and spleen in 92% (403 of 437) of the men and

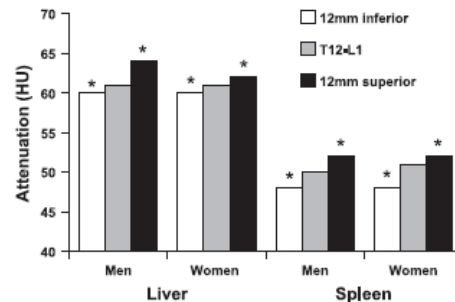


Fig. 2. Mean attenuation values for liver and spleen images obtained at 12 mm superior and inferior to T<sub>12</sub>–L<sub>1</sub>. HU, Hounsfield units. \*Significantly different from the mean attenuation at T<sub>12</sub>–L<sub>1</sub>,  $P < 0.005$ .

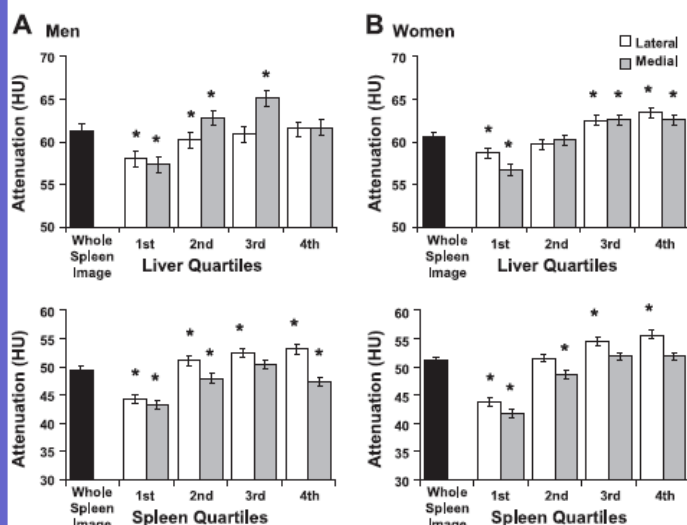


Fig. 3. Mean (SD) attenuation of liver and spleen by region in men (A) and women (B). \*Significant regional differences from the whole liver and spleen image,  $P < 0.05$ .

women studied. Furthermore, we observed that the attenuation or liver fat score was relatively homogeneous, implying that little variability exists in the deposition of fat throughout the  $T_{12}$ - $L_1$  image. These observations suggest that the use of a CT protocol that includes a low-dose vertebral scout for location of the  $T_{12}$ - $L_1$  intervertebral space, followed by acquisition of a single image at  $T_{12}$ - $L_1$ , is a practical, reliable method for routine measurement of liver fat in research and clinical settings.

The accuracy of CT to estimate liver fat in vivo by comparison to histological determination of fat from liver biopsies was first described in the early 1980s (3, 4). In those studies, the CT number (attenuation values in HUs) was a strong, inverse correlate of liver fat from biopsy samples. However, because an overlap exists between normal and abnormal liver HU values (13), the absolute liver density determined by CT may not be sensitive for predicting abnormal liver fat content. Because a constant relationship exists between liver and spleen attenuation in individuals with normal livers, it was shown that the ratio of mean liver to spleen attenuation values provides a useful index of liver fat (14). Simultaneous measurement of liver and spleen attenuation to characterize liver fat in obesity was first reported by Goto et al. (7) in a study wherein the difference in the ratio of liver to spleen attenuation values were reported to be associated with insulin clearance and insulin sensitivity. A limitation of this study is that the authors did not clearly identify the landmark employed for acquisition of the CT image. That we observed a stepwise increase in both liver and spleen attenuation values from the images acquired 12 mm inferior and superior to  $T_{12}$ - $L_1$  underscores the importance of proper landmarking to avoid differences in attenuation attributable to positioning error. Recently, Kelley et al. (9) used  $T_{11}$ - $T_{12}$  as a landmark for imaging liver and spleen in men and women with Type 2 diabetes mellitus. In that study, the authors

did not report the frequency for which the liver and spleen were observed nor whether any gender difference existed. The results of our study confirm that  $T_{11}$ - $T_{12}$  is a useful landmark in men. In women, however, the ability of the image at  $T_{11}$ - $T_{12}$  to identify the liver and spleen was substantially less by comparison to  $T_{12}$ - $L_1$ . Hence, our recommendation is that a single axial CT image at the  $T_{12}$ - $L_1$  level is extremely useful for simultaneous identification of liver and spleen for both men and women with wide variation in age, visceral adiposity, and obesity. However, it is noteworthy that, while neither age nor visceral adiposity had any effect on liver and spleen appearance within the  $T_{12}$ - $L_1$  image, subjects with an elevated BMI had a slightly lower success rate at that level. This point may be important for future studies to consider, especially when acquiring images in a morbidly obese sample of men and women. Because our sample contained relatively few subjects with a BMI in excess of  $35 \text{ kg/m}^2$ , further research is required to establish whether  $T_{12}$ - $L_1$  remains the optimal location in these individuals.

The region-by-region analysis of liver and spleen performed in this study sheds light on patterning of tissue attenuation in both organs. To our knowledge, this is the first study to employ a systematic sampling of liver and spleen that includes a comparison from medial to lateral, quartiles from anterior to posterior, and replication of these regions on images above and below to identify attenuation patterning in liver and spleen. Our objective in characterizing these regions was to identify specific areas of the liver and spleen that may best represent the whole image so that optimal locations for regions of interest could be recommended. However, although many of the regions varied statistically from the mean attenuation of the whole liver image, the magnitude was on average  $<2.0$  HU. From a clinical perspective, this is a minor variation in light of reports suggesting that a 14-HU increase in liver attenuation is

observed as a consequence of a modest 6% reduction in body weight (12). Furthermore, our findings suggest that methodologies that measure liver fat by assessment of regions of interest, including biopsy and magnetic resonance spectroscopy, need not be particular with respect to placement of the regions of interest, provided there is consistency in placement for serial measurements. Accordingly, with CT, it seems reasonable to recommend that the index of liver and spleen attenuation be derived from a mean score of the entire image. This would avoid potential bias introduced by variable placement of a region of interest and would gain the advantage of a much larger sample of tissue for estimating liver fat.

It is also important to note that with CT attenuation alone it is not possible to quantify liver fat. Because the molecular composition of lipid, water, and lean tissue within each voxel influences the resulting attenuation value, small variations in one may mask changes in the other. For example, it is entirely possible that elevations in the water component of a voxel may alter (increase) the measured attenuation, leading to the erroneous conclusion that the absolute lipid content was altered (decreased). This represents a challenge to the researcher when trying to interpret subtle changes in attenuation that may result from a given perturbation.

The findings of our study extend current knowledge with respect to CT-measured tissue characteristics of the liver and spleen and offers evidence for the improvement of methodology in CT image acquisition. Indeed, that the attenuation values within the liver are relatively homogeneous lends support to protocols that acquire liver fat measures within only a small region of interest. Furthermore, our results provide a compelling argument for the use of a single CT image at T<sub>12</sub>-L<sub>1</sub> as a practical, reliable method for routine measurement of liver fat in research and clinical settings.

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### 7.3.0. List of Publications and Abstracts

## PEER-REVIEWED MANUSCRIPTS

Kuk JL, **Davidson LE**, Hudson R, Kilpatrick K, and Ross R. "Effect of dietary fat intake on the relationship between liver fat and insulin sensitivity in sedentary, abdominally obese older men" Submitted to *Appl Physiol Nutr Metab*, 2007.

Kilpatrick K, Kuk JL, Davidson LE, Hudson R, Ross R. "Skeletal muscle mass is not related to glucose tolerance or insulin sensitivity in overweight and obese men and women" In press at *Med Sci Sports Exer*, 2007.

**Davidson LE**, Kuk JL, Church T, and Ross R. "Measurement of liver fat by computed tomography" *J Appl Physiol*. 100(3):864-8, 2006.

Lee SJ, Kuk JL, **Davidson LE**, Hudson R, Kilpatrick K, Graham TE, and Ross R. "Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes" *J Appl Physiol*. 99(3):1220-1225, 2005.

## PEER-REVIEWED PRESENTATIONS

**Davidson LE**, Kuk JL, McMillan K, Janiszewski P, Hudson R, Kilpatrick K, Ross R. "Influence of Exercise Modality on Skeletal Muscle, Fat, and Functional Fitness in Older Men and Women: A Randomized Controlled Trial" CSEP Conference, Toronto, Ontario, November 2007.

**Davidson LE**, Kuk JL, Ross R. "Morphologic and Metabolic Adaptations to Resistance and/or Aerobic Exercise in Abdominally Obese Older Men and Women: A Randomized Controlled Trial" NAASO Conference, New Orleans, LA, October 2007.

**Davidson LE**, Kuk JL, Hudson R, Kilpatrick K, and Ross R. "Effect of dietary fat intake on the relationship between liver fat and insulin sensitivity in sedentary, abdominally obese older men" NAASO Conference, Boston, MA, October 2006  
Published abstract: *Obesity Research*, 14:A147, 2006.

**Davidson LE**, Hudson R, Kilpatrick K, Ross R. "Novel assessment of hepatic steatosis by computed tomography" CSEP Conference, Ottawa, Ontario, October 2005.  
Published Abstract: *Can J Appl Physiol*, 30:S20, 2005.

**Davidson LE**, Kuk JL, Ross R. "Independent relationships among abdominal adipose depots, liver fat, cardiorespiratory fitness, and insulin resistance in abdominally obese older men and women" NAASO Conference, Vancouver, BC, October 2005.  
Published Abstract: *Obesity Research*, 13:A126, 2005.

**Davidson LE**, Kuk JL, Ross R. "Liver volume as a marker of hepatic fat in men" NAASO Conference, Las Vegas, NV, October 2004.  
Published Abstract: *Obesity Research*, 12:A137, 2004.

**Davidson LE**, Janssen I, Hudson R, Kilpatrick K, Ross R. "Insulin resistance corresponds to obesity rather than aging in women" OEP Conference, Barry, Ontario, January 2004.

Watts M, **Davidson LE**, Lee SJ, Hudson R, Kilpatrick K, Ross R. "Abdominal adiposity, skeletal muscle composition, liver fat and insulin resistance in obese men" OEP Conference, Barry, Ontario, January 2004.

**Davidson LE**, Janssen I, Hudson R, Kilpatrick K, Ross R. "Age-related reduction in glucose uptake is explained by corresponding increase in obesity, not aging per se" CSEP Conference, Niagara-on-the-Lake, Ontario, October 2003.  
Published Abstract: Canadian Journal of Applied Physiology, Z8:S45, 2003.

**Davidson LE**, Peterson T, Tucker L. "Television viewing habits and measured cardiorespiratory fitness in 277 women" National ACSM Conference, St. Louis, MO, May 2002.  
Published Abstract: Medicine and Science in Sports and Exercise, 34(5):S66, 2002

**Davidson LE**, Peterson T, Bailey B, LeCheminant J, Tucker L. "Objectively measured changes in physical activity predict changes in abdominal fat: a prospective 20-month study" NAASO Conference, Quebec City, October 2001.  
Published Abstract: Obesity Research, 9(Suppl 3): 2001.

## **BOOK CHAPTERS**

Kuk JL, Saunders TJ, **Davidson LE**, Ross R. "Age-related Changes in Total and Regional Fat Distribution" in Aging and Human Body Composition: Medical Measurement and Therapeutic Applications. *Humana Press*, 2007.