The role of cardiorespiratory fitness and the effectiveness of exercise in altering visceral adipose tissue and cardio-metabolic risk factors in post-menopausal South Asian women

by

Iris Aline Lesser

M.Sc., University of Alberta, 2010
B.Sc., Dalhousie University, 2008

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Name: **Iris Aline Lesser**

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Title: ***The role of cardiorespiratory fitness and the effectiveness of exercise in altering visceral adipose tissue and cardio-metabolic risk factors in post-menopausal South Asian women***

Examining Committee: **Chair:** Miriam Rosin
Professor

Scott Lear
Senior Supervisor
Professor

Dawn Mackey
Supervisor
Assistant Professor

Peter Katzmarzyk
Supervisor
Professor
Pennington Biomedical Research Center

David Clarke
Internal Examiner
Assistant Professor

Robert Ross
External Examiner
Professor
Department of Kinesiology
Queens University

Date Defended/Approved: November 20, 2015

Ethics Statement

SFU

The author, whose name appears on the title page of this work, has obtained, for the research described in this work, either:

a. human research ethics approval from the Simon Fraser University Office of Research Ethics,

or

b. advance approval of the animal care protocol from the University Animal Care Committee of Simon Fraser University;

or has conducted the research

c. as a co-investigator, collaborator or research assistant in a research project approved in advance,

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Abstract

Background: South Asians have higher rates of type 2 Diabetes and cardiovascular disease (CVD) than Europeans with earlier disease onset. South Asians have been shown to have a unique obesity phenotype of greater visceral adipose tissue (VAT) at a given body size which may explain the higher cardio-metabolic risk factors compared to Europeans. Exercise has been shown to reduce VAT in Europeans but it is unknown if it is also effective in South Asians given their unique obesity phenotype.

Objectives: The objectives of this thesis were threefold; 1) to explore the association between cardiorespiratory fitness (CRF) and VAT; 2) to assess the role of standard exercise and Bhangra dance in altering VAT and 3) to assess the association between exercise-induced change in VAT and change in cardio-metabolic risk in post-menopausal South Asian women.

Methods: Multi-slice computed tomography was used to assess VAT, aerobic fitness via metabolic testing and cardio-metabolic risk factors through a 12-hour fasting sample. Seventy-five post-menopausal South Asian women were randomized into either three weekly sessions for 12-weeks of standard exercise, Bhangra dance or a non-exercise control group. One-way ANOVA was used to compare VAT across tertiles of CRF. General linear models were used to assess whether VAT was reduced in exercise compared to the referent control group. Bivariate correlations were used to assess the associations between change in VAT with change in cardio-metabolic risk factors.

Results: Physically inactive post-menopausal South Asian women with higher levels of CRF were shown to have lower levels of VAT. There was a non-significant reduction in VAT after 12-weeks of aerobic exercise compared to the referent control group while the Bhangra dance group exhibited a significant improvement in CRF. The change in VAT was significantly associated with change in markers of glucose regulation.

Discussion: Cardiorespiratory fitness is associated with VAT; however, a 12-week aerobic exercise program did not significantly reduce VAT in South Asian women. Nevertheless, those who reduced VAT saw improvements in cardio-metabolic risk factors. There may be a South Asian VAT “resistant” phenotype; however, Bhangra dance appears to be an effective physical activity option for increasing CRF.

Keywords: South Asian; Cardiorespiratory Fitness; Visceral Adipose Tissue; Cardio-metabolic risk factors; Exercise; Bhangra Dance

Dedication

This thesis is dedicated to the South Asian community of Surrey, British Columbia. It is my hope that this research can translate into greater uptake of physical activity and a reduction in the prevalence of chronic disease which has a devastating impact on this community.

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List of Acronyms

ALT	Aluminotransferase
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
BMI	Body Mass Index
CRF	Cardiorespiratory Fitness
CRP	C Reactive Protein
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
HR	Heart Rate
SAAT	Subcutaneous Abdominal Adipose Tissue
TAAT	Total Abdominal Adipose Tissue
TG	Triglycerides
VAT	Visceral Adipose Tissue
VO_2peak	Peak oxygen uptake
WC	Waist Circumference

Glossary

Aluminotransferase	An enzyme which measures liver inflammation
Apolipoprotein B	The primary protein of high-density lipoprotein cholesterol that drives the promotion of fat efflux to the liver for excretion
Apolipoprotein A	The primary protein of low-density lipoprotein which is responsible for movement of fat to cells and tissues, considered to be a primary driver of plaque formation
Body Mass Index	A ratio of weight to height used to define body size
Cardiorespiratory Fitness	The ability of the circulatory and respiratory systems to provide oxygen to the musculoskeletal system during dynamic activity
C Reactive Protein	An inflammatory marker produced by the liver
High Density Lipoprotein Cholesterol	Involved in the removal of excess cholesterol by the liver and therefore known as the ‘good’ cholesterol
Homeostatic Model Assessment of Insulin Resistance	A surrogate for insulin sensitivity assessed by a mathematical equation based on fasting insulin and glucose
Insulin	A hormone that is involved in blood glucose regulation. Elevated fasting insulin is an indication of insulin resistance; a precursor to type 2 diabetes
Low Density Lipoprotein Cholesterol	Involved in the accumulation of excess cholesterol in the arteries and therefore known as the ‘bad’ cholesterol
Peak Oxygen Consumption	The highest oxygen consumption achieved during a graded exercise test
Post Menopausal	A decrease in the ovaries production of estrogen and progesterone resulting in the cessation of the menstrual cycle
South Asian	Refers to individuals with ethnic origins from India, Pakistan, Sri Lanka, Nepal or Bangladesh
Subcutaneous Abdominal Adipose Tissue	Abdominal fat located outside the inner abdominal wall
Total Abdominal Adipose Tissue	Abdominal fat located both inside and outside the inner abdominal wall
Triglycerides	A measure of circulating lipids in the bloodstream
Visceral Adipose Tissue	Abdominal fat located within the inner abdominal wall

Chapter 1.

Introduction

1.1. South Asian Population Statistics

South Asian ethnicity represents individuals who have ethnic roots from the Indian subcontinent, a large geographical area inclusive of Bangladesh, India, Nepal, Sri Lanka and Pakistan. As of 2013, the population of South Asia was estimated at 1.8 billion or approximately one quarter of the world population. In some countries South Asians make up a sizeable portion of the minority population. For instance, In England and Wales, populations from India, Pakistan and Bangladesh have increased 34%, 55% and 56% respectively from 2001 to 2011 and migrants from India comprise the largest of the foreign born population in the United Kingdom (Centre on Dynamics of Ethnicity, 2012). In Canada, South Asians are the largest and fastest growing immigrant population: between 2001 and 2006, the South Asian population increased by more than 35% to 1.3 million, while the general Canadian population increased by only 5.4% (Statistics Canada, 2010). By 2031, it is expected that the Canadian South Asian population will nearly triple to 3.6 million (Statistics Canada, 2010).

1.2. Associated Ethnic Health Risk

Non-communicable disease, such as type 2 Diabetes (T2D) and cardiovascular disease (CVD), are increasing rapidly in South Asia accounting for one to two thirds of all deaths in the region (Siegel, Patel & Ali 2014). When compared to other Canadian ethnic groups, Canadian South Asians have higher cardio-metabolic risk factors (Anand et al., 2000) (such as dyslipidemia and impaired fasting glucose) which have been demonstrated to lead to a disproportionately higher burden of T2D (Garduno-Diaz and Khokhar, 2011) and CVD (Yusuf et al., 2001, Joshi et al., 2007).

1.2.1. Type 2 Diabetes and South Asians

The prevalence of T2D in India is predicted to increase from 7.6 to 9.1% (50.8 to 87.0 million) from 2010 to 2030 representing a 72% increase in T2D (Shaw et al., 2010). Higher rates of impaired glucose tolerance are observed in South Asians, which lead to a three-fold greater risk of progression to T2D than among Europeans (Oldroyd et al., 2007). In the United Kingdom, prevalence of T2D in South Asians is five times higher than those of the indigenous European population (Gholap et al., 2011) and in the US, prevalence of T2D is the highest in South Asians when compared to other ethnic minorities (Misra et al., 2010). Immigrants in Canada from South Asia have a 3 to 4 times greater risk for development of T2D when compared to immigrants from Western countries (Creatore et al., 2010) and a recent review of fifty Canadian studies suggests a 2.25 greater odds of T2D in South Asians compared to Caucasians (Rana et al., 2014). In addition, the onset of T2D occurs at a younger age (5-10 years earlier), increasing the likelihood of associated complications such as CVD (Mather et al., 1998) and South Asians with T2D have an increased likelihood of mortality compared to Europeans (Swerdlow et al., 2004). The mechanisms behind the elevated prevalence of T2D in South Asians is diverse but biologic factors such as central adiposity and insulin resistance, impaired beta cell function and genetic predisposition are all potential contributors (Hu, 2011).

1.2.2. Cardiovascular Disease and South Asians

In 2005, CVD was the leading cause of mortality in India, claiming responsibility for 39% of all deaths in the country (World Health Organization, 2005). In the South Asian population CVD occurs at an earlier age with a greater prevalence of individuals diagnosed before the age of 40 (Joshi et al., 2007) and a mortality rate in those under the age of 30 that is 3 times higher than Caucasians in the United Kingdom (Balarajan, 1992). Compared to Caucasian Canadians, South Asian men (42% vs. 29%) and women (29% vs. 19%) exhibit a higher prevalence of age-standardized death from coronary artery disease (Sheth et al., 1999). In addition, prevalence rates of hospitalization by ethnicity have found that South Asians have the highest age-standardized rate of hospitalization for acute myocardial infarction (Nijjar et al., 2010) and a greater percentage of South Asian patients with acute coronary syndrome have T2D with hospitalization (Raghavan et al., 2008).

While T2D is a prominent risk factor for CVD, other traditional risk factors have also been shown to predict enhanced CVD risk. Specifically, the INTERHEART study found nine risk factors for CVD which make up 86% of the population-attributable risk of an acute myocardial infarction in the South Asian population; ratio of apolipoprotein B to A, smoking, hypertension, diabetes, waist to hip ratio, psychosocial factors, physical activity, alcohol intake and fruit and vegetable consumption (Joshi et al., 2007). As well as these traditional risk factors, a number of non-conventional risk factors are emerging in the South Asian population such as; dysfunctional HDL-cholesterol (Dodani et al, 2008), elevated C-reactive protein (Mohan et al., 2005) and lipoprotein a (Anand et al., 2000) which may further explain the elevated CVD risk seen in the South Asian population.

1.3. Visceral Adipose Tissue

Type 2 Diabetes and CVD have a common foundation of excess body fat (obesity), as obesity is associated with an increased risk for T2D and CVD (Reeder et al., 1997, Pouliot et al., 1994, McGill et al., 2002), and is an independent risk factor for all-cause mortality (Katzmarzyk, Ardern 2004). In particular, an excess of adiposity around the abdomen is associated with an increased risk for CVD independent of body mass index (BMI) (Yusuf et al., 2005, Rexrode et al., 1998). The increased risk of abdominal obesity above that of general obesity is reflective of excess visceral adipose tissue (VAT) (the fat within the inner abdominal wall), which has been shown to be highly associated with cardio-metabolic risk (Despres et al., 2008a, Despres et al., 1991), and an independent predictor of all-cause mortality in men (Kuk et al., 2006).

Abdominal adipose tissue is typically defined as either subcutaneous abdominal adipose tissue (SAAT) or VAT. These two depots differ in both their metabolic activity as well as their anatomical location. The inner abdominal wall is used as a landmark to differentiate between these two depots with SAAT located beneath the skin and outside of the inner abdominal wall and VAT located within the inner abdominal wall. A commonly cited theory of the high metabolic activity of VAT is its location relative to the portal vein, which is thought to augment disease risk due to the greater release of free fatty acids to the hepatic circulation (Kissebah 1996). However, this theory has been debated and it is likely the distinct morphological characteristics of VAT, such as adipocyte cell size and number, lipolytic responsiveness, lipid storage capacity and inflammatory cytokine production, which lead to metabolic dysfunction (Tchernof, Despres, 2013). Adipose tissue from the subcutaneous depot may be more dependent on hyperplasia while that of the VAT depot is dependent on adipocyte hypertrophy (Drolet et al., 2008) resulting in larger adipocytes which are thought to be more metabolically active than smaller adipocytes (Bjorntorp et al., 1971). This may be due to the positive association between adipocyte size and lipoprotein lipase activity, an enzyme involved in triglyceride breakdown, and therefore a primary determinant of triglyceride storage and free fatty acid flux (Votruba et al., 2007). Individuals with elevated VAT also demonstrate altered expression and/or secretion of important inflammatory factors and adipokines that may alter lipolysis through altered insulin sensitivity such as low adiponectin and elevated C reactive protein, TNF-α and IL-6 (Cartier et al., 2010, Cote et al., 2005, Lemieux et al., 2001, Tchernof, Despres, 2013).

1.3.1. Visceral Adipose Tissue in South Asians

In South Asians, the rising prevalence of obesity and a preponderance of abdominal obesity is thought to be directly responsible for the increasing trend of T2D and CVD in this population (Anand et al., 2000, Lean et al., 2001, Misra, Khurana 2011). One hypothesis for the prevalence of abdominal obesity seen in the South Asian population is a lower capacity for fat storage in subcutaneous depots resulting in overflow to other depots; primarily VAT (Sniderman et al., 2007). Forouhi et al. compared abdominal CT scans of South Asians and European men and women in the UK and found higher VAT despite a lower BMI and WC in South Asian men and a substantially greater VAT at a greater BMI and WC in South Asian women (Forouhi et al., 2007). In addition, Canadian data from our lab has shown greater VAT at the same BMI, waist circumference and body fat as well as a lower lean mass in South Asians compared to Europeans (Lear 2007a, Lear 2007b, Lear et al., 2009) all of which contributes to a more deleterious cardio-metabolic profile (Lear et al., 2009, Lear et al., 2012, Kohli et al., 2010, Anand et al., 2011, Raji et al., 2001). Excess VAT has been shown to explain elevated cardiovascular risk in South Asian populations in both Canada (Lear et al., 2012) and the United Kingdom (Eastwood et al., 2015) which may be related to the enlarged adipocytes seen in the VAT depot in the South Asian population when compared to Caucasian Canadians (Anand et al., 2011).

1.3.2. Exercise and Visceral Adipose Tissue

Lifelong participation in physical activity results in numerous health benefits and has been shown to provide primary and secondary prevention for over 25 health conditions (Warburton et al., 2010). Regular physical activity is recommended for the prevention and management of obesity and its associated risks such as T2D and CVD, and in particular, these recommendations stress the importance of physical activity to reduce abdominal obesity to manage risk (Despres et al., 2008b, Despres et al., 2009, Haskell et al., 2007). Global recommendations by the World Health Organization for physical activity suggest people should attain 150 minutes per week of moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity physical activity or an equivalent combination. For additional health benefits adults are encourage to increase their moderate-intensity aerobic physical activity to 300 minutes per week or 150 minutes of vigorous-intensity physical activity or an equivalent combination (World Health Organization Guidelines, 2010).

Previous research has shown aerobic exercise to be effective at reducing VAT when prescribed at a variety of exercise doses ranging from; 2 to 12 months, 2 to 7 times per week for 34 to 63 minutes per session, in both men and women with differing obesity and metabolic status (Boudou et al., 2001, Giannaopoulou et al., 2005, Mourier et al., 1997, Murphy et al., 2012, O'Leary et al., 2006, Ross et al., 2004, Ross et al., 2000, Short et al., 2003) (Table 1.1). Given the challenges that have been described in the literature with achieving significant weight loss with exercise alone (Swift et al., 2014), it is of additional interest to study the effect of exercise on the VAT depot because it has been shown to be reduced independent of weight loss (Ross 2000, Lee 2005). Furthermore, exercise is more effective in reducing VAT than caloric restriction after controlling for the effect of body fat loss (Giannapoulou et al., 2005, Murphy et al., 2012). The above research suggests that physical activity may specifically target loss of VAT independent of a significant change in body mass. This loss in VAT may be due to exaggerated lipid mobilization from the abdominal region compared to subcutaneous adipose tissue (Arner et al., 1990) and that omental and mesenteric adipocytes are more sensitive to lipolytic stimulation of catecholamines (Fried et al., 1993).

Given the effectiveness of exercise at preferentially altering VAT it may be an effective preventative strategy to alter T2D and CVD risk in South Asians; however, almost all of the randomized controlled trials have been done in European populations, with none conducted in South Asians. It is therefore unknown whether the relationship between VAT and exercise applies to other ethnicities.

Table 1.1. Randomized controlled trials of exercise training with visceral adipose tissue as the outcome

Study	Duration (wks)	Frequency (times/wk)	Time (min/day)	Sample Size (exercise)	Δ VAT (pre to post)
Boudou et al.	8	3	34	8	-69.1 cm^2
Giannapoulou et al.	14	3	50	11	-529 cm^3
Mourier et al.	8	3	34	6	-75.7 cm^2
Murphy et al.	52	6	62	16	-490 mL
O'Leary et al.	12	5	60	16	-39.4 cm^2
Ross et al.	14	7	63	12	-0.7 kg
Ross et al.	12	7	63	14	-52 cm^2
Short et al.	16	3	60	5	-11 cm^2

1.4. Physical Inactivity in the South Asian Population

South Asian immigrants report lower levels of physical activity than Europeans in New Zealand, the United Kingdom and Canada (Kolt et al., 2007, Fischbacher, Hunt & Alexander 2005, Liu et al., 2010, Williams et al., 2011). For instance, in Canada, 62.8% of South Asians reported being physically inactive, the highest of any other ethnic group in Canada, compared to 50.3% of Caucasians (Liu et al., 2010). The health survey for England found that Indian, Pakistani and Bangladeshi men were 12%, 30% and 45% less likely, respectively, to meet physical activity guidelines when compared to the general population (Fischbacher, Hunt & Alexander 2004). This is a concern because low levels of physical activity may explain over 20% of the excess CVD mortality in South Asians, making physical inactivity a strong contributor to mortality (Williams et al., 2011). Physical inactivity may therefore be a key target for intervention.

1.5. South Asian Women and Elevated Health Risk

South Asian women are even less likely to participate in physical activity than South Asian men (Daniel, Wilbur 2011). Measurements of physical activity by accelerometry in South Asian women in the United Kingdom found 65% of older South Asian women were failing to meet physical activity guidelines (Curry, Thompson, 2014). The reasons for low physical activity participation rates may have their roots in South Asian culture as physical activity is not a part of daily routine (Khanam, Costarelli 2008) with language, religious beliefs and cultural practices as barriers to physical activity uptake. Primary barriers to physical activity in South Asian women in Canada are reported as lack of time due to work and family, and lack of motivation (Caperchione et al., 2013) while South Asian women in the United Kingdom report facilitators such as exercising in a social setting, and having a role model as well as individual goal setting (Jepson et al., 2012; Horne et al., 2013). It is therefore necessary to take into account cultural preferences if promoting physical activity in the South Asian population (Lawton et al., 2006) and this may require innovative thinking in order to increase the likelihood of physical activity uptake and maintenance (Mundra et al., 2012).

Of particular risk among the South Asian population are women after menopause as studies in post-menopausal women of other ethnicities have demonstrated that menopause is associated with increased risk for T2D and CVD (Rosano et al., 2007). This appears coincident with changes in body composition that include enlargement of the VAT depot (Janssen et al., 2015). Compared to pre-menopausal women, post-menopausal women present with an increase in VAT that is independent of age and can occur with little or no increase in body weight, waist circumference or adiposity in other regions of the body (Toth et al., 2000, Zamboni et al., 1992, Franklin, Ploutz-Snyder & Kanaley 2009). Several other studies have directly implicated enlargement of the VAT depot to explain much of the increased CVD risk with menopause (Toth et al., 2000, Zamboni et al., 1992, Piche et al., 2008). Moreover, VAT is reported to be an independent predictor of myocardial infarction in post-menopausal women but not in men (Nicklas et al. 2004). While similar data are lacking in South Asian post-menopausal women, they do present with elevated CVD risk compared to pre-menopausal women (Tandon et al., 2010), higher levels of obesity (Garg et al., 2010) and lower levels of physical activity (Fischbacher, Hunt & Alexander 2004). Interestingly, earlier studies in post-menopausal women of European background have reported significant reductions in VAT after aerobic exercise (Giannopoulou et al., 2005, Nicklas et al., 2009).

1.6. Bhangra Dance as a Physical Activity Opportunity

Previous data from within my lab found that, compared to Europeans, South Asians reported that they were less comfortable attending a fitness/gym centre and were more likely to state that they do not have access to appropriate equipment for exercise. In addition, our community partners have confirmed the need for physical activity programs targeted to South Asians to take into account these cultural issues. To raise levels of physical activity among South Asians in Canada, it is important to promote alternative culturally-appropriate types of physical activity that may be more acceptable and familiar to South Asians than are conventional standard exercise activities and may improve adherence to a physically active lifestyle. This approach has been successful in Chinese populations using Tai Chi (Manson et al., 2015) and in native Hawaiians using Hula dancing;(Maskarinek et al., 2015) with both studies demonstrating improved recruitment and adherence to the activities. Towards this end, I performed a pilot survey of women attending a temple in Vancouver to determine physical activity preferences. Among women, one of the top choices was dance as “currently participating in” or “most interested in participating in”.

Bhangra dance, a culturally rooted dance from the Punjab region of India, has been suggested as a culturally relevant low cost alternative to standard aerobic exercise that involves the whole body musculature and provides aerobic benefits (Unnikrishnan, Kalra & Garg, 2012). Mundra state, “Bhangra… may turn out to be the magic wand which can arrest the spread of obesity” (Mundra 2012). A recent study in Canada used South Asian dance to determine whether a cultural program of physical activity would impact physical, mental or social health. This small study of 27 women who completed a 6 week, 2 days per week program showed a high level of adherence attending 82% of exercise classes. In addition, women reported feeling less stress and tired while having more energy and life satisfaction (Vahabi, Dhamba, 2015).

1.7. Rationale

South Asians represent an important and growing immigrant population in Canada who are susceptible to T2D and CVD at a younger age. In addition, South Asians have a unique obesity phenotype of elevated VAT at a given body size, which accounts for some of this increased risk compared to Caucasians. While aerobic exercise is effective at preferentially reducing VAT in European populations, it is unknown if it would have the same effect in South Asians given their unique obesity phenotype. Lastly, South Asians participate less in physical activity than Caucasians, specifically older South Asian women who are at greater health risk. Bhangra dance may reflect cultural practices of the South Asian population. Therefore, this thesis was designed to assess the role of cardiorespiratory fitness in determining VAT in post-menopausal South Asian women, to determine whether both standard aerobic exercise and Bhangra dance are effective at reducing VAT and cardio-metabolic risk factors in post-menopausal South Asian women, and to determine whether exercise-induced reductions in VAT are associated with improved cardio-metabolic risk factors in post-menopausal South Asian women.

1.8. Thesis Objectives

The objectives of this thesis were threefold: 1) to assess the association between cardiorespiratory fitness and VAT (Chapter 3); 2) to assess the effectiveness of standard exercise and Bhangra dance in reducing VAT (Chapter 4); and lastly 3) to assess the association between changes in VAT with changes in cardio-metabolic risk factors (Chapter 5) in a population of post-menopausal South Asian women who had abdominal adiposity and were physically inactive.

1.8.1. Rationale for Chapter 3

Chapter 3 aims to examine the association between cardiorespiratory fitness (CRF) level and VAT in physically inactive, post-menopausal South Asian women. Low CRF is a well-accepted risk factor for T2D and CVD, and is influenced by physical activity (Bouchard, Rankinen & Timmons 2011). In Europeans, CRF is negatively associated with the accumulation of VAT (Haufe et al., 2010, Janssen et al., 2004) and those categorized with high CRF have been shown to have lower amounts of VAT than those categorized with low CRF (Brock et al., 2001, O'Donovan et al., 2009). In addition, a recent review by Gill et al., suggested that a low fitness phenotype may play a role in explaining the increased risk of T2D and CVD in the South Asian population (Gill, Celis-Morales & Ghouri 2014). This is supported by the lower CRF seen in South Asian men compared to European men (Ghouri et al., 2013). Given the unique obesity phenotype and its associated disease risk in South Asians, it is necessary to understand the association between CRF and body fat distribution in this population. Therefore, the purpose of this chapter was to determine whether CRF, as determined by peak oxygen uptake (VO_2peak), was associated with body fat distribution and abdominal fat - specifically VAT - in physically inactive, post-menopausal South Asian women. Additionally, I aimed to explore whether CRF was associated with VAT independent of body mass index (BMI).

1.8.2. Rationale for Chapter 4

Chapter 4 aims to assess whether research in Caucasian populations which has shown that exercise can preferentially reduce VAT (Ross, Bradshaw 2009) applies in a South Asian population where VAT tends to be greater at a given body size. Given the unique obesity phenotype and putative differing adipocyte biology (Tchernof, Despres 2013), the exercise research on Caucasians may not fully apply. In addition, South Asians have substantially lower levels of leisure time physical activity (Fischbacher,Hunt & Alexander, 2004; Liu et al., 2010, Williams et al., 2011). This is especially true for South Asian women who are less likely to participate in physical activity than South Asian men (Daniel, Wilbur 2011). Therefore, South Asian women may be an ideal target population to assess the effectiveness of physical activity in reducing VAT and lowering risk for T2D and CVD. However, the physical activity should be reflective of the cultural practices of this population (Lawton et al., 2006) in order to increase physical activity uptake. To this end, I investigated the effectiveness of both a standard exercise program as well as a culturally relevant exercise program of Bhangra dance on VAT deposition and cardio-metabolic risk factors in physically inactive post-menopausal South Asian women. This chapter provides the results of this randomized controlled trial that was funded by the Canadian Institutes of Health Research. If Bhangra dance is effective it will provide scientific rationale for promoting a culturally relevant form of physical activity in the South Asian population that will theoretically increase physical activity uptake.

1.8.3. Rationale for Chapter 5

The aim of chapter 5 is to assess the association between change in body composition, specifically VAT, with changes in cardio-metabolic risk factors. Obesity or excess body fat is associated with increased insulin resistance, T2D and CVD (Yusuf et al., 2005). In South Asians, the obesity phenotype of higher fat mass and lower lean mass explains a large amount of the ethnic variation in insulin sensitivity suggesting a role of excess body fat in elevated T2D and CVD risk (Lear et al., 2009). Exercise-induced reduction in VAT and total body fat is an effective mechanism to improve cardio-metabolic risk factors in European populations (Fabbrini et al., 2010; Arsenault et al., 2009; Bouchonville et al., 2014) but this has not been proven in South Asians.

The clinical relevance of this study depends on the ability to feasibly measure VAT in patients. However, direct measurements of abdominal adipose tissue and total body fat are difficult and expensive to obtain and expose a patient to radiation. Therefore, alternative measures, such as simple anthropometric measures, are needed to overcome these feasibility issues. Waist circumference (WC) is a useful clinical marker of VAT, and higher WC is associated with elevated CVD risk factors (Despres, 2014). The associations between VAT and WC remain after weight loss (Pare et al., 2001). However, whether WC is effective for determining VAT-derived improvements in cardio-metabolic risk is unclear given that change in WC could represent a combination of change in subcutaneous abdominal adipose tissue (SAAT) in addition to a change in VAT. While a reduction in VAT may underlie exercise-induced improvements in cardio-metabolic risk factors (Borel et al., 2012), direct measurements of abdominal adipose tissue or total body fat are difficult to obtain, WC and BMI respectively may be simplistic clinical alternatives for assessing change in cardio-metabolic risk factors achieved with aerobic exercise training. Further, whether exercise-induced changes in commonly used measurements such as WC are independently related to changes in cardio-metabolic risk factors in South Asians is unknown.

1.9. References

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Chapter 2.

Community Outreach and Research Methods

2.1. Community Outreach

While this project was not designed with the use of community based participatory research methods it was dependent on community engagement which promotes many of the same values. Community engagement is often solicited throughout the research process via participant recruitment, the intervention itself, and the dissemination of results (Israel et al. 2010) and this process is thought to be particularly valuable in research involving ethnic minorities (De las Nueces et al. 2012). Developing and conducting a research study without community input tends to result in uninformed research that is not directly translatable to the community and leads to low uptake of research findings. In addition, engaging the community in research projects yields increased research participation in ethnic minority communities (Yancey, Ortega & Kumanyika 2006). I therefore created a South Asian advisory committee to meet on a regular basis to engage in the research process that spanned development, implementation (including a media strategy for participant recruitment), and knowledge translation.

2.2. South Asian Advisory Committee

As stated above, community engagement was instrumental in this study and therefore the conversation commenced by determining that an advisory committee was necessary that would be aware of and engaged in the needs of the South Asian community. The South Asian advisory committee was instrumental in a number of ways as discussed below. First, a community advisory panel ensures that the research is conducted according to community needs and is culturally appropriate. In the case of this study, we solicited input on the health needs of the South Asian population and specifically older women in the community. This was inclusive of engaging the committee on a physical activity option that was appropriate for the population which we aimed to serve and the best individuals to instruct the physical activity classes. The community advisory committee met three times annually from the inception to completion of this project and provided feedback on recruitment and knowledge translation (Figure 2.1) and helped me to liaise with the South Asian community in the Greater Vancouver area.

2.2.1. Committee Members and Their Qualifications

Paul Bains: Mr.Bains is a prominent figure in the South Asian community and is the vice chair of the Canada-India Network Society.

Rosie Dhaliwal: Ms. Dhaliwal is engaged in health promotion at Simon Fraser University and has worked with the South Asian population providing nutritional expertise.

Manpreet Dhillon: Ms. Dhillon is a co-founder of the South Asian Professional Women’s Network and is thus well connected to South Asian women in the community.

Dr. Arun Garg: Dr. Garg is a physician and president of the Canada-India Network Society, the Director of the South Asian Health Institute within the Fraser Health Authority and sits on the India President’s Council at Simon Fraser University.

Mandeep Patrola: Mrs. Patrola is a director of the Vancouver International Bhangra Celebration as well as a previous member of the UBC Bhangra team and is extensively involved in South Asian media.

Dr. Parmjit Sohal: Dr. Sohal is a family physician in the Surrey community who has published on the prevalence rates of Diabetes in the South Asian community.

Dr. Jeff Sommers: Dr. Sommers is the manager of Research and Health Initiatives for the Heart and Stroke Foundation of British Columbia.

These individuals were chosen as they are representative of the South Asian community as physicians, policy makers and community members. An equal number of women were appointed to the committee in order to ensure representation of the needs of South Asian women that were recruited for this study.

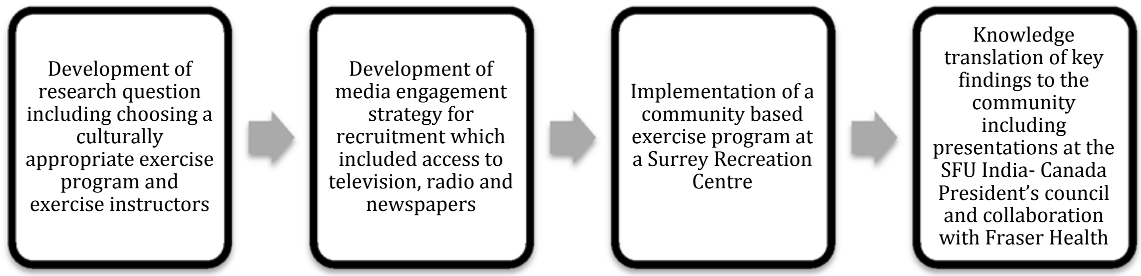

Figure 2.1. Input from South Asian Advisory Committee

2.3. Bhangra Dance as a Culturally Relevant Exercise Program

While the primary aim of this exercise trial was to determine whether exercise would be effective at reducing VAT, an additional goal was to find an exercise program in which South Asians may be more inclined to participate and therefore we sought to assess whether a culturally relevant exercise program would be effective from a health perspective. In the grant development stage of this study, our primary focus was on yoga because it is more commonly featured in the literature and has positive effects on health in the South Asian community. However, after further discussion with our South Asian Advisory Committee, it became apparent that Bhangra dance may be a better option due to the excitement it generates in the community, specifically through the Vancouver International Bhangra Celebration, an annual Bhangra event. In addition, I performed a pilot survey of women attending a temple in Vancouver to determine physical activity preferences. Among women, one of the top choices was dance as "currently participating in" or "most interested in participating in". From an exercise physiology standpoint, this seemed like a more appealing intervention because we aimed to assess whether aerobic exercise would reduce VAT and it is challenging to substantially increase heart rate and alter caloric expenditure in yoga.

2.4. Partnership with City of Surrey Department of Parks, Recreation and Culture

The majority of exercise interventions are conducted in research laboratories where participants must leave their community in order to participate in the exercise program. While this approach is more convenient for researchers and may lead to better study control, it tends to limit participation and is not generalizable to community-based exercise in which the primary goal is to increase physical activity in the community. Therefore, we approached the City of Surrey about conducting the exercise program in one of their local recreation centres. North Surrey Recreation Centre was chosen due to its central location in Surrey and its proximity to public transit, including Skytrain access. Furthermore, this partnership minimized the project cost because the City of Surrey provided the subjects with complementary access to the recreation centre. Indeed, the city was highly supportive of the study because they want to increase physical activity in the South Asian community. Another benefit of our partnership was the potential for long-term sustainability of the program.

2.5. Participant Recruitment

Extensive effort was invested to recruit South Asian women subjects who met the inclusion criteria for this study. Community engagement was of primary importance in finding women who were interested in taking part in this research study. The study was discussed on many popular South Asian television shows in the community, such as; the Harpreet Singh Show, OMNI News, and Punjabi Sports, as well as popular radio stations such as RedFM, Radio India, and RJ1200. These interviews were set up in order to educate the South Asian community on the high prevalence of noncommunicable diseases as well as the unique role that exercise can play in improving health. These were often call-in shows (Radio India, RJ1200) where listeners could ask questions about exercise and discuss concerns they had about their own health with the study coordinator (IAL) who is a certified exercise physiologist. Lastly, Simon Fraser University Media Affairs created a video of the program that gave an inside look at the Bhangra dance program and the rationale for the research. This video generated additional excitement in the community and led to a number of community news articles that resulted in interested participants calling in. This video can be found at http://www.sfu.ca/university-communications/media-releases/2014/study-looks-at-impact-of-bhangra-on-south-asian-womens-health.html.

2.6. Steps to Ensure Participant Adherence

After an individual was screened for the study and expressed interest in participating they were booked for an in-person meeting to discuss the study in detail with the project manager (IAL) and, if necessary, a volunteer translator who was fluent in both English and Punjabi. The subjects were free to withdraw from the study at any time. Challenges of conducting research in the community often include the tendency of prospective subjects to enroll in a study despite not planning on following through on this commitment. Spending the time getting to know each participant, their rationale for wanting to sign up for the study and what they hoped to achieve, allowed the project manager (IAL) to appropriately educate them about the study and whether it was appropriate for them. The majority of the women who showed up for these appointments were adherent to the baseline appointments and were excellent research participants.

2.7. Dissemination of Results

The South Asian community advisory committee was well positioned to disseminate the results to the community. The access to the South Asian media during participant recruitment provided an ideal opportunity for knowledge translation. Once final study results are published the project manager (IAL), will discuss study findings with the community via these media outlets. The final goal will be to offer Bhangra to the community as a low-cost physical activity option, in which the South Asian community advisory committee has expressed interest in doing, and can provide access to community options.

2.8. References

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Chapter 3.

The Association between Cardiorespiratory Fitness and Abdominal Adiposity in Postmenopausal, Physically Inactive South Asian Women

3.1. Introduction

South Asian ethnicity is associated with an increased prevalence of cardio-metabolic risk factors (such as dyslipidemia and impaired fasting glucose) which leads to a disproportionately greater risk of type 2 diabetes (T2D) (Gardun-Diaz et al., 2012) and cardiovascular disease (CVD) compared to Europeans (Joshi et al., 2007; Yusuf et al., 2001). For example, in the UK the prevalence of T2D in South Asians is five times higher than those of the indigenous European population (Ghopal et al., 2011). In addition, the onset of T2D occurs approximately 5-10 years earlier in South Asians than persons of other ethnicities (Joshi et al., 2007), increasing the likelihood of associated complications such as CVD (Mather et al., 1998).

In South Asians, the rising prevalence of obesity and a preponderance of abdominal obesity are thought to be directly responsible for the increasing trend of T2D and CVD in this population (Anand et al., 2000; Lean et al., 2001; Misra and Khurana, 2011). Contributing to this increased risk is that South Asians have been shown to have greater visceral adipose tissue (VAT) at the same body mass index (BMI), waist circumference (WC) and body fat mass as Europeans (Lear et al., 2007; Lear et al., 2012). Of particular risk among the South Asian population are women after menopause because studies of post-menopausal women of other ethnicities show that menopause is associated with increased risk for T2D and CVD (Rosano et al., 2007). This finding appears coincident with changes in body composition that occur after menopause, which include enlargement of the VAT depot (Janssen et al., 2015) and reduced cardiorespiratory fitness (CRF) (Lynch et al., 2002).

Low CRF is a well-accepted risk factor for T2D and CVD, and is influenced by physical activity as well as genetic heritability (Bouchard et al., 2011). In Europeans, CRF is negatively associated with the accumulation of VAT (Haufe et al., 2010; Janssen et al.,

2004) and those categorized with high CRF have been shown to have lower amounts of VAT than those categorized with low CRF (Brock et al., 2011; O'Donovan et al., 2009). Although the exact mechanisms linking CRF and VAT amount are unclear it is possible that a greater uptake in fat oxidation is seen among individuals with a higher CRF due to a greater proportion of slow-twitch oxidative, type 1 muscle fibers and therefore, a lower CRF would lead to impairments in fat oxidation (Kelley and Simoneau, 1994).

In a recent review by Gill et al., the authors suggested that low fitness may play a role in explaining the increased risk of T2D and CVD in the South Asian population (Gill et al., 2014). This contention is supported by the lower CRF seen in South Asian men compared to European men (Hall et al., 2010) which suggests a potential role of low CRF in its association with VAT. Given the unique obesity phenotype and its associated disease risk in South Asians, it is necessary to understand the association between CRF and body fat distribution in this population. Therefore, the purpose of this study was to determine whether CRF, as determined by peak oxygen uptake (VO_2peak), was associated with body fat distribution and abdominal fat - specifically VAT - in physically inactive, post-menopausal South Asian women. Additionally, I aimed to explore whether CRF was associated with VAT independent of BMI. I hypothesized there would be a negative association between CRF and VAT and that this association would be independent of BMI.

3.2. Methods

This study was a cross-sectional baseline analysis of participants enrolled in a registered randomized controlled trial (ClinicalTrials.gov #NCT01766453). While 75 women were enrolled in the study only 63 women agreed to participate in metabolic testing and a further 8 did not reach VO_2peak based on criterion discussed below, resulting in 55 study participants. Participants were recruited from the South Asian community in the Greater Vancouver area through local media including television, radio, newspapers, local temples, community events and word of mouth. Individuals were eligible to participate in the study if they were post-menopausal (one year since their last menstrual cycle), had not engaged in regular physical activity in the previous 6 months and had a WC of 80 cm or greater (cut off for abdominal obesity for South Asian women) (Alberti et al., 2005). Individuals were not eligible to participate if they reported having been diagnosed with CVD or T2D. All participants provided written informed consent, and this study was approved by the Simon Fraser University and Providence Health Care Research Ethics Boards.

3.2.1. Exercise Testing

Participants completed a treadmill test using the Bruce Protocol (Bruce et al., 1990), a common maximal exercise test employed in clinical populations. The test began at 1.7 mph and a 10% grade; the speed and grade were increased progressively until the participant reached volitional exhaustion. Prior to testing each participant, a gas calibration and volume calibration was completed using standard procedures. Heart rate was assessed by 12-lead electrocardiography throughout the test for safety purposes. Metabolic data were collected simultaneously during the treadmill test on a breath-by-breath basis using a calibrated metabolic system (VMax SensorMedics, Houston, Texas). VO_2 was acquired as a 20-second moving average throughout the test. Participants were encouraged verbally throughout the test in an attempt to achieve a maximal effort. Those participants who reached volitional fatigue as well as either a respiratory exchange ratio of 1.05 at peak exercise or 85% of predicted maximal heart rate were considered to have achieved a VO_2peak (measured in mL/kg/min). Eight of the 63 women who completed the treadmill test did not meet these criteria and were excluded from further analyses.

3.2.2. Computed Tomography Assessment of Abdominal Fat

Abdominal fat was assessed through multi-slice computed tomography scanning by a radiology technician at St. Paul's Hospital. The initial image was acquired at the L4-L5 interverterbral disk and four 10 mm slices taken every 5 cm above this landmark and two below this landmark. Scan parameters were set at 120kVp, 300mA for one second, 10 mm thickness, 512 by 512 matrix using a 48 cm field of view. All seven CT slices were obtained at the same time. All scans were void of participant identity prior to assessment to avoid any interpretation bias. Using the standard attenuation range of -190 to -30 Hounsfield units for adipose tissue, the cross-sectional areas were determined using imaging software (SliceOmatic v4.2 Tomovision, Montreal, Quebec). Total abdominal adipose tissue (TAAT) was calculated as all pixels within this attenuation range in the abdominal image. VAT was calculated as all pixels in this attenuation range within the inner abdominal wall. Subcutaneous abdominal adipose tissue (SAAT) was calculated as the difference between TAAT and VAT. Volumes were calculated as the average of the two closest scans divided by the distance between the scans. All areas were then added together for volume. Scan analyses were completed by the same individual, with a coefficient of variation based on repeat analysis of 1.21% at the L4-L5 scan.

3.2.3. Body Composition Measures

Body composition measures were completed by the study coordinator (IAL). Mass in kilograms and height in metres were assessed with participants in light clothing (or hospital gowns), footwear removed and pockets emptied. BMI was calculated as mass in kilograms over height in meters squared. Waist circumference was recorded in centimetres as the average of two measures taken against the skin at the point of maximal narrowing from the anterior view (midway between the top of the iliac crest and the bottom of the lowest rib) following a normal expiration. Body composition was assessed using a dual energy x-ray absorptiometry (DXA) scanner (Hologic Discovery QDR 4500w, Bedford, Massachusetts) to determine lean body mass (kg), total body fat mass (kg), and percent body fat. The percentage of total body fat was calculated by dividing total body fat mass by total body mass.

3.3. Statistical Analysis

The following data were natural log transformed following visual inspection of P-P plots: BMI, body mass, total body fat, body fat percentage, lean body mass, visceral adipose tissue, subcutaneous abdominal adipose tissue, total abdominal adipose tissue, VO_2peak and time to exhaustion. Natural log transformed data are presented as geometric means with 95% confidence intervals while all remaining data are presented as means and standard deviations.

Pearson product-moment correlation coefficients were used to assess the linear association between the dependent variable of VO_2peak, and the independent variables of WC, BMI, total body fat, body fat percentage, lean body mass, SAAT, VAT and TAAT. Participants were then categorized into tertiles of VO_2peak in order to visualize the associations and separate ANOVAs were used to assess differences in each independent variable between tertiles of VO_2peak, with post hoc comparisons using the Bonferonni test.

Finally, linear regression analyses were used to model the association between abdominal fat – SAAT, VAT and TAAT – and VO_2peak (mL/kg/min). Separate multiple linear regression models were constructed with, SAAT, VAT and TAAT as the predictor variables of interest and VO_2peak as the outcome variable. For each predictor, models were first adjusted for age and then separately for BMI and body fat percentage to examine these relationships independent of body size. BMI and body fat percentage were assessed for collinearity using variance inflation factors and it was not significant. Statistical analysis was completed using SPSS v. 19.0 and significance was set at $p<0.05$.

3.4. Results

There were 55 women who completed aerobic fitness testing with a mean age of 57 years. Women had a mean BMI of 29 kg/m^2, WC of 93.1 cm and body fat percentage of 42.0% (Table 3.1). The mean VO_2peak obtained was 23.1 mL/kg/min, with 92% of participants reaching their predicted maximal HR (220-age). The average respiratory exchange ratio (RER) was 1.07, with 72% of women surpassing an RER of 1.0. All of the women reported having reached volitional exhaustion (Table 3.1).

There were negative relationships between VO_2peak and lean body mass (R^2=0.199, $p<0.001$), SAAT (R^2=0.299, $p<0.001$), TAAT (R^2=0.315, $p<0.001$) and body fat percentage (R^2=0.117, p=0.011). Scatterplots of VO_2peak versus WC, VAT, BMI and body fat are displayed in Figure 3.1.

Compared to women in the lowest tertile of VO_2peak (13.8-21.8 mL/kg/min), women in the highest tertile (25.0-27.7 mL/kg/min) had significantly lower WC ($p<0.001$), BMI ($p<0.001$), total body fat ($p<0.001$), body fat percentage (p=0.004), and lean body mass (p=0.017). Compared to women in the lowest tertile of VO_2peak, women in the middle tertile had significantly lower BMI (0.039) and women in the highest tertile compared to the middle tertile had significantly lower WC (P=0.009), BMI (p=0.002) and total body fat (p=0.004). Compared to women in the lowest tertile of VO_2peak, women in the highest tertile had significantly lower inner-abdominal fat as measured by SAAT, VAT and TAAT compared to women in the highest tertile of VO_2peak ($p<0.001$) (Figure 3.2). Women in the highest tertile compared to the middle tertile had significantly lower inner-abdominal fat as measured by SAAT ($p=0.007$), VAT ($p=0.002$) and TAAT ($p<0.001$) (Figure 3.2).

In linear regression analyses, all associations between VO_2peak and inner-abdominal fat variables (SAAT, VAT and TAAT) were significant after adjustment for age (Table 3.2). Associations between VO_2peak and inner-abdominal fat variables remained significant after adjustment for body fat percentage but were no longer significant after adjustment for BMI. When comparing the models with SAAT and the models with VAT, there were stronger associations for SAAT.

3.5. Discussion

This is to our knowledge the first study to directly measure CRF in postmenopausal South Asian women and to examine the relationships between CRF and a variety of measures of body composition and inner-abdominal fat. This is unique as there is a paucity of research on CRF and obesity focusing on South Asian women of this age. In the current study of physically inactive post-menopausal South Asian women, VO_2peak was negatively associated with abdominal fat - SAAT, VAT and TAAT, as well as BMI, lean body mass, total body fat, body fat percentage and WC. Women in the highest tertile of VO_2peak had lower amounts of SAAT, VAT and TAAT as well as a lower body mass, WC, body fat and lean body mass than those in the lowest tertile of VO_2peak. Associations of VO_2peak with SAAT, VAT, and TAAT were independent of age and body fat percentage but not independent of age and BMI. Associations between VO_2peak and SAAT were somewhat stronger than associations between VO_2peak and VAT.

Our finding that CRF was negatively associated with SAAT, VAT and TAAT in physically inactive post-menopausal South Asian women is consistent with Janssen and Haufe who found men and women of European and African American origin with the highest CRF to have the lowest VAT (Janssen et al., 2004; Haufe et al., 2010). The results of our regression models suggest that SAAT may have a stronger relationship with VO_2peak than VAT and that this relationship remains even after accounting for VAT in the model.

While associations between abdominal fat (VAT, SAAT and TAAT) and VO_2peak were observed when adjusting for percent body fat, they were no longer apparent after adjusting for BMI. This is likely due to the inverse association between lean body mass and VO_2peak (i.e., women in our study in the lowest tertile of VO_2peak had the highest amount of lean body mass). Increased lean mass can be a result of additional body mass due to heightened load-bearing requirements (Forbes and Welle, 1983). This finding contradicts our other observations that those in the lowest tertile of VO_2peak exhibited a body composition generally associated with more deleterious health; higher abdominal and body fat. In contrast to our findings in postmenopausal South Asian women, European men had higher lean body mass among those with the highest CRF (Arsenault et al., 2007). This higher lean body mass may explain, at least in part, why the association between CRF and abdominal fat was independent of BMI in previous studies but not replicated in the current study (Arsenault et al., 2007; Haufe et al., 2010; Janssen et al., 2004).

Individuals in the highest tertile of VO_2peak had lower SAAT, VAT and TAAT than those in the lowest and middle tertiles. Significantly lower amounts of VAT among those with a higher level of CRF have previously been found in both men (O'Donovan et al., 2009) and women (Brock et al., 2007) but not specifically in women of South Asian ethnicity, as measurement of CRF levels in the South Asian population is rare. It is unknown whether low levels of CRF may be causal to the unique obesity phenotype observed in the South Asian population of high VAT independent of BMI (Lear et al., 2007). Given the low CRF in the South Asian population (Hall et al., 2010), it is possible that there exists a genetic predisposition to lower CRF. Individuals who are predisposed to lower CRF through genetic heritability are more likely to show dysregulation in insulin, mitochondrial deficiencies and lipid oxidation (Bouchard et al., 2011). Interestingly, lipid oxidation has been shown to be lower during exercise in South Asian men compared to European men despite no differences observed at rest (Hall et al., 2010). This suggests there may be an ethnicity-specific response to exercise in regards to fat mobilization that may explain the link between CRF and body composition. This may be further supported by the observation that South Asian men need to undertake a higher level of physical activity to achieve the same level of cardio-metabolic risk as European men (266 minutes/week for the former compared to 150 minutes/week for the latter) (Celis-Morales et a., 2012) as lipid oxidation is associated with insulin sensitivity (Hall et al., 2010).

It has been well established that exercise is effective at reducing VAT in men and women of European origin (Mourier et al., 1997; O'Leary et al., 2006; Ross et al., 2007; Short et al., 2003). Exercise may preferentially target abdominal fat as VAT has an increased responsiveness to adrenergic activation (Arner, 1995) resulting in greater mobilization of triglycerides from this anatomical location. Women in our study were physically inactive and therefore we cannot draw the conclusion that lower VAT among those with higher CRF was due to an exercise training response; instead, lower VAT among those with higher CRF may have been due to genetic heritability. Further research is necessary to determine if exercise has a similar response on VAT in South Asian women, as previously seen in European populations.

We purposely studied post-menopausal South Asian women because they have increased cardiovascular risk. This is important to note because menopause is associated with an increase in adiposity, specifically in the VAT depot. This is likely due to post-menopausal increases in bioavailable testosterone (Janssen et al., 2015) as well as a reduction in CRF (Lynch et al., 2002). Our finding of a negative association between body composition and abdominal fat with VO_2peak is similar to what has been shown in premenopausal European women (Abdulnour et al., 2012) although further research in premenopausal South Asian women would be necessary for ethnic-specific conclusions to be drawn.

This study has limitations. We aimed to recruit physically inactive women, and we relied on self-report of physical activity during eligibility screening. While objectively measured physical activity may have been more accurate, it is more common to over report rather than under report physical activity levels (Cleland et al., 2010); thus we believe our methods were suitable to recruit a physically inactive study population. Participants were encouraged to exercise to volitional exhaustion during the treadmill test, but personal comfort level may have dictated the termination of the test. However, the average respiratory exchange ratio was 1.07, indicating that participants were relying on anaerobic metabolism and therefore working at a high intensity. In addition, women were encouraged throughout the test to continue exercising until they felt that they could no longer continue, such that they reached volitional exhaustion. Finally, the sample size was relatively small, and therefore, further research on a larger population as well as a comparison to an active control group should be conducted to try to replicate the current findings.

Higher levels of CRF were associated with lower BMI, WC, body fatness and abdominal fat (SAAT, VAT and TAAT). We found a negative relationship between VO_2peak and abdominal fat that was independent of age and body fatness but not BMI. Further research is needed to examine the effectiveness of exercise in altering body composition and specifically abdominal fat in post-menopausal South Asian women, as well as to examine the effectiveness of exercise at altering VO_2peak in this population. This study provides support for the role of exercise in altering disease prevalence in a high-risk South Asian population. In addition, it is necessary to determine if SAAT is reduced to a greater extent than VAT with exercise in a South Asian population due to the stronger association of SAAT with CRF.

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Table 3.1. Descriptive data of study participants for anthropometrics and cardiorespiratory fitness

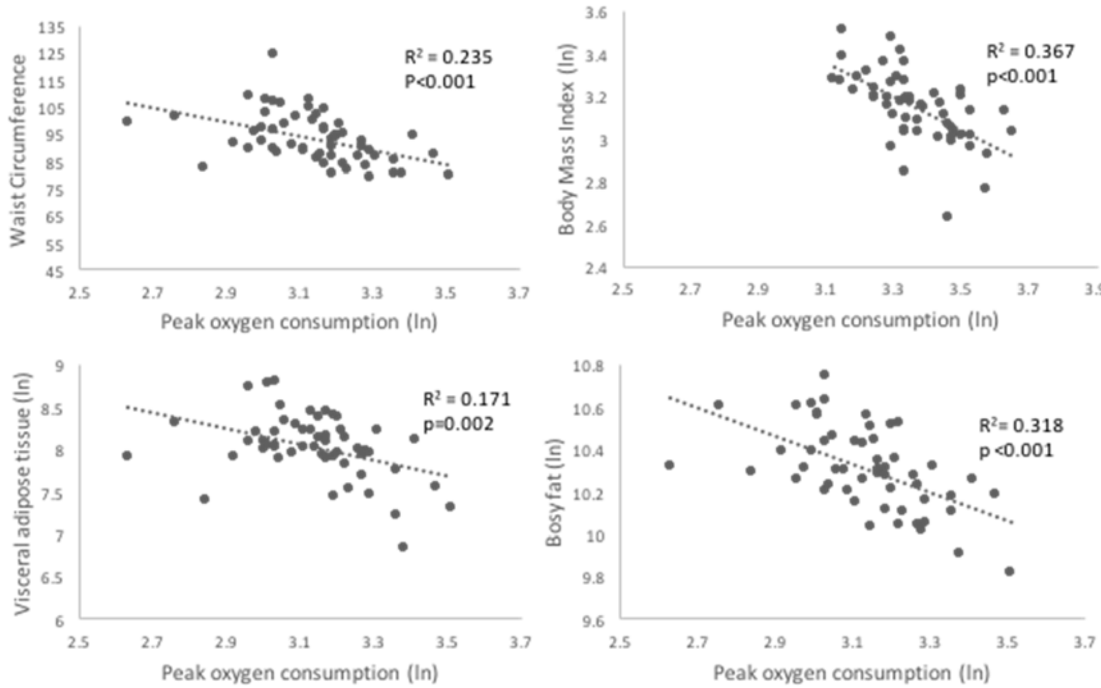
Variable	n=55
Age (years)	57 ± 6
Body Mass Index (kg/m^2) *	29.0 (28.0, 30.0)
Waist Circumference (cm)	93.1 ± 9.3
Body Mass (kg) *	68.1 (62.0, 74.7)
Total Body Fat (kg) *	29.8 (28.3, 31.4)
Body Fat (%) *	42.0 (40.9, 43.1)
Lean Body Mass (kg) *	39.0 (37.7, 40.3)
Visceral Adipose Tissue (cm^3) *	3023 (2730, 3344)
Subcutaneous Abdominal Adipose Tissue (cm^3) *	8467 (7895, 9082)
Total Abdominal Adipose Tissue (cm^3) *	11591 (10829, 12419)
VO_2Peak (mL/kg/min) *	23.1 (22.1, 24.2)
VO_2Peak (mL/kg lean mass/min) *	65.1 (61.6, 68.9)
VO_2Peak (L/min) *	1.67 (1.61, 1.73)
Measured Maximal HR (bpm)	150 ± 18
Percent of Predicted Maximal HR at test completion	92.0 ± 10.7
Maximal Respiratory Exchange Ratio	1.07 ± 0.11
Time to Exhaustion (minutes) *	5.2 (4.8, 5.5)

*data are presented as geometric mean and 95% confidence interval. Predicted Maximal Heart Rate determined by 220-age.

Table 3.2. Multiple linear regression analysis of the association between cardiorespiratory fitness and measure of inner-abdominal fat

Abdominal Adiposity	Standardized Beta	95% Confidence Intervals	P value
SAAT (cm^3) *			
Model 1: Adjusted for age only	-0.549	-0.497, -0.201	<0.001
Model 2: Adjusted for age and body fat percentage	-0.552	-0.534, -0.167	<0.001
Model 3: Adjusted for age and BMI	-0.195	-0.340, 0.093	0.257
VAT (cm^3) *			
Model 1: Adjusted for age only	-0.410	-0.291,-0.068	0.002
Model 2: Adjusted for age and body fat percentage	-0.337	-0.269, -0.027	0.018
Model 3: Adjusted for age and BMI	-0.056	-0.148, 0.198	0.689
TAAT (cm^3) *			
Model 1: Adjusted for age only	-0.564	-0.512, -0.216	<0.001
Model 2: Adjusted for age and body fat percentage	-0.576	-0.556, -0.187	<0.001
Model 3: Adjusted for age and BMI	-0.209	-0.370, 0.100	0.254

Figure 3.1. Regression analysis of body composition and cardiorespiratory fitness



VO_2 Peak: peak oxygen uptake, WC: waist circumference, BMI: body mass index, VAT: visceral adipose tissue

The following variables are presented as natural log transformations; VO_2 peak, body mass index, body fat, and VAT.

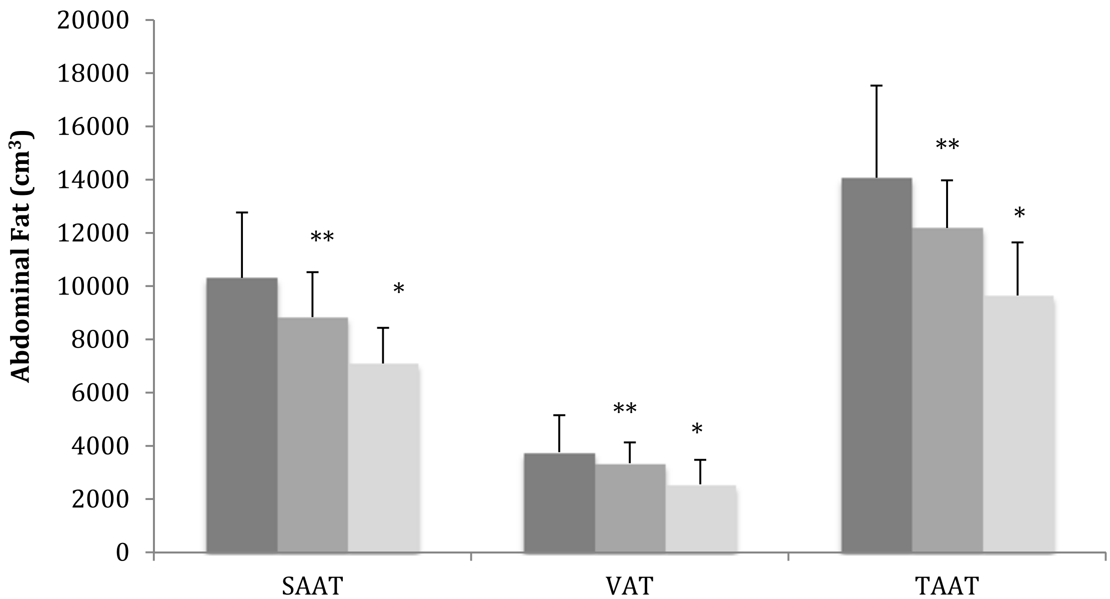


Figure 3.2. Mean amount of SAAT, VAT and TAAT measured using multi-slice imaging depicted by tertiles of VO_2peak (mL/kg/min)

Tertiles of VO_2peak (tertile 1-light grey, tertile 2-medium grey, tertile 3- dark grey). There was a significant difference in the amount of SAAT, VAT and TAAT between tertiles 1 and 3 ($p<0.001$) as shown by * and between tertiles 2 and 3 ($p<0.01$) as shown by **.

SAAT: subcutaneous abdominal adipose tissue, VAT: visceral adipose tissue, TAAT: total abdominal adipose tissue

Chapter 4.

Effectiveness of a standard aerobic exercise program and a culturally relevant Bhangra dance program on visceral adipose tissue and cardio-metabolic risk factors in post-menopausal South Asian women

4.1. Introduction

South Asian ethnicity is associated with a greater risk of type 2 diabetes (T2D) (Garduno-Diaz, Khokhar 2011) and cardiovascular disease (CVD) compared to Europeans (Gholap et al. 2011). For example, in the UK the prevalence of T2D in South Asians is five times higher than those of the indigenous European population (Gholap et al. 2011). In addition, the onset of T2D occurs approximately 5-10 years earlier in South Asians than persons of other ethnicities (Joshi et al. 2007), increasing the likelihood of associated complications such as CVD (Mather, Chaturvedi & Fuller 1998).

The rising prevalence of obesity and a preponderance of abdominal obesity in South Asians are thought to be directly responsible for the increasing trend of T2D and CVD in this population (Anand et al. 2000, Lean et al. 2001, Misra, Khurana 2011). Compared to other ethnic groups, South Asians have a unique and deleterious obesity phenotype of increased body fat, greater visceral adipose tissue (VAT) and a lower lean body mass independent of waist circumference or body mass index (BMI) (Lear et al. 2007). It is this increased amount of VAT that is implicated in the greater risk for T2D and CVD in South Asians (Lear et al. 2012).

Physical activity is a central tenet of strategies for the prevention and treatment of obesity, as well as for lowering T2D and CVD risk. However, South Asians have substantially lower levels of leisure time physical activity (Fischbacher, Hunt & Alexander 2004, Liu et al. 2010, Williams et al. 2011). Research in Caucasian populations has shown that exercise can preferentially reduce VAT (Ross, Bradshaw 2009). However, this has not been investigated in a South Asian population where VAT tends to be greater at a given body size, which along with the putative differing adipocyte biology (Arner et al.

1990), one cannot expect that exercise research on Caucasians may apply to South Asians. Given that South Asian women are less likely to participate in physical activity than South Asian men (Daniel, Wilbur 2011) and menopause is associated with increased risk for T2D and CVD (Rosano et al. 2007), post-menopausal South Asian women may be an ideal target to assess the effectiveness of physical activity in reducing VAT and lowering risk for T2D and CVD. An important consideration is that physical activity interventions should also be reflective of the cultural practices of this population (Lawton et al. 2006). In this regard, I investigated the effectiveness of both a standard exercise program as well as a culturally relevant exercise program of Bhangra dance on VAT deposition and cardio-metabolic risk factors in physically inactive post-menopausal South Asian women through a single-blinded randomized controlled trial.

4.2. Methods

4.2.1. Study Population

From November to August 2014, 184 women responded to advertisements for the study through local media consisting of television, radio, newspapers, local temples, community events and word of mouth. Individuals were eligible to participate in the study if they were post-menopausal (one year since their last menstrual cycle), had not engaged in regular physical activity in the previous six months and had a waist circumference (WC) of ≥80 cm (cut off for abdominal obesity for South Asian women) (Alberti et al. 2005). Fluency in English was not a requirement as all study research personnel were fluent in Punjabi; the predominant South Asian language in the community. Individuals were excluded if they reported having been diagnosed with CVD or T2D. After speaking to a research assistant, 70 women chose not to participate due to time commitment, concerns over the CT scan or a lack of interest (Figure 3.1). The remaining 114 women underwent screening for the study inclusion criteria. Thirty-nine women were excluded due to ineligibility and the remaining 75 women participated in the study. This study was registered at ClinicalTrials.gov (trial registration number: NCT01766453) and approved by the Simon Fraser University and Providence Health Research Ethics Boards.

4.2.2. Primary Outcome

The primary outcome of this study was the change in VAT volume in the Bhangra dance group compared to the non-exercise control and the standard exercise compared to the non-exercise control. Multi-slice computed tomography scanning was used to assess VAT volume. Most studies assessing VAT have used a single cross-sectional slice the between the 4^{th} and 5^{th} lumbar disk (L4-L5), however, intra-subject variability is high in the abdominal fat depot limiting the utility of assessing VAT using a single cross-sectional image. Single slice abdominal scans have also been criticized for their validity in detecting changes in VAT with weight loss because changes in VAT are detected more profusely 5-10 cm above the traditional L4-L5 area (Brown et al., 2015). This finding suggests that multiple slice scans should be used in an intervention study.

After an initial image acquired at the L4-L5 interverterbral disk, three 10mm slices were taken every 5 cm above this landmark and two below this landmark. Scan parameters were set at 120kVp, 300mA for one second at a 10 mm thickness within a 512 by 512 matrix using a 48 cm field of view. All six CT slices were obtained at the same time. Using the standard attenuation range of -190 to -30 Hounsfield units for adipose tissue, the cross-sectional areas were determined for each individual slice using imaging software (SliceOmatic v4.2 Tomovision, Montreal, Quebec) and VAT was calculated as all pixels in this attenuation range within the inner abdominal wall. The VAT volume was calculated as the average of the two closest scans multiplied by the distance between the scans. All five volumes were then added together for the total VAT volume. We additionally assessed total abdominal adipose tissue (TAAT) as calculated as all pixels within this attenuation range in the abdominal image and subcutaneous abdominal adipose tissue (SAAT) calculated as the difference between TAAT and VAT. Scan analyses were completed by the same individual, with a coefficient of variation for the analysis of 1.21% at the L4-L5 scan. All scans were void of participant identity prior to assessment to avoid any interpretation bias.

4.2.3. Body Composition Analysis

Mass in kilograms and height in metres were assessed with participants in light clothing (or hospital gowns), footwear removed and pockets emptied. Body mass index was assessed as mass in kilograms over height in meters squared. Waist circumference

(WC) was recorded in centimetres as the average of two measures taken against the skin at the point of maximal narrowing from the anterior view following a normal expiration. Body composition was assessed using a dual energy x ray absorptiometry (DXA) scanner (Hologic Discovery QDR 4500w, Bedford, Massachusetts) to determine lean body mass (kg), total body fat mass (kg), and percent body fat. The percentage of total body fat was calculated by dividing total body fat by total body mass.

4.2.4. Cardio-metabolic Risk Factor Assessment

Cardio-metabolic risk factors were measured after a 12 hour overnight fast and 48-hour abstinence from alcohol. Blood samples were collected by venipuncture and immediately processed and assessed. Serum and plasma assays (glucose and insulin) were conducted by standard procedures in the St. Paul's Hospital Laboratory, Vancouver, Canada. Method accuracy, inter- and intra-assay precision meets the stringent criteria required by the Canadian External Quality Assessment Laboratory. Low density lipoprotein cholesterol was assessed using the Friedewald equation (Friedewald, Levy & Fredrickson 1972).

4.2.5. Exercise Testing

Participants completed a treadmill test using the Bruce Protocol (Bruce et al., 1990). The test began at 1.7 mph and a 10% grade with the speed and grade increasing progressively every three minutes until the participant reached volitional exhaustion. Total test time was recorded as time to exhaustion (TTE). Prior to testing each participant, a gas calibration and volume calibration was completed using standard procedures. Heart rate was assessed by electrocardiography throughout the test for safety purposes. Metabolic data were collected simultaneously during the treadmill test on a breath-by-breath basis using a calibrated metabolic system (VMax SensorMedics, Houston, Texas). VO_2 was acquired as a 20-second average throughout the test. Participants were encouraged verbally throughout the test in an attempt to achieve a maximal effort. Those participants who reached volitional fatigue as well as either a respiratory exchange ratio of 1.05 at peak exercise or 85% of predicted maximal heart rate were considered to have achieved a VO_2peak.

4.2.6. Lifestyle Measures

Physical activity was determined by the 4-week modified Minnesota LTPA questionnaire and reported as the average weekly kilocalories (kcal/wk) expended. Dietary intake was assessed using a three day food record at baseline and post-intervention to identify the number of kilocalories consumed and was analyzed using the ESHA Food Processor SQL Software (Salem, OR). South Asian recipes were input into the database using standardized recipes from a nutritionist.

4.2.7. Sample Size

For our power calculation, I used data from Giannapoulou et al. in which post-menopausal women with T2D underwent a 14-week exercise intervention and had VAT assessed volumetrically (Giannopoulou et al. 2005). These authors reported a pre/post difference of 529 cm^3 and a standard deviation of 521 cm^3 (the average of the baseline groups). With alpha set at 0.025 to account for two comparisons in the primary outcome and a power of 0.80 resulting in 20 participants needed for each group. To account for a possible 25% drop-out rate, 25 participants per group were recruited and enrolled.

4.3. Study Procedures

Participants were randomly assigned to one of the following interventions (Figure 3.1); i) control, ii) standard exercise or iii) Bhangra dance. Restricted randomization was done with a web-based randomization system. Participants were randomized using computer generated random block sizes of 3, 6 and 9. A randomization research assistant not involved in participant recruitment or participants assessments performed randomization and informed participants of their group assignment. Participants were informed by the randomization research assistant to not inform the project coordinator (IAL) of their group assignments during participant assessments. Control participants were asked to maintain their current physical activity and diet for the duration of the 12 week study and were offered the Bhangra dance program at study completion as an incentive for participation. Participants in the standard exercise group underwent a 12 week aerobic exercise program 3 times per week with a female South Asian personal trainer at a local fitness centre. The program consisted of a 10 minute group warm up, 40 minutes of aerobic conditioning and a 10 minute group cool down. The prescribed exercise intensity was individualized based on maximal heart rate achieved during the exercise test. Heart rate (HR) was prescribed at 55% of HRmax and increased 10% every 3 weeks with the last 3 weeks of the program prescribed at 85% of HRmax. Aerobic exercise was performed on the treadmill, bicycle or elliptical machine. Heart rate was assessed by the personal trainer using a Polar HR monitor (Lachine, Quebec) every 10 minutes of the conditioning period and the intensity was adjusted up or down if the participant was below or above the required heart rate respectively. Participants in the Bhangra dance group underwent a 12 week program 3 times per week with a South Asian female Bhangra instructor at a local fitness centre. The program consisted of a 10 minute group warm up consisting of stretching and body weight exercises, 40 minutes of Bhangra dance and a 10 minute group cool down. Bhangra dance is a form of folk dance which originates from the Punjab area of India and consists of high intensity jumps, kicks and upper body movement to Bhangra music. The intensity of the program progressed over the 12 week period as the women became more technically skilled and fitness levels improved. Participants were encouraged to maintain their HR throughout the workouts and to modify any exercises that they found too challenging.

4.4. Statistical Analyses

The primary analysis was intent-to-treat with all participant data included in the analysis. Those participants who were lost-to-follow-up or missing data were considered 'failures' and their data assumed unchanged from baseline. Residual plots for all variables were plotted and assessed for model adequacy and insulin was log transformed prior to regression modeling. The following cases were excluded for follow-up change due to technical error: CT scan (n=1), VO_2peak (n=3), time to exhaustion (n=1). In addition, the following cases were excluded as outliers VAT (n=1), glucose (n=1) and SAAT (n=2) based on visual determination using residual plots.

Pre-post comparisons were assessed using the signed rank test, and mean change in variables between groups was compared using the Kruskal-Wallis test for non-parametric means. All outcomes were modeled using linear regression with the post-intervention values as the dependent variable and baseline values, treatment and baseline physical activity as independent variables to assess differences at trial endpoint between exercise programs and control. Three additional analyses were run for the primary outcome of VAT in the same manner described above: 1) Intent to treat analysis but with exercise groups pooled compared to the control group 2) Adherent participants (attended more than 24/36 exercise classes) from each exercise group compared to the control group, and 3) Adherent participants but with exercise groups pooled compared to the control group. Bivariate Pearson correlations assessed change in VAT and SAAT with change in physical activity volume (as measured by exercise class attendance), VO_2peak, glucose and insulin. All analyses were completed using SAS Version 9.2.

4.5. Results

A total of 75 participants were recruited (November 2013 to August 2014) and randomized to control (n=26), SE (n=23) or BD (n=26). Figure 4.1 outlines the participant flow for recruitment and follow-up for the study. Participants who were recruited for this study were on average 57 ± 6 years old, the majority of women spoke Punjabi at home and were predominantly born in India. Approximately one third of women recruited for the study were taking thyroid, BP or cholesterol lowering medication (Table 4.1). The average BMI was 29.6 ± 3.9 with 91% of participants in the overweight category and body fat was 41.7 ± 4.6 %. The primary outcome of VAT volume and secondary outcomes were clinically similar between groups at baseline (Table 4.1).

Adherence to the exercise interventions was based on attendance at the 36 prescribed exercise classes. The average attendance in the BD and SE program was 28 ± 12 and 24 ± 9 respectively, of the 36 delivered exercise classes with attendance ranging from 1 to 36 classes. Three women in the SE group (due to lack of enjoyment) and one women (due to injury) in the BD group did not attend classes after the first week of the program.

4.5.1. Outcomes

There was a significant difference across groups in the mean change of SAAT ($p<0.01$), TAAT ($p=0.02$) and BMI ($p=0.04$) (Table 4.2). In within-group pre-post comparisons there was a significant reduction in VAT ($p=0.040$) and WC ($p=0.037$) in the standard exercise program, and decreases in SAAT ($p<0.001$), TAAT ($p<0.001$), BMI (p=0.027), WC (p<0.001), HC (p=0.014), body fat (p=0.036), glucose (p=0.039) and VO_2peak (p<0.001) in the Bhangra dance program.

4.5.2. Primary Outcome

Figure 4.2 shows the individual change in VAT by group. Table 4.3 shows the comparison of the median change in the Bhangra dance and standard exercise groups compared to the control group after adjusting for the baseline value of the indicated variable and for leisure-time physical activity. When compared to the control group there was no significant reduction in the primary outcome of VAT after 12 weeks for either the Bhangra dance (-59.59 cm^3, 95%CI: -172.39, 54.22) or standard exercise program (-97.55 cm^3, 95% CI: -216.22, 21.12) (Figure 4.3). When both the Bhangra dance and standard exercise groups were pooled there was no significant reduction in the primary outcome of VAT (-77.40 cm^3, 95% CI: -178.14, 23.33) in comparison to the control group. When only adherent participants were included in analyses as defined by attending at least 24 out of the 36 classes there was a significant reduction in the primary outcome of VAT in the standard exercise group (-127 cm^3, 95%CI: -246, -8) but not the Bhangra dance group (-95 cm^3, 95% CI: -204, 14) compared to control. Exercise groups were pooled because VAT reduction was similar in both exercise groups. When both the Bhangra dance and standard exercise groups from the adherent participants were pooled there was a significant reduction in the primary outcome of VAT (-109 cm^3, 95% CI: -205, -13) compared to the control group.

4.5.3. Secondary Outcomes

There was a significant reduction in SAAT (-230 cm^3, 95% CI: -414, -46), p=0.015) and TAAT (-356 cm^3, 95% CI:-634, -78), p=0.013 after the 12 week Bhangra dance program but not the standard exercise program (p>0.05) compared to the control group (Figure 4.3). There was also a significant improvement in VO_2peak (1.9 mL/kg/min, 95% CI: 0.4, 3.5, p=0.013) and time to exhaustion (0.74 minutes, 95% CI: 0.05, 1.42, p=0.0348) in the Bhangra dance compared to control group. In secondary analyses there were significant differences between Bhangra dance and standard exercise in change in VO_2peak (1.97, 95% CI: 0.49, 3.46, p<0.05) and change in SAAT (-298.6, 95% CI: -522.9, -74.3, p<0.001). There was no significant association between change in VO_2peak or change in physical activity ($p>0.05$), as measured by the minutes of exercise class attendance, with change in VAT. There were no significant changes for any of the adiposity measures or insulin and glucose compared to the control group (Table 4.3). There were significant positive correlations ($r = 0.244$ to 0.494) between change in VAT and TAAT with change in glucose and insulin ($p<0.001$) but these associations were not seen with change in SAAT ($p>0.05$) (Data not shown).

4.6. Discussion

Neither 12 weeks of standard exercise or Bhangra dance were effective at reducing VAT. However, when the exercise groups from the adherent participants were pooled there was a significant reduction in VAT. The Bhangra dance program significantly improved VO_2peak while significantly reducing SAAT. With respect to our primary outcome there was no significant change in VAT in either the standard exercise or Bhangra dance program compared to the control group. The lack of a significant improvement in VAT is inconsistent with previous exercise interventions in European populations (Ross et al., 2004). While exercise has been shown to preferentially target abdominal fat in Europeans due to an increased responsiveness to adrenergic activation in VAT (thereby resulting in greater mobilization of triglycerides from this anatomical location) (Arner, 1995) others have reported that lipid oxidation is lower during exercise in South Asian men compared to European men (Hall et al., 2010). This finding suggests that there may be an ethnicity-specific response to exercise in regards to fat mobilization such that a greater exercise stimulus (beyond the current PA guidelines) may be needed to mobilize and reduce VAT in South Asians. When analyses were restricted to only those who attended at least two thirds of exercise sessions with both exercise groups combined, we did find a reduction in VAT compared to control.

While the exercise interventions were not effective at reducing VAT, in secondary analyses, we did find that the Bhangra dance but not the standard exercise program to be effective at statistically reducing SAAT and TAAT. It has previously been shown that exercise of a vigorous intensity can improve abdominal fat while exercise of a more moderate intensity is not always effective (Irving et al., 2008). Our standard exercise program was designed to adhere to current intensity recommendations for exercise (Garber et al. 2011) while our Bhangra dance program was a group fitness class that did not assign individual heart rate intensities. While purely speculative, it is not unusual in social fitness classes for exercise to be performed at a higher intensity due to the lack of awareness of the discomfort of exercise (Luettgen et al., 2012). When comparing the intensity of the Bhangra dance and standard exercise programs it is likely that the intensity achieved during Bhangra dance was much greater as reflected in the significant improvement in aerobic fitness in the Bhangra dance but not in the standard exercise group. Therefore, Bhangra dance may be a more appropriate physical activity program due to its vigorous intensity and associated improvement in aerobic fitness.

Since South Asian women participate in very little physical activity, (Daniel, Wilbur 2011) we designed our study to include a form of exercise that is part of South Asian culture, namely Bhangra dance, with the intention that this would be more acceptable to our target participants (Lawton et al. 2006). Women in both exercise training groups were encouraged to attend exercise classes and were contacted if they missed a class. However, despite the consistent protocol, the attendance at the Bhangra dance program was visually higher (78%) than the standard exercise program (67%). Dance interventions (Mangeri et al., 2014), specifically Bhangra dance, have shown excellent adherence when offered as an exercise program due to their perceived improved energy levels, decreased stress and an enjoyable social environment (Vahabi et al., 2015). In personal statements from the Bhangra dance participants, we received similar feedback indicating their enjoyment of the Bhangra dance program for its social aspect and fun atmosphere. It is therefore possible that, in addition to the possibly greater exercise intensity of the Bhangra dance mentioned above, the actual enjoyment of the Bhangra dance program led to greater motivation, which in turn factored into the positive outcomes not seen in the standard program.

This study has limitations. We aimed to recruit physically inactive women, and we relied on self-report of physical activity during eligibility screening. While objectively measured physical activity may have been more accurate, it is more common to over report rather than under report physical activity levels (Cleland et al. 2014); thus we believe our methods were suitable to recruit a physically inactive study population. Changes in dietary intake were monitored by two measures of 24-hour diet recall and therefore all changes in caloric intake over the 12-week program may not have been effectively captured. While we had an extensive list of inclusion criteria that may affect generalizability of the results, they were representative of the majority of our target population as most post-menopausal South Asian women are sedentary (Babakus, Thompson, 2012) and abdominally obese (Jesmin et al., 2013).

In conclusion, neither a Bhangra dance nor a standard exercise program was effective at reducing VAT compared to a non-exercise control group in post-menopausal South Asian women. Given that our exercise programs followed methodology (based on intensity and amount) effective at reducing VAT in Europeans, it is possible that the South Asian population may have a more ‘exercise-resistant’ VAT depot. However, despite this, Bhangra dance was effective at reducing SAAT, while improving exercise capacity while standard exercise was not. Therefore, Bhangra dance appears to be an effective culturally appropriate intervention for reducing risk some risk factors for T2D and CVD in this high risk population. Future research should be conducted to determine what amount of exercise stimulus is needed to reduce VAT in this population and to investigate the effect of exercise programs in South Asian men.

4.7. References

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Table 4.1. Baseline measures of study participants

	Control (n=26)	Standard Exercise (n=23)	Bhangra Dance (n=26)
Age (yrs)	57.7 ± 6.1	56.4 ± 6.9	57.7 ± 6.2
Education			
High School or less	12 (46%)	11 (48%)	18 (69%)
Some college or more	14 (54%)	12 (52%)	8 (31%)
Language			
Punjabi	22 (85%)	14 (61%)	24 (92%)
English	4 (15%)	5 (22%)	0 (0%)
Other	0 (0%)	4 (17%)	2 (8%)
Duration of Residence (yrs) *	29.9 (22.8, 37.0)	29 (23.0, 37.0)	17.9 (11.5, 34.0)
Employment Status			
Unemployed	16 (62%)	11 (48%)	16 (62%)
Employed	10 (38%)	12 (52%)	10 (38%)
Marital Status			
Married	23 (88%)	18 (78%)	22 (85%)
Separated or Divorced	1 (4%)	5 (22%)	0 (0%)
Widowed	2 (8%)	0 (0%)	4 (15%)
Place of Birth			
South Asia	25 (96%)	19 (83%)	24 (92%)
Africa	0 (0%)	3 (13%)	2 (8%)
Pacific Islands	1 (4%)	0 (0%)	0 (0%)
East Asia	0 (0%)	1 (4%)	0 (0%)
LTPA (kcal)	206 ± 265	190 ± 232	170 ± 247
Dietary Intake (kcal)			
Weekday Diet (kcal)	1655 ± 519	1532 ± 651	1844 ± 501
Weekend Diet (kcal)	1762 ± 725	1637 ± 633	1787 ± 597
VAT (cm^3)	2324 ± 764	2778 ± 972	2566 ± 1104
TAAT (cm^3)	8187 ± 1821	9399 ± 2544	8823 ± 2626

SAAT (cm^3)	5683 ± 1397	6621 ± 1872	6257 ± 1810
Body Mass (kg)	72.7 ± 8.9	74.5 ± 10.6	74.0 ± 11.6
BMI (kg/m^2)	28.9 ± 3.5	29.9 ± 3.5	30.0 ± 4.6
WC (cm)	92.8 ± 7.4	95.8 ± 8.7	93.8 ± 9.7
Body Fat (kg)	30.7 ± 5.7	32.9 ± 6.7	31.4 ± 8.0
Body Fat (%)	42.6 ± 4.5	44.9 ± 4.0	42.8 ± 5.0
Lean Body Mass (kg)	39.1 ± 5.2	38.4 ± 4.9	39.2 ± 4.9
Glucose (mmol/L)	5.4 ± 0.5	5.8 ± 0.8	5.6 ± 0.7
Insulin (pmol/L) *	87.4 (70.3, 108.9)	95.4 (81.9, 111.1)	75.4 (59.8, 95.2)
VO_2peak (mL/kg/min)	24.2 ± 4.1	22.1 ± 3.7	22.4 ± 6.2
TTE (minutes)	5.3 ± 1.2	5.2 ± 1.2	5.1 ± 1.4

Leisure Time Physical Activity (LTPA), Visceral Adipose Tissue (VAT), Subcutaneous Abdominal Adipose Tissue (SAAT), Total Abdominal Adipose Tissue (TAAT), Body Mass Index (BMI), Waist Circumference (WC), Peak Oxygen Consumption (VO_2peak), Time to Exhaustion (TTE).

* Variables subjected to natural log transformation due to non-normality and presented as median and 95% confidence intervals.

Table 4.2. Pre-post comparisons and group comparisons for change

	Control (n=26)		Standard Exercise (n=23)		Bhangra Dance (n=26)		Group change p-value between groups
	Pre	Post	Pre	Post	Pre	Post	
VAT (cm^3)	2359 (1874, 2741)	2490 (1874, 2662)	2602 (2162, 3122)	2454 (2071, 2951) *	2365 (1687, 3227)	2395 (1610, 3162)	0.346
SAAT (cm^3)	5856 (5233, 7004)	5736 (4989, 6955)	6237 (5146, 8401)	6383 (5100, 8484)	5880 (4975, 6718)	5342 (4774, 6541) ***	0.008
TAAT (cm^3)	8789 (7058, 9491)	8245 (7058, 9602)	9379 (7485, 10903)	9098 (7485, 10938)	8344 (6999, 9509)	7433 (6935, 9980) ***	0.024
Body Mass (kg)	71.1 (65.3, 75.4)	70.6 (66.8, 75.5)	74.0 (65.4, 81.6)	73.1 (63.3, 83.5)	69.6 (65.8, 75.7)	69.2 (64.4, 76.4)	0.057
BMI (kg/m^2)	27.9 (26.6, 31.8)	28.0 (25.8, 31.3)	28.6 (27.8, 32.5)	28.6 (27.4, 33.3)	28.3 (26.9, 31.9)	28.2 (26.3, 32.0) **	0.042
WC (cm)	92.3 (87.5, 97.0)	91.5 (89.8, 94.5)	95.8 (89.3, 102.0) *	91.8 (89.5, 98.5)	93.1 (88.5, 98.5)	90.4 (83.3, 94.8) ***	0.251
Body Fat (kg)	30.1 (26.3, 33.8)	30.1 (24.6, 33.8)	32.6 (27.1, 39.6)	30.0 (26.2, 39.0)	29.5 (25.7, 33.8)	30.2 (24.9 33.6) *	0.591
Body Fat (%)	42.3 (38.2, 45.7)	41.2 (36.9, 43.8)	44.7 (41.2, 47.2)	43.6 (40.6, 45.8)	42.3 (38.5, 46.3)	42.3 (38.8, 45.3)	0.763
Lean Body Mass (kg)	37.8 (35.7, 42.7)	38.9 (36.2, 42.7)	38.4 (34.0, 42.1)	38.9 (35.3, 42.7)	39.0 (35.3, 42.3)	39.4 (35.8, 41.7	0.527

Glucose (mmol/L)	5.5 (5.0, 5.7)	5.4 (5.1, 5.7)	5.7 (5.4, 6.1)	5.4 (5.2, 6.0)	5.4 (5.1, 6.0)	5.4 (5.0, 5.6) *	0.435
Insulin (pmol/L)	84.0 (62.0, 129.0)	95.0 (62.0, 141.0)	101.0 (73.0,117.0)	82.0 (64.0, 129.0)	79.0 (52.0, 107.0)	75.5 (56.0, 91.0)	0.629
VO_2Peak (mL/kg/min)	23.8 (22.9, 25.1)	24.3 (23.5, 26.7)	20.8 (20.1, 25.0)	23.2 (20.2, 26.5)	23.2 (20.7, 26.2)	25.7 (23.8, 28.1) ***	0.061
TTE (minutes)	5.5 (4.2, 6.0)	5.0 (4.2, 6.0)	5.4 (4.3, 6.0)	5.3 (4.2, 6.3)	5.3 (4.1, 6.0)	6.0 (4.5, 6.7)	0.164

Standard Exercise (SE), Bhangra Dance (BD), Visceral Adipose Tissue (VAT), Subcutaneous Abdominal Adipose Tissue (SAAT), Total Abdominal Adipose Tissue (TAAT), Body Mass Index (BMI), Waist Circumference (WC), Peak Oxygen Consumption (VO_2peak), Time to Exhaustion (TTE).

Signed rank test significance indicators for pre-post comparisons *p<0.05, **p<0.01, ***p<0.001

Overall p-value represents group differences using the Kruskal Wallis test

Table 4.3. Parameter estimates with 95% confidence intervals for secondary outcomes for standard exercise and Bhangra dance compared to control in intent to treat analysis

Variable	Standard Exercise Parameter estimates (95%CI)		Bhangra Dance Parameter estimates (95%CI)	P-value
BMI (kg/m^2)	0.0 (-0.4, 0.5)	0.892	-0.4 (-0.8, 0.0)	0.073
WC (cm)	-0.4 (-2.5, 1.8)	0.741	-1.2 (-3.2, 0.9)	0.249
Body Mass (kg)	-0.0 (-0.9, 0.9)	0.981	-0.7 (-1.5, 0.2)	0.131
Body Fat (kg)	-0.2 (-1.4, 0.9)	0.680	-0.6 (-1.7, 0.5)	0.278
Body Fat (%)	-0.2 (-1.5, 1.2)	0.808	-0.3 (-1.5, 1.0)	0.686
Lean Body Mass (kg)	0.2 (-0.8, 1.2)	0.660	-0.2 (-1.2, 0.8)	0.647
Glucose (mmol/L)	-0.03 (-0.23, 0.17)	0.775	-0.13 (-0.32, 0.06)	0.179
Insulin (pmol/L)	-0.07 (-0.16, 0.03)	0.147	-0.05 (-0.14, 0.04)	0.241
VO_2Peak (mL/kg/min)	-0.0 (-1.6, 1.5)	0.963	1.9 (0.4, 3.5)	0.013
TTE (minutes)	0.25 (-0.45, 0.96)	0.474	0.74 (0.05, 1.42)	0.035

Standard Exercise (SE), Bhangra Dance (BD), Body Mass Index (BMI), Waist Circumference (WC), Peak Oxygen Consumption (VO_2peak), Time to Exhaustion (TTE).

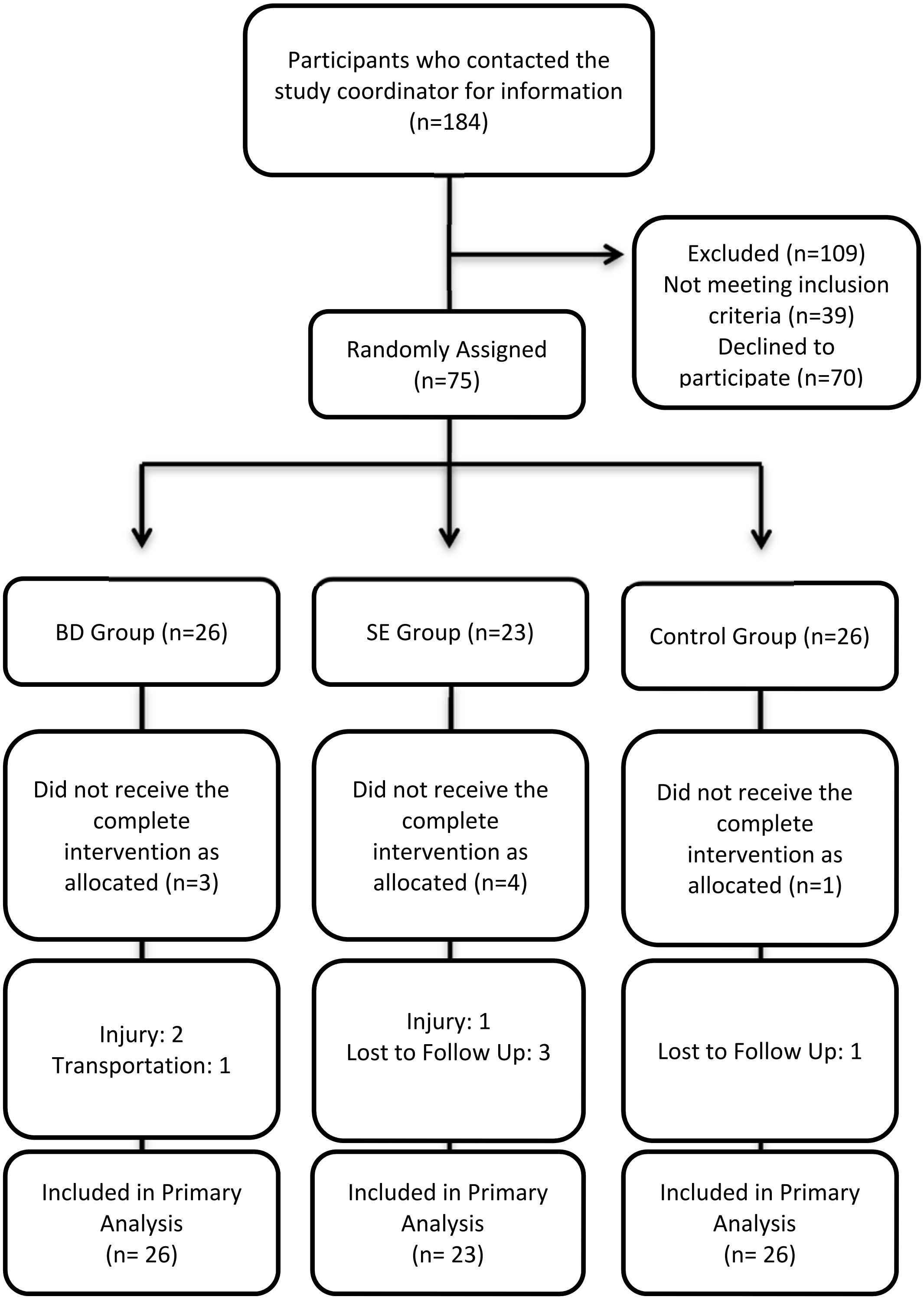

Figure 4.1. Diagram of participant flow through the study

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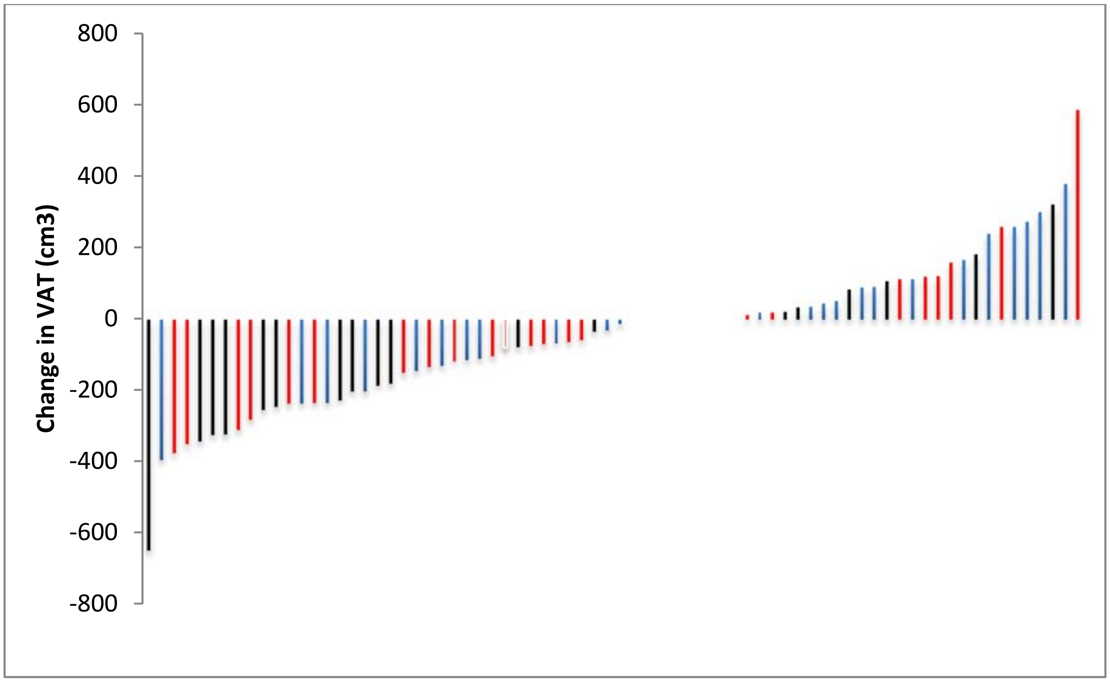

Figure 4.2. Individual change in visceral adipose tissue

Standard exercise (black bars), Bhangra dance (red bars), Control group (blue bars).

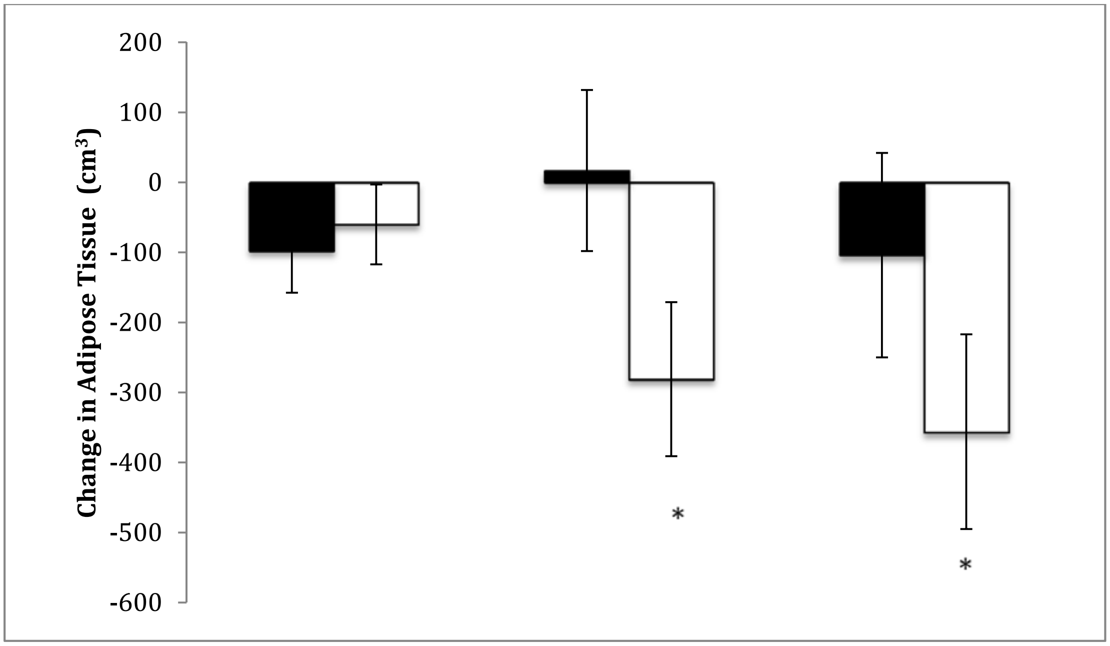

Figure 4.3. **Regression coefficients for change in visceral, subcutaneous and total abdominal adipose tissue respectively**

Going from left to right, for the Standard Exercise (black bars) and Bhangra Dance (open bars) compared to control group. Error bars represent standard error * $p<0.05$ as compared to control group.

Chapter 5.

Exercise-induced change in visceral adipose tissue predicts change in cardio-metabolic risk factors independent of change in waist circumference in post-menopausal South Asian women

5.1. Introduction

South Asians make up one quarter of the world's population and are a sizeable ethnic group in many Western countries. South Asian ethnicity is associated with a greater risk of type 2 diabetes (T2D) (Gholap et al., 2011) and cardiovascular disease (CVD) (Garduno-Diaz, Khokhar 2011), which may be due to their unique and deleterious South Asian obesity phenotype of increased body fat, greater visceral adipose tissue (VAT), and lower lean-body mass compared to Europeans (Lear et al. 2007). The South Asian obesity phenotype explains much of the variance in insulin sensitivity associated with ethnicity, suggesting a role of excess body fat in elevated T2D and CVD risk (Lear et al., 2009). Furthermore, elevated cardio-metabolic risk factors in South Asians such as cholesterol and glucose, are largely explained by greater amounts of VAT than Europeans (Lear et al. 2012). At particular risk among the South Asian population are women after menopause, as studies in post-menopausal women of other ethnicities have demonstrated that menopause is associated with increased risk for T2D and CVD (Rosano et al., 2007). This also appears coincident with changes in body composition that include enlargement of the VAT depot (Janssen et al., 2015).

Reductions in both VAT and total body fat have been suggested as primary targets for reducing the prevalence of T2D and CVD (Janiszewski and Ross, 2009). While removing VAT through surgical means has proven unsuccessful at altering cardio-metabolic risk factors (Fabbrini et al. 2010), aerobic exercise is effective at reducing VAT and total body fat while improving cardio-metabolic risk in European populations (Arsenault et al. 2009, Bouchonville et al. 2014), due to the reduction of VAT through alpha-adrenergic activation that occurs during aerobic exercise (Arner et al. 1990).

Reduced VAT may explain exercise-induced improvement in cardio-metabolic risk factors (Borel et al., 2012), but direct measurements of abdominal adipose tissue and total body fat are difficult to obtain and may expose a patient to radiation; therefore, simple anthropometric measures to overcome these feasibility issues are needed. Waist circumference (WC) has been identified as a simple anthropometric clinical marker of VAT, and a larger WC is associated with elevated CVD risk (Despres 2014). It has been suggested that associations between VAT and WC remain after weight loss (Pare et al., 2001); however, whether WC is effective for determining VAT-derived improvements in CVD risk is unclear given that change in WC could represent a combination of a change in subcutaneous abdominal adipose tissue (SAAT) in addition to a change in VAT (Lemieux et al. 2000). In addition, it is unknown whether exercise-induced change in body composition alters CVD risk in post-menopausal South Asian women as previously seen in European populations.

My primary objective was to assess the associations between changes in VAT, SAAT, WC, percent body fat and BMI with changes in cardio-metabolic risk factors following a 12-week supervised aerobic exercise intervention in inactive, post-menopausal South Asian women. Our secondary objective was to assess whether the associations between changes in VAT and total body fat and change in cardio-metabolic risk were independent of changes in WC and BMI, respectively. Our tertiary objective was to explore whether the measurement of VAT and total body fat would explain variability in changes in cardio-metabolic risk (CMR) over and above the changes in WC and BMI, which are tools commonly used in clinical practice.

5.2. Methods

5.2.1. Study Population

This study was a secondary analysis of data from a registered randomized controlled trial (ClinicalTrials.gov #NCT01766453). Participants were women recruited from the South Asian community in the Greater Vancouver area through local media including television, radio, newspapers, local temples, community events, and word of mouth. Individuals were eligible to participate in the study if they were post-menopausal (one year since their last menstrual cycle), had not engaged in regular physical activity in the previous 6 months, and had a waist circumference of 80 cm or greater (cut off for abdominal obesity for South Asian women) (Alberti et al. 2005). Individuals were not eligible to participate if they reported having been diagnosed with CVD or T2D. All participants provided written informed consent, and this study was approved by the Simon Fraser University and Providence Health Care Research Ethics Boards.

5.2.2. Computed Tomography Scanning for Abdominal Adiposity

Multi-slice computed tomography scanning was used to assess VAT volume. After an initial image acquired at the L4-L5 interverterbral disk, three 10 mm slices were taken every 5 cm above this landmark and two below this landmark. Scan parameters were set at 120kVp, 300mA for one second, 10 mm thickness, 512 by 512 matrix using a 48 cm field of view. All six CT slices were obtained at the same time. To minimize as much error as possible, each scan was assessed for anatomical matching by a trained technician. Using the standard attenuation range of -190 to -30 Hounsfield units for adipose tissue, the cross-sectional areas were determined using imaging software (SliceOmatic v4.2 Tomovision, Montreal, Quebec). VAT was calculated as all pixels in this attenuation range within the inner abdominal wall. Volumes were calculated as the average of the two closest scans multiplied by the distance between the scans. All areas were then added together for volume. We additionally assessed total abdominal adipose tissue (TAAT) calculated as all pixels within this attenuation range in the abdominal image and subcutaneous abdominal adipose tissue (SAAT) calculated as the difference between TAAT and VAT. Scan analyses were completed by the same individual, with a coefficient of variation for the analysis of 1.21% at the L4-L5 scan. All scans were void of participant identity prior to assessment to avoid any interpretation bias.

5.2.3. Body Composition Analysis

Mass in kilograms and height in metres were assessed with participants in light clothing (or hospital gowns), footwear removed and pockets emptied. Body mass index was assessed as mass in kilograms over height in metres squared. Waist circumference was recorded in centimetres as the average of two measures taken against the skin at the point of maximal narrowing from the anterior view following a normal expiration. Body composition was assessed using a dual energy x ray absorptiometry (DXA) scanner

(Hologic Discovery QDR 4500w, Bedford, Massachusetts) to determine lean body mass (kg), total body fat mass (kg), and percent body fat. The percentage of total body fat was calculated by dividing total body fat by total body mass.

5.2.4. Cardio-metabolic Risk Factor Assessment

Cardio-metabolic risk factors were measured after a 12-hour overnight fast and 48-hour abstinence from alcohol. Blood samples were collected by venipuncture and immediately processed and assessed. Serum and plasma assays (total cholesterol, high density lipoprotein cholesterol, non high-density lipoprotein cholesterol, triglycerides, glucose, insulin, apolipoprotein A, apolipoprotein B, aluminotransferase, C-reactive protein) were conducted by standard procedures in the St. Paul's Hospital Laboratory, Vancouver, Canada. Method accuracy, inter- and intra-assay precision meets the stringent criteria required by the Canadian External Quality Assessment Laboratory. Low density lipoprotein cholesterol was calculated using the Friedewald equation (Friedewald, Levy & Fredrickson 1972). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as fasting glucose multiplied by fasting insulin divided by 22.5 (Matthews et al., 1985).

5.2.5. Exercise Testing

Participants completed a treadmill test using the Bruce Protocol (Bruce, Kusumi & Hosmer 1973). The test began at 1.7 mph and a 10% grade with the speed and grade increasing progressively until the participant reached volitional exhaustion. Prior to testing each participant, a gas calibration and volume calibration was completed using standard procedures. Heart rate was assessed by electrocardiography throughout the test for safety purposes. Metabolic data were collected simultaneously during the treadmill test on a breath-by-breath basis using a calibrated metabolic system (VMax SensorMedics, San Diego, California). VO_2peak was acquired as the highest 20-second average at the end of the test. Participants were encouraged verbally throughout the test in an attempt to achieve a maximal effort. Time to exhaustion was measured by time spent on the treadmill protocol prior to volitional exhaustion.

5.3. Exercise Intervention

Participants included in this study participated in either a progressive standard aerobic exercise program or a Bhangra dance program, 3 times per week for 12 weeks and these two groups were combined for the analyses. The standard aerobic exercise program consisted of a 10 minute group warm up, 40 minutes of aerobic conditioning and a 10 minute group cool down. The prescribed exercise intensity was individualized based on maximal heart rate achieved during the exercise test. Heart rate (HR) was prescribed at 55% of HRmax and increased 10% every 3 weeks with the last 3 weeks of the program prescribed at 85% of HRmax. The participant heart rate was assessed by the personal trainer every 10 minutes of the conditioning period and the exercise intensity was adjusted if necessary. The Bhangra dance program consisted of a 10 minute group warm up, 40 minutes of Bhangra dance and a 10 minute group cool down. Bhangra dance is a form of folk dance which originates from the Punjab area of India and consists of high intensity jumps, kicks and upper body movement to Bhangra music. The intensity of the program progressed over the 12 week period as the women became more technically skilled and fitness levels improved.

5.4. Statistical Analysis

Baseline data are presented as mean and standard deviation for continuous data and number and percentage for categorical data. Change data were calculated as post values minus pre values. A paired t-test was used to assess change in body composition and cardio-metabolic risk factors after a 12-week aerobic exercise program. To answer our primary objective, Pearson bivariate correlations were used to assess the association between change in body composition and cardio-metabolic risk factors with change in the independent variables; VAT, SAAT, WC, body fat and BMI. To answer our secondary objective, separate linear regression models were created for those risk factors that were correlated with VAT as the dependent variables and change in VAT, SAAT, WC, body fat and BMI as the independent variables. Age and change in VO_2peak were included as covariates to assess whether association were independent of change in aerobic fitness. To answer out tertiary objective, models with VAT and SAAT were additionally adjusted for change in WC (Figure 5.1.), and the model with body fat was additionally adjusted for change in BMI, to assess whether these associations were independent of change in WC and BMI. Statistical significance was set at <0.05. Analyses were conducted using SPSS Version 23.0.

5.5. Results

Forty-nine women participated in the exercise programs and were 57 ± 6 years of age. Women were predominantly from India (87.8%) and spoke Punjabi (77.6%). Adherence to the exercise interventions was based on attendance to the 36 prescribed exercise classes and was 72%. Table 5.1 shows the pre- and post-data for abdominal adiposity, body composition and aerobic fitness. There was a significant reduction after the exercise intervention in VAT, TAAT, SAAT, waist circumference, body fat percent, and glucose and a significant improvement in VO_2peak ($p<0.05$).

Figure 5.2 depicts the inter-individual change in VAT, SAAT and WC over the course of the 12-week intervention in ascending order of change in VAT. There were more individuals who had the same direction of change as VAT when assessing SAAT compared to WC. Figure 5.3 depicts the inter-individual change in body fat over the course of the 12-week intervention in ascending order of body fat with BMI. There appeared to be a similar pattern of change in body fat with change in BMI.

Correlations between change in cardio-metabolic risk factors with change in body composition variables of interest; VAT, SAAT, WC, BMI and body fat are presented in Table 5.2. There were significant positive associations between change in VAT and change in WC with change in glucose ($r=0.494$, $p<0.001$ and $r=0.328$, $p=0.023$), insulin ($r=0.491$, $p<0.001$ and $r=0.322$, $p=0.024$) and HOMA-IR ($r=0.603$, $p<0.001$ and $r=0.370$, $p=0.010$) and change in BMI with change in insulin ($r=0.412$, $p=0.003$) and HOMA-IR ($r=0.452$, $p=0.001$) ($p<0.05$) (Table 5.2). Correlations between change in body composition with other body composition variables of interest; VAT, SAAT, WC, BMI and body fat are presented in Table 5.2. In addition, change in VAT was significantly associated with change in BMI ($r=0.551$, $p<0.001$) and body fat ($r=0.333$, $p=0.019$) but not change in WC ($r=0.189$, $p=0.193$) or SAAT ($r=0.206$, $p=0.156$) while there was a significant association between change in BMI and change in WC ($r=0.284$, $p=0.048$), SAAT ($r=0.428$, $p=0.002$) and body fat ($r=0.487$, $p<0.001$).

Separate multiple linear regression analyses with change in VAT, SAAT, WC, BMI and body fat as the independent variables and glucose, insulin and HOMA-IR as the dependent variables (due to their significant correlations) adjusted for age and change in VO_2peak were created. There was a significant association with change in VAT and change in glucose (β = 0.453, p=0.004), insulin (β = 0.617, p<0.001) and HOMA-IR (β=0.641, p<0.001). These associations remained after adjustment for change in WC or change in SAAT. There was a significant association between change in WC and change in HOMA-IR (β = 0.337, p=0.043) but no statistically significant change in glucose (β = 0.271, p=0.105) or insulin (β = 0.297, p=0.076) (Table 5.3). There were no significant associations between change in body fat and markers of glucose regulation after adjustment for age and change in VO_2peak. Further adjustment for change in BMI did not alter these results (Data not shown).

5.6. Discussion

A 12-week exercise program in previously inactive post-menopausal women reduced VAT, SAAT, TAAT, WC, body fat and fasting blood glucose and improved aerobic fitness. Bivariate correlations showed significant associations between change in VAT and change in WC with change in glucose, insulin and HOMA-IR. As well, change in BMI correlated with change in insulin and HOMA-IR. The relationship between change in VAT and change in glucose, insulin and HOMA-IR remained significant after adjusting for age and change in aerobic fitness, and after further adjusting for change in WC or change in SAAT. Change in WC was only significantly associated with change in HOMA-IR after adjustment for age and change in aerobic fitness.

Previous research has shown that WC is the best indicator of VAT and related CVD risk (Pouliot et al. 1994) but whether this remains true after an exercise intervention is not well studied. In a weight loss study Pare et al., found change in VAT was associated with change in WC, however, this study did not assess change in cardio-metabolic risk (Pare et al., 2001). In the current study, the association between change in VAT with change in glucose, insulin and HOMA-IR remained significant even after adjusting for change in WC; and change in VAT was not associated with change in WC. A similar study in a Japanese population found change in VAT to be significantly associated with the change in cardio-metabolic risk factors, while no such association was observed for WC;

the authors suggested that change in WC may not be a good indicator of weight loss and improvement in metabolic risk factors (Yamakage et al. 2014). The results of our study also indicate that change in VAT is a better predictor of an improvement in markers of glucose regulation than change in WC in this population of post-menopausal South Asian women. We found that change in WC was only associated with change in HOMA-IR but not with changes in glucose or insulin.

Our results agree with those of previous exercise studies researching the relationships between changes in adiposity measures and insulin sensitivity in European populations, which have shown that reduced VAT is associated with improved insulin sensitivity (O'Leary et al., 2006, Nicklas et al., 2009, Gan et al., 2003, Cnop et al., 2002). We extend the existing body of knowledge by reporting these relationships in post-menopausal South Asian women, a population at high-risk of CVD and T2D who possess a unique obesity phenotype. Similar to the present study, Cnop et al., found a significant association between change in VAT and change in insulin resistance, and this association remained independent of BMI (Cnop et al. 2002). Furthermore, VAT was reported as an independent risk factor for insulin resistance even after taking into account SAAT (Ross et al. 2002). We also found the change in VAT to be significantly associated with change in markers of glucose regulation, independent of change in SAAT. Visceral adipose tissue has previously been shown to explain the elevated cardio-metabolic risk in the South Asian population compared to Europeans (Lear et al., 2012). However, the study was cross-sectional and did not determine whether altering VAT through aerobic exercise could improve cardio-metabolic risk in a South Asian population. The association between VAT reduction and improvements in markers of glucose regulation provides support for aerobic exercise in the South Asian population to alter the high prevalence of T2D and CVD (Gholap et al., 2011) as those who do reduce their VAT deposition through aerobic exercise tend to see improvements in HOMA-IR.

Visceral adipose tissue is associated with hepatic steatosis (Perseghin, 2011) and systemic inflammation resulting in the development of hepatic insulin resistance (Bastard et al., 2006; Preis et al., 2010). It is therefore not surprising that exercise induced improvements in VAT are associated with improvements in markers of glucose regulation, however, it is interesting that these improvements were observed independent of a change in aerobic fitness. It is beneficial to understand that these individuals may be improving their risk factors even if it is not apparent through simple anthropometric monitoring. We did not observe an association between change in VAT with change in lipids, apolipoprotein A or B, aluminotrasferase or C reactive protein, however this may have been due to the minimal change seen in these risk factors after 12 weeks of exercise.

Limitations of this study include the crude measurement of insulin sensitivity through HOMA-IR. While fasting insulin measures have been shown to be a useful surrogate for insulin sensitivity, (Lorenzo et al. 2010) it would have been beneficial to have a measurement of both peripheral and hepatic insulin sensitivity as achieved using the hyperinsulinemic-euglyemic clamp method in conjunction with an isotopic tracer (Dunn et al. 2012). In addition, the study sample was limited to a homogenous population of abdominally obese, post-menopausal South Asian women and therefore results cannot be generalized to South Asian men or pre-menopausal women. Despite these limitations, this study used the gold standard of CT imaging for the assessment of VAT and provides novel information regarding the role of exercise on obesity and cardio-metabolic risk in a population of post-menopausal South Asian women.

In conclusion, we found significant associations between change in VAT with changes in fasting insulin, glucose and HOMA-IR in post-menopausal South Asian women after a 12- week aerobic exercise training program. The association between change in VAT and these cardio-metabolic risk factors was independent of change in WC and SAAT and therefore a reduction in VAT is an important indicator of improvements in glucose regulation despite not seeing a reduction in WC. South Asian women should be encouraged to engage in aerobic activity to reduce their risk of type 2 diabetes and CVD, and physicians should be aware of improvements in glucose regulation that may be seen with exercise training that are not observed through reductions in WC.

5.7. References

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Table 5.1. Paired t-tests assessing pre-post change in abdominal fat, body composition, cardio-metabolic risk factors and aerobic fitness

	Pre	Post	P-value
Visceral Adipose Tissue (cm^3)	2665 ± 1039	2591 ± 1039	0.017
Total Abdominal Adipose Tissue (cm^3)	9093 ± 2577	8860 ± 2684	0.003
Subcutaneous Abdominal Adipose Tissue (cm^3)	6428 ± 1829	6268 ± 1892	0.014
Body Mass Index (kg/m^2)	30.0 ± 4.1	29.8 ± 4.2	0.199
Waist Circumference (cm)	94.8 ± 9.2	92.4 ± 9.2	0.001
Body Fat (%)	43.8 ± 4.6	43.0 ± 4.6	0.021
Apolipoprotein A (g/L)	1.60 ± 0.24	1.57 ± 0.28	0.423
Apolipoprotein B (g/L)	0.98 ± 0.30	0.92 ± 0.33	0.121
Total Cholesterol (mmol/L)	5.17 ± 1.18	5.03 ± 1.01	0.197
Triglycerides (mmol/L)	1.43 ± 0.91	1.37 ± 0.66	0.446
High Density Lipoprotein Cholesterol (mmol/L)	1.56 ± 0.40	1.54 ± 0.38	0.340
Low Density Lipoprotein Cholesterol (mmol/L)	2.90 ± 0.86	2.87 ± 0.83	0.691
Non High Density Lipoprotein Cholesterol (mmol/L)	3.41 ± 1.09	3.45 ± 0.99	0.742
Aluminotransferase (U/L)	24.5 ± 11.3	23.1 ± 8.2	0.248
C- Reactive Protein (mg/L)	2.4 ± 1.7	2.7 ± 1.9	0.055
Glucose (mmol/L)	5.67 ± 0.77	5.43 ± 0.49	0.004
Insulin (pmol/L)	93.7 ± 41.6	91.6 ± 53.0	0.741
Homeostatic Model Assessment of Insulin Resistance	3.5 ± 1.8	3.3 ± 2.1	0.403
Peak Oxygen Uptake (mL/kg/min)	22.8 ± 3.7	24.7 ± 4.5	<0.001
Time to Exhaustion (minutes)	5.1 ± 1.2	5.5 ± 1.8	0.115

Significance set at $p<0.05$

Change data were calculated as post values minus pre values

Table 5.2. Pearson bivariate correlations between change in body composition variables of interest and change in cardio-metabolic risk factors

	Δ VAT	Δ SAAT	Δ WC	Δ Body Fat	Δ BMI
Δ TAAT	0.573 ***	0.920 ***	0.371 **	0.233	0.579 ***
Δ VAT	-	0.206	0.189	0.333 *	0.551 ***
Δ SAAT	0.206	-	0.352 *	0.120	0.428 **
Δ BMI	0.551 ***	0.428 **	0.284 *	0.487 ***	-
Δ WC	0.189	0.352 *	-	-0.153	0.284 *
Δ Body Fat Percent	0.125	-0.043	-0.310 *	0.922 ***	0.192
Δ Apolipoprotein A	0.078	0.136	0.132	-0.100	0.151
Δ Apolipoprotein B	-0.228	0.025	0.129	-0.347 *	-0.151
Δ Total Cholesterol	-0.148	0.074	0.023	-0.019	-0.77
Δ Triglycerides	-0.089	-0.086	0.117	0.013	-0.19
Δ HDL Cholesterol	0.065	0.227	0.025	0.113	0.133
Δ LDL Cholesterol	-0.112	0.241	0.070	-0.127	-0.018
Δ Non HDL Cholesterol	-0.134	-0.126	0.000	-0.017	-0.129
Δ Aluminotransferase	0.173	0.052	0.275	0.055	0.226
Δ C Reactive Protein	0.075	0.101	0.144	0.234	0.275
Δ Glucose	0.494 ***	0.075	0.328 *	0.249	0.266
Δ Insulin	0.491 ***	0.155	0.322 *	0.136	0.412 **
Δ HOMA-IR	0.603 ***	0.165	0.370 **	0.198	0.452 **

Table 5.2 – notes (continued from previous page)

*represents p <0.05, ** represents p <0.01, *** represents p<0.001

Change data presented as post value minus pre value

Total abdominal adipose tissue (TAAT), visceral adipose tissue (VAT), subcutaneous abdominal adipose tissue (SAAT), body mass index (BMI), waist circumference (WC), high density lipoprotein (HDL), low density lipoprotein (LDL), homeostatic model assessment of insulin resistance (HOMA-IR)

Table 5.3. Multiple regression analyses for body composition variables of interest with markers of glucose regulation

	Δ Visceral Adipose Tissue	Δ Subcutaneous Abdominal Adipose Tissue	Δ Waist Circumference
Glucose			
Model 1a	0.453 **	0.116	0.271
Model 1b	0.424 **	0.016	-
Model 1c	0.460 **	-	-
Insulin			
Model 2a	0.617 ***	0.154	0.297
Model 2b	0.587 ***	0.048	-
Model 2c	0.628 ***	-	-
Homeostatic Model Assessment of Insulin Resistance			
Model 3a	0.641 ***	0.176	0.337 *
Model 3b	0.606 ***	0.056	-
Model 3c	0.647 ***	-	-

*represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$

Change data presented as post value minus pre value

Model a: Adjusted for age and change in VO_2peak, Model b: Models with VAT and SAAT additionally adjusted for Waist Circumference, Model c: Models with VAT and WC additionally adjusted for SAAT

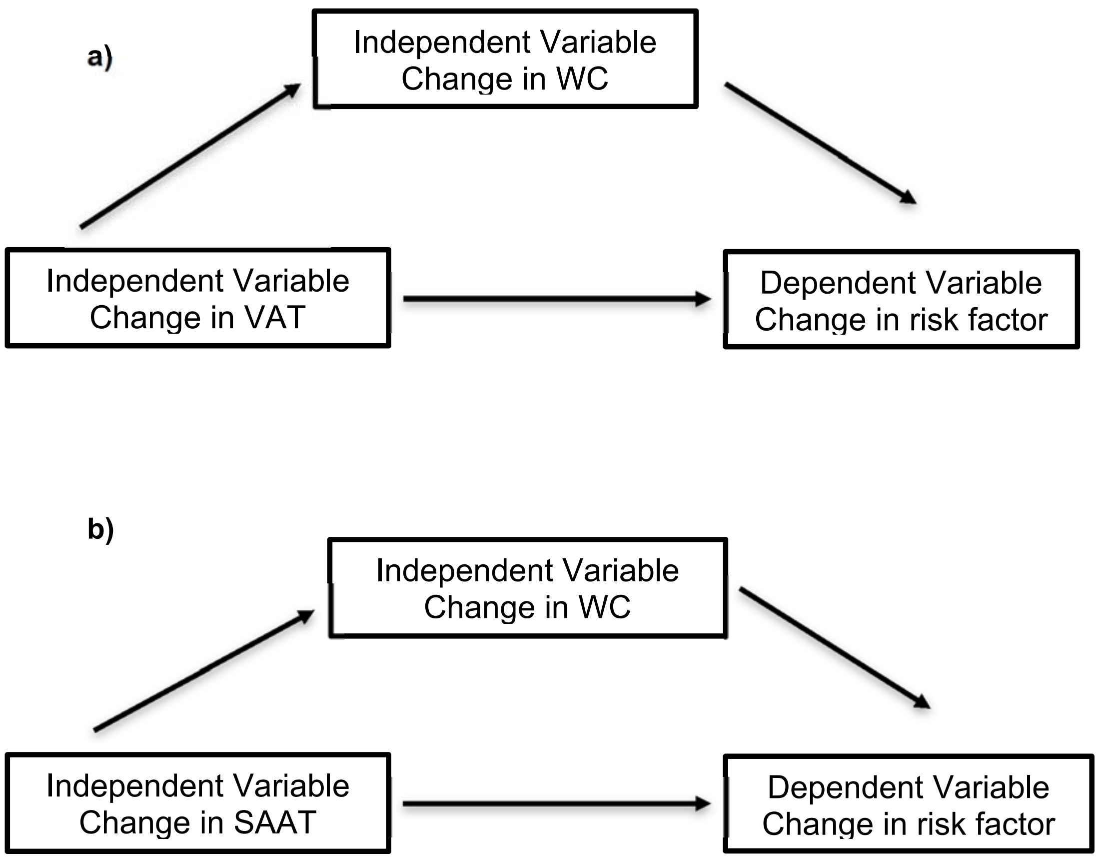

Figure 5.1 Depiction of the role of change in a) visceral and b) subcutaneous abdominal adipose tissue with change in waist circumference and change in cardio-metabolic risk factors

WC: Waist circumference, VAT: Visceral adipose tissue, SAAT: Subcutaneous abdominal adipose tissue

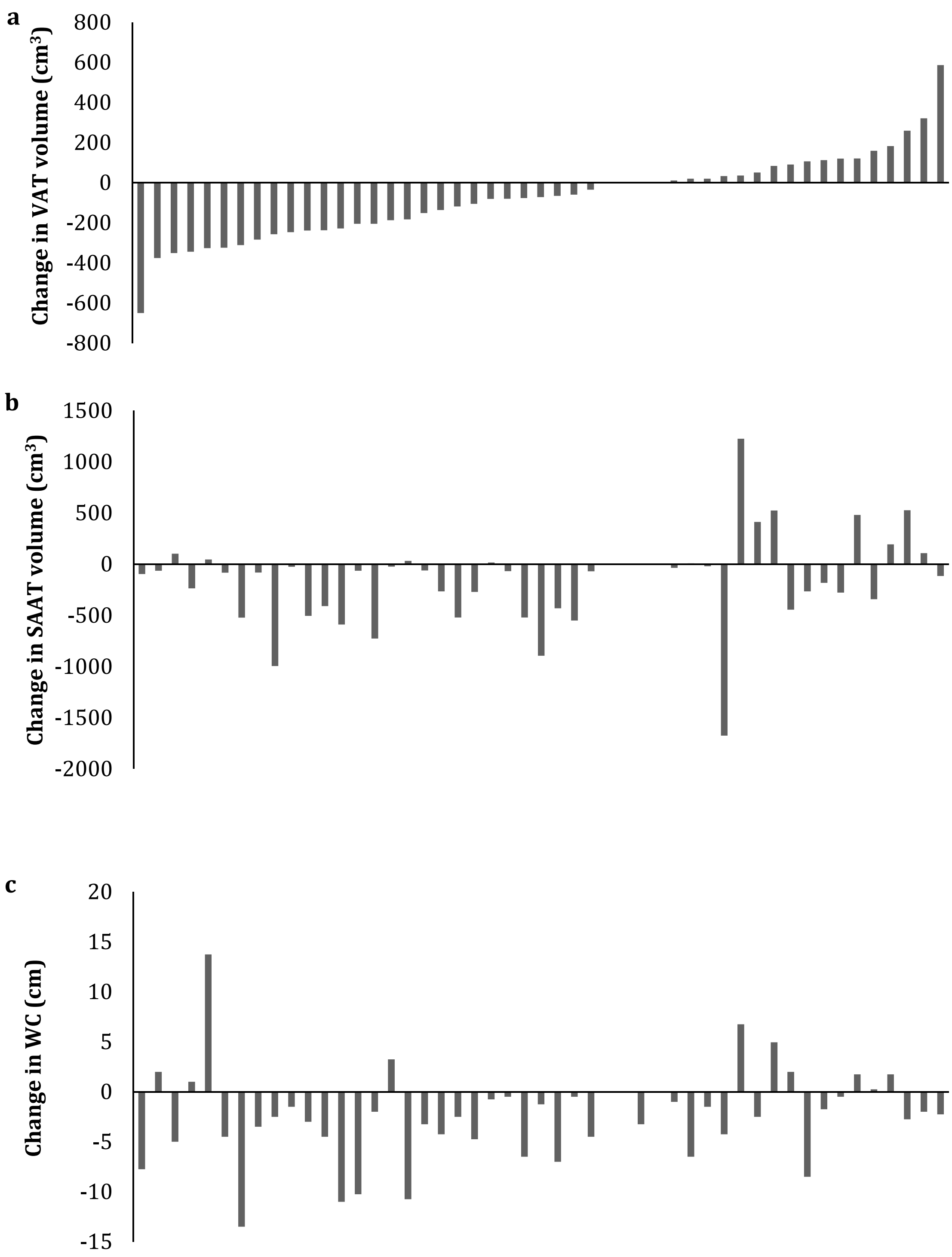
a
800
600
400
200
0
-200
-400
-600
-800
Change in VAT volume (cm³)
b
1500
1000
500
0
-500
-1000
-1500
-2000
Change in SAAT volume (cm³)
c
20
15
10
5
0
-5
-10
-15
Change in WC (cm)

Figure 5.2 Histograms comparing individual changes in subcutaneous abdominal adipose tissue (SAAT) and waist circumference (WC) with visceral adipose tissue (VAT)

(a) Individual changes in VAT volume are represented by decreasing order, **(b)** Individual changes in SAAT in the same order as histogram A, **(c)** Individual changes in WC in the same order as histogram A

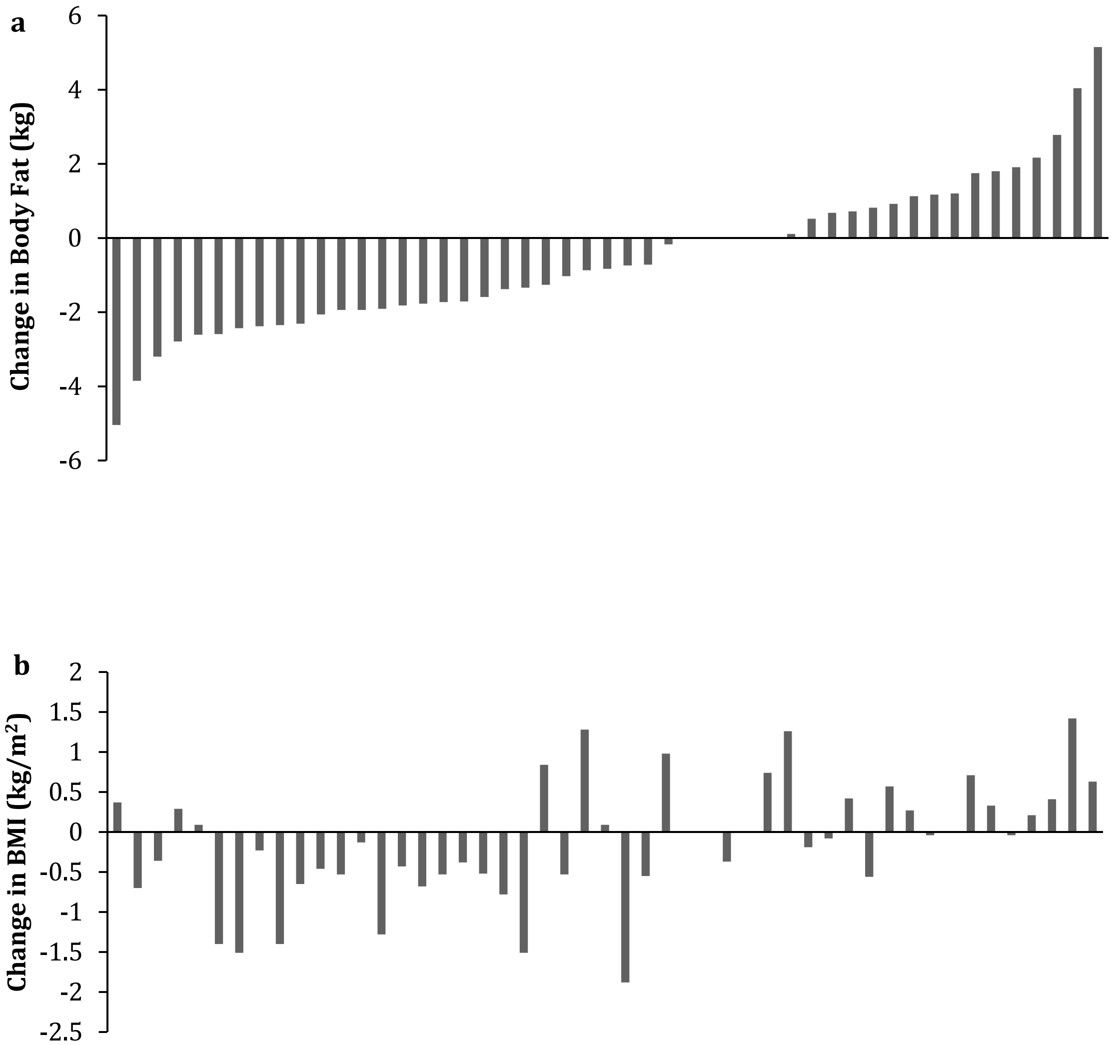

Figure 5.3. Histograms comparing individual changes in body fat with body mass index (BMI)

a) Individual changes in body fat are represented by decreasing order, **(b)** Individual changes in BMI in the same order as histogram A

Chapter 6.

Further Discussion and Conclusions

6.1. Thesis Objectives and Main Findings

The objectives of this thesis were threefold: 1) to assess the association between cardiorespiratory fitness (CRF) and visceral adipose tissue (VAT) (Chapter 3); 2) to assess the effectiveness of standard exercise and Bhangra dance in reducing VAT (Chapter 4); and lastly 3) to assess the association between exercise-induced changes in VAT with changes in cardio-metabolic risk factors (Chapter 5) in a population of post-menopausal South Asian women who had abdominal adiposity and were physically inactive.

The following are the main findings from Chapter 3:

- Physically inactive, post menopausal South Asian women who had a higher peak oxygen uptake (VO_2peak) had lower abdominal fat as indicated by lower subcutaneous abdominal adipose tissue (SAAT), VAT and total abdominal adipose tissue (TAAT)
- Associations of VO_2peak with SAAT, VAT, and TAAT were no longer significant after adjustment for BMI and therefore these associations depend on body size.

The following are the main findings from Chapter 4:

- Women who underwent a 12-week exercise program of either Bhangra dance program or a standard exercise program did not significantly alter their VAT compared to a control group of no exercise.
- When adherent participants from the exercise groups were pooled there was a significant reduction in the primary outcome of VAT in comparison to the control group.
- Bhangra dance significantly improved aerobic fitness while reducing SAAT and TAAT compared to control, however the standard exercise did not.

The following are the main findings from Chapter 5:

- A 12 week exercise program reduced VAT, TAAT, SAAT, WC, body fat percentage and fasting glucose as well as improved cardiorespiratory fitness in post-menopausal South Asian women.
- At the end of the 12-week exercise program there were significant associations between change in VAT and WC with change in glucose, insulin and homeostatic model assessment of insulin resistance (HOMA-IR)
- Associations between change in markers of glucose regulation and change in VAT were independent of change in WC.

The following sections provide further discussion on areas of scientific research that are subject to ongoing scientific debate and further address the main findings of this thesis: dose vs intensity of exercise for VAT reduction; heterogeneous response to exercise training; and ethnic specific response to exercise.

6.2. Dose and Intensity of Exercise

There is great debate in the literature regarding whether it is the intensity or the amount of exercise that is responsible for improvements in abdominal fat. Specific to this study, both the standard exercise and the Bhangra dance program were prescribed 3 times per week for one hour including a warm up and cool down for 12 weeks and were therefore of similar exercise dose. However, exercise programs differed in their prescribed intensity as observed by a higher heart rate (HR) in the Bhangra dance program (Figure 6.1) than seen in the standard exercise program (as assessed by an average HR over the 12 week program). These exercise programs were not designed to compare intensity but were naturally divergent due to the comparison of a prescribed exercise program with a group fitness program (Bhangra dance) where exercise intensity is not controlled but a result of participant motivation and enthusiasm. As a result, the Bhangra dance program showed a significant improvement in VO_2peak when compared to the control group while the standard exercise program did not. In addition, in post hoc analysis when the Bhangra dance and standard exercise programs were compared, VO_2peak was higher in the Bhangra dance program.

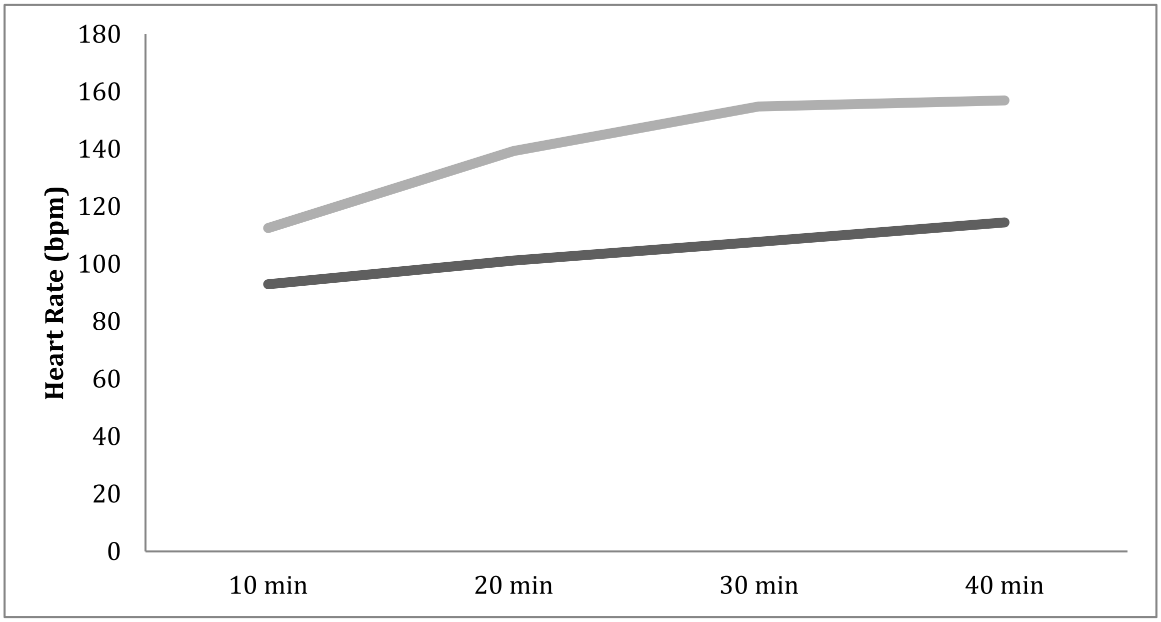

Figure 6.1. Heart rate responses

Heart rate responses from two different participants during a 40 minute program (excluding warm up and cool down) of either Standard Exercise (Dark Grey Bar) or Bhangra Dance (Light Grey Bar).

There are conflicting results in the literature when attempting to examine the role of dose vs. intensity in VAT reduction. A randomized controlled trial published in the Annals of Internal Medicine elegantly assessed the role of intensity and exercise amount in altering WC (Ross et al. 2015). This study found no superiority of exercise intensity at a fixed exercise dose over in altering WC when prescribing a low-amount, low-intensity exercise, a high-amount, low-intensity exercise and a high-amount, high-intensity exercise 5 times per week for 24 weeks in 300 abdominally obese adults compared to control. However, Irving et al. observed a required intensity threshold above the lactate threshold to achieve a reduction in VAT when controlling for exercise dose in obese women (Irving et al. 2008). Regarding the importance of exercise dose, a systematic review found 10 metabolic equivalent hours per week of aerobic exercise was necessary to see a systematic reduction in VAT (Ohkawara et al. 2007) which would be equivalent to brisk walking 30 minutes 5 days per week. We did not find either standard exercise or Bhangra dance to be effective at reducing VAT compared to control after 12 weeks but a longer program may have yielded differences between programs. In addition, there was a significant reduction in SAAT in the Bhangra dance program that was not seen in the standard exercise program, which may be evidence of an intensity disparity. It is evident that the debate of dose vs. intensity will continue and in order to apply this to the South Asian population future randomized controlled trials will be necessary examining exercise dose and intensity as separate entities.

6.3. Response Variation to Exercise

It has been well established that there is a high degree of response variation to an exercise stimulus where despite high adherence there are individuals who do not respond as predicted to the intervention. In fact, some individuals may show an adverse response to an exercise stimulus such as reduced aerobic fitness in response to aerobic exercise training (Bouchard et al. 2012). This varied response to exercise was observed in this study where there was a highly heterogeneous response to VAT reduction resulting in a high standard error (Figure 4.2.). While at one time this was considered to be statistical noise it is now the target of a new theory in exercise intervention research known as personalized medicine (Winett et al. 2014). It is challenging to determine whether participants in this study who did not alter their VAT deposition after 12 weeks of exercise were low responders or whether this was an ethnicity- and population-specific resistance to VAT change, which potentially resulted from lower fat oxidation amongst South Asians (Hall et al. 2010) and in post-menopausal women (Abildgaard et al. 2013). This in turn leads us to another area of research debate; a divergent response to exercise based on ethnic origin.

6.4. Ethnicity-Specific Response to Exercise

Physical activity guidelines have been developed based on evidence from studies primarily of Caucasian populations (Warburton et al., 2010) and therefore the effectiveness of varying amount and intensity of physical activity required to alter health outcomes may not be applicable to other ethnicities. Current physical activity recommendations suggest 150 minutes per week of moderate physical activity or 75 minutes per week of vigorous physical activity (US Guidelines). Preliminary evidence suggests that there may be an ethnicity-specific response to physical activity in Chileans (Celias-Morales et al., 2011) and this may also apply to South Asians due to the lower cardiorespiratory fitness and fat oxidation levels observed in South Asian men (Hall et al., 2010). In support of this statement, a cross-sectional study was designed to compare cardio-metabolic risk factors in South Asian and European men matched for age and BMI at the currently prescribed physical activity guidelines of 150 minutes per week of moderate-physical activity. This study, which assessed physical activity objectively using accelerometry, found a significantly higher cardio-metabolic risk when meeting the recommended guidelines in South Asian men compared to European men. In fact, 266 minutes per week of moderate physical activity was necessary in the South Asian men to match the cardio-metabolic risk level of European men who were meeting the physical activity guidelines of 150 minutes per week of moderate physical activity (Celias-Morales et al., 2013). This supports our finding that South Asians may have a more exercise resistant VAT depot that may require a greater exercise stimulus to achieve the same improvements as observed in Europeans. Given that our exercise stimulus was prescribed based on current physical activity guidelines supports the notion that evidence-based physical activity guidelines are necessary in this population and further research is necessary to determine the appropriate exercise dose for health benefits. Indeed, based on their findings, Celias-Morales et al. suggest 200 to 250 minutes per week of moderate physical activity in the South Asian population to achieve health benefits. It is noteworthy that the subjects were all male and that the calculations were based on a cross-sectional analysis (Celias-Morales et al., 2013).

6.5. Limitations

As with any study there were limitations to the research discussed in this thesis; however, due to the strong research design they are minimal and unlikely to have had an effect on research outcomes. The role of nutrition on the effect of exercise tends to be a confounding factor. In the current randomized controlled trial, diet was assessed using a three-day food record before and after the exercise intervention in order to assess whether caloric restriction was increased with the common compensatory effect of exercise (Dohle, Wansink & Zehnder 2015). While this is a standard methodology to account for diet in exercise studies, it is limited in its effectiveness due to the high error in diet recalls.

A recent study that compared a 24-hour diet record to the doubly labeled water method for assessing energy expenditure in five countries in the African diaspora noted an underreporting of energy intake by 17.9 to 52.1% (Orcholski et al. 2015). It is therefore challenging to control for diet when relying on self-report.

Participant adherence to the exercise intervention averaged 72% or 26 of the 36 prescribed exercise classes which is a moderate adherence rate but lower than studies which have looked at the effect of exercise on VAT in laboratory based settings where adherence is generally 90% or even higher. However, community-based physical activity options are effective due to their convenience and community support (Fischer et al., 2014) and therefore more likely to lead to greater physical activity uptake after study completion. In addition, the Bhangra dance program was not based on a prescribed exercise intensity and this limited our ability to look at the role of energy expenditure or intensity of exercise.

Computed tomography (CT) and magnetic resonance imaging (MRI) are optimal methods for assessing body composition. Nevertheless, CT imaging is the preferred method for assessing VAT due to its high resolution and easy acquisition comparatively to MRI. One predominant concern is the duration of scan acquisition with MRI, which may result in claustrophobia, problems remaining still and difficulty with breath holding which can create motion artefact due to abdominal movement. Even those patients who remain still, there may be motion artefact due to movement of the lower bowel. Therefore, for the clinical assessment of VAT, CT appears to be a more appropriate test. However, in CT imaging technical error may be a concern when assessing VAT at more than one time point. During CT imaging a technician uses a landmark at the L4 vertebrae to determine images above and below. It is therefore possible that technical error may reduce ones' ability to successfully match scans before and after an intervention if this landmark is mistakenly determined. To minimize as much error as possible, each scan was assessed for anatomical matching by a trained technician.

6.6. Internal and External Validity

Internal validity in this study depends on the degree to which the change in VAT is attributed to the intervention of either aerobic exercise or the lack of aerobic exercise as seen in the control group. I argue that this study had high internal validity for the following reasons: 1) study design of a single-blinded randomized controlled trial with a referent control group, 2) the assessor was blinded to group assignment and, 3) computer-based randomization. In similar previous studies, one or more of these three design considerations are normally omitted, thus decreasing the internal validity of the study. In addition, participant adherence was high in follow-up testing. Only three individuals were lost to follow up with the remaining 72 completing a minimum of a home visit with assessment of body mass and WC resulting in a 96% follow up rate. Lastly, the primary outcome of this study, CT scanning of the abdomen for VAT volume, did not involve participant motivation and therefore were not biased by testing familiarity or the psychological impact of participants in the control group wanting to improve despite not receiving the intervention.

External validity in this study is dependent on the ability to extrapolate the homogenous population of our participants as well as the intervention itself to the larger population from which the study group was sampled. While we limited our study to post-menopausal women who were physically inactive and had abdominal obesity this is highly generalizable as the majority of older South Asian women would meet these criteria. However, the sections below provide scientific rationale as to potential differences one may observe in men (6.6.1 and pre-menopausal women (6.6.2) and the need for further research in these populations. In addition, the delivery of this exercise intervention in a community recreation centre with a local exercise instructor allows for ecological validity.

6.6.1. Extrapolation of Findings to Men

This was the first study to assess the role of cardiorespiratory fitness and exercise training on VAT and cardio-metabolic risk factors in a population of physically inactive post-menopausal South Asian women. In order to extrapolate these findings to men, further research would need to be conducted due to the sex differences in the response to exercise training and lipid oxidation. A systematic review on VAT reduction in predominately Caucasian populations noted a greater reduction in VAT at a given exercise dose in males than females (Vissers et al. 2013). Men have greater rates of both lipolysis and lipogenesis in VAT compared to women (Williams, 2004) likely due to greater adrenergic stimulation in the VAT depot (Jensen et al. 1996).

6.6.2. Extrapolation of Findings to Premenopausal Women

The women in this study were specifically recruited based on post-menopausal status and differences may exist in VAT deposition and mobilization in pre-menopausal women (Abildgaard et al. 2013). Menopause leads to a significant decrease in circulating estrogen levels, which has been postulated to be associated with alterations in fat oxidation as greater fat oxidation is observed in pre-menopausal women (Carter, Rennie & Tarnopolsky 2001). Lower fat oxidation during exercise was seen in post-menopausal women compared to premenopausal women and this closely correlated with VAT (Abildgaard et al. 2013). This suggests that while abdominal adiposity may be more prevalent in post-menopausal women, it is also more resistant to change and therefore these findings cannot be directly extrapolated to pre-menopausal women of South Asian ethnicity.

6.7. Knowledge Translation

Knowledge translation is an important component of any research study as it is the application of knowledge to the public that has a direct impact on society. Our ability to conduct this research study with the input of a South Asian Advisory Committee and community partnerships has led to a unique opportunity to directly translate research into action. While our hypothesis that 12 weeks of exercise did not alter VAT compared to a control group was rejected, there were a number of findings that could directly impact the health of the community. Primarily, women who exhibited decreased VAT over the course of the 12-week exercise intervention also exhibited significantly improved glucose, insulin and HOMA-IR, such that exercise should be prescribed as a primary intervention in post-menopausal South Asian women.

In addition, this study successfully showed the importance of culturally relevant exercise programming with women expressing excitement over the Bhangra dance program. They found it fun and enjoyed the social environment of being surrounded by women similar to themselves and they were able to improve their aerobic fitness. Many community organizations have expressed interest in the results of this study, including Surrey Parks, Recreation and Culture, YMCA Community Health, Fraser Health, Simon Fraser University and Fraser Health. It is expected that this study will be used as a foundation for physical activity prescription in the South Asian community both locally and nationally. Not all research has the privilege of having such a direct impact on the health of the community and the results of these publications will extend beyond academia. However, this is just the beginning because many scientific questions that remain unanswered, which I discuss below.

6.8. Future Research

This thesis provides a starting point for discussing the impact of exercise as a preventative measure in the South Asian community. To date, research is lacking on the influence of exercise on cardio-metabolic risk factors and obesity in the South Asian community. Given that South Asians represent nearly a quarter of the global population it is necessary to develop robust scientific literature around the field of exercise and health in the South Asian population.

A number of questions remain unanswered that are priorities for future research: 1) What role does exercise dose and intensity play in altering VAT and improving CVD risk? 2) Would exercise alter VAT deposition in the same manner in men and pre-menopausal women? 3) What were the reasons that VAT was not significantly reduced with 12 weeks of aerobic exercise? 4) Why did some people respond positively to the intervention while others did not? and 5) Do physical activity guidelines of 150 minutes per week of moderate physical activity apply to the South Asian population?

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