ASSOCIATION BETWEEN CARDIORESPIRATORY FITNESS AND METABOLIC RISK FACTORS IN A POPULATION WITH MILD TO SEVERE OBESITY

KATHY DO

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

GRADUATE PROGRAM IN KINESIOLOGY AND HEALTH SCIENCE

YORK UNIVERSITY

TORONTO, CANADA

JUNE 2016

Abstract

High cardiorespiratory fitness (CRF) is associated with favorable health outcomes, independent of BMI, however it is unknown if this still applies to individuals with moderate to severe obesity. Patients from the Wharton Medical Clinic were categorized as mild or moderate/severe obesity and fit or unfit. High CRF was associated with a lower risk of low HDL cholesterol for only those with mild obesity. Conversely, high CRF was associated with a lower risk for elevated blood pressure for only the moderate/severe obesity group. However, high CRF was associated with a lower risk for elevated waist circumference for both obesity groups. There was no difference in the risk of elevated fasting glucose or triglycerides for any of the obesity or CRF groups. Generally, the beneficial effect of having a high CRF was similar in the moderate/severe obesity group compared to the mild obesity group.

Co-Authorship

The co-authors of the manuscript contained within this thesis are Dr. Jennifer L. Kuk, Dr. Ruth E. Brown, Dr. Sean Wharton, and Dr. Christopher I. Ardern. KD, REB and JLK: Study concept and design, analysis and interpretation of the data. KD wrote the manuscript draft. All authors were responsible for the revision of the manuscript for intellectual content.

Acknowledgements

I would first like to thank my parents who have supported and motivated me throughout my life. Both of you have always stood by my side throughout my many successes and failures and were proud of me no matter what. Thank you for all the hard work and sacrifice you both endured in order to allow for my brothers and I to be where we are today.

Kevin, you are my irreplaceable other half. Thank you for being my best friend and keeping me grounded since grade 10. All the success that I have had in and out of school could not have happened without you by my side. You have always been there for me to let out all my stress and worries and keep me constantly smiling and laughing even during the hard times of my life. Thank you for constantly reminding me that hard work and perseverance does not go unnoticed but at the same time reminding me of the importance of remaining in the present and appreciating the little things in life.

I would also like to thank my lab mates, Arsh, Lilian, Naseem and Rebecca. Without you girls I do not know if I could have endured those long days in the lab. Thank you for all the girl chats we had during our breaks, memories we were able to make together on the west coast, and making the lab feel like a second home. Elizabeth, William, and Sumaira, I really enjoyed getting to bond with you all during our long shifts entering data and it truly made coming to work more enjoyable. To Ruth, you were a great mentor to me when I was beginning to explore the world of research and your work ethic and success was inspirational. Thank you Mike for seeing the potential in me as a volunteer which began my long journey in the Kuk Lab. To Dr. Chris Ardern, it has been a privilege to learn from you this past year and thank you for always being readily available to help me despite your busy schedule.

Last but certainly not least, I cannot express how grateful I am for having the opportunity to be a volunteer, research assistant, and graduate student with Dr. Jennifer Kuk. Funny how our first ever interaction was when you stopped your lecture in KINE 1020 to call me out on the chair that I did not even break. You are a kind and caring person that always wants what is best for her students. It took some time to get used to the fact that you would answer my questions by simply redirecting the question back at me. This made me learn that you believed in my ability and saw the potential in me. When I reflect back on my time at York, I can honestly say that meeting you and learning under your supervision was a blessing. Without you and the opportunities that were presented to me because of you, I would have not been able to go on to pursue my passion in medicine. You believed in me when I didn't believe in myself and because of that I was able to grow and mature and just be more confident in myself. I couldn't have asked for a better supervisor and lab mom and hope that I made you proud over the years.

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1.0 General Introduction

Obesity is the most prevalent metabolic disease in the world and is the 5th leading cause of mortality worldwide (1). By 2030, obesity is anticipated to affect more than 1 billion people worldwide (2), in large part due to the ever increasing accessibility of calorically dense food and sedentary lifestyles (3). It is well established that obesity is associated with many chronic conditions such as type 2 diabetes, hypertension, dyslipidemia, cancer (4–7) as well as an increased risk of cardiovascular disease and all-cause mortality (5,8,9). Visceral adipose tissue, a type of abdominal adiposity, is more highly associated with negative health consequences related to obesity as compared to overall obesity (10). Although evidence suggests that a 5% to 10% reduction in body weight is associated with improvements in health risk (11,12), not everyone may benefit from a reduction in weight (13,14). There is a subgroup of individuals with obesity who are metabolically healthy as they are protected from the negative health consequences associated with obesity (15,16). Although the underlying mechanism is not well established, one of many hypotheses is that it is partly mediated by having high cardiorespiratory fitness (CRF) (17,18).

Physical activity (PA) is recommended for the prevention and management of obesity as it is associated with improvement in obesity-related risk factors (19,20). Since many epidemiological studies rely on self-reported PA data - which is prone to self-report bias as compared to CRF measurements - CRF is often a stronger predictor of health outcomes than self-reported PA (21,22). It is well established that low CRF is inversely associated with cardiometabolic risk and overall mortality, independent of BMI (23–26). However, it is still unclear whether the beneficial effect of CRF is still present in populations with moderate-to-severe obesity as much of the literature is restricted to populations that are normal weight, overweight, or mild obesity. Therefore, the aim of the present thesis is to examine the association between CRF and metabolic risk factors in a population with mild-to-severe obesity.

2.0 Review of Literature

Introduction

Obesity is known to be a significant risk factor for the pathogenesis of many cardiometabolic abnormalities (4,9,27,28). Given the increase in prevalence (2,29,30), obesity is the focus of public health concern worldwide. Engaging in physical activity (PA) and maintaining a high cardiorespiratory fitness (CRF) level are lifestyle interventions recommended for individuals with obesity for weight management (20). However, weight loss is not always the most important outcome given that many studies find that PA and high CRF have also been shown to be associated with a reduction in health risk without weight loss (19,31,32). Moreover, not all individuals with obesity have an adverse metabolic profile (15,16). The fit-fat paradox is one of many possible hypotheses to why these individuals with obesity are metabolically healthy due to their high CRF levels (17).

The following review will describe in more detail the current knowledge on the increased risk of morbidity and mortality associated with obesity. This review will also discuss the benefits of PA and CRF to health, with a specific focus on the fit-fat paradox.

Obesity

Obesity is defined as a chronic and progressive condition characterized by excess fat accumulation in the body that can impair health (33). Obesity is a major public health concern worldwide and is the fifth leading cause of global death (1). The prevalence of obesity in Canada is increasing over time (29). From 1985 to 2011, obesity rates have increased from 6% to 18% (29). The prevalence of more severe obesity increasing at a much greater rate compared to overweight or mild obesity (29). This indicates that not only will more individuals be classified as obese but they are more likely to be in more severely obese. The annual cost of obesity and its related aliments on Canada's health care system is approximately 4.6 to 7.1 billion dollars (29).

Body mass index (BMI) has traditionally been used to assess excess weight and characterize obesity, where obesity is defined as having a BMI $\geq$ 30.0 kg/m^2. Obesity can be further grouped into three subclasses: class I obesity: BMI between 30.0 kg/m^2 - 34.9 kg/m^2; class II obesity: BMI between 35.0-39.9 kg/m^2, and; class III obesity: BMI $\geq$ 40 kg/m^2. Although BMI is the most commonly used method to classify obesity, there are limitations as BMI does not differentiate between the fat free mass and fat mass and does not account for body fat distribution (34). It is now established that fat distribution may be more important in determining health risk than overall total body fat (35). In particular, abdominal obesity is strongly correlated with negative health outcomes compared to overall obesity (35–37).

Waist circumference (WC) is a relatively easy anthropometric measure of the amount of adipose tissue around the abdomen. It has been shown that WC is a stronger predictor of obesity-related health risk compared to BMI (37). However, it has been reported that the use of WC in combination with BMI allows for a more accurate identification of those with increased obesity-related health risk within each BMI category (38–40). Therefore, the use of waist circumference and BMI together is more sensitive in measuring abdominal adipose tissue and determining overall health risk than either measure alone and overall more feasible in clinical settings than magnetic resonance imaging or computed tomography scans.

Adipose tissue is known to function similar to an endocrine organ by releasing different factors such as cytokines and pro-inflammatory markers that disturb metabolic homeostasis and influence the pathogenesis of obesity-related comorbidities (41–43). Adipose tissue can be categorized into two main depots: subcutaneous adipose tissue or visceral adipose tissue (41,43). Subcutaneous adipose tissue is the fat depot between the skin and abdominal muscle wall (43). Visceral adipose tissue is the fat depots within the intrathoracic and intra-abdominopelvic regions (43). Fat can also be stored in tissues other than adipose tissue such within liver, skeletal muscle, and the heart which is collectively known as ectopic fat (43). It has been demonstrated that there is a stronger association between visceral adipose tissue and cardiometabolic dysfunction than subcutaneous adipose tissue (44). Visceral adipocytes are larger in size and since the size of the adipocyte is positively associated with the amount of adipokines released, visceral adipocytes have greater adipokine secretion than subcutaneous adipocytes (42,43,45). There are also differences in the density and affinity of receptors for insulin, catecholamines, and adenosine between visceral and subcutaneous adipose tissue (42). Visceral adipose tissue is more responsive to the lipolytic effect of catecholamines and less sensitive to the anti-lipolytic effects of insulin as compared to subcutaneous adipose tissue (42). This overall increased lipolytic activity can result in increased mobilization of free fatty acids from the visceral adipocytes into the portal vein that connects to the liver (42). Accumulation of free fatty acids in the liver alters liver metabolism as very low-density lipoprotein cholesterol and glucose production is enhanced and hepatic clearance of insulin is disrupted (46). Overall, this contributes to the onset and progression of hyperinsulinemia, hyperglycemia, and fatty liver disease (41).

Obesity can also influence the cardiovascular system structure and function due to the overall increase in total blood volume and cardiac output required by the large quantity of metabolically active adipose tissue (47). For example, obesity can lead to the thickening of the left ventricle as the heart compensates for the higher workload and increased systemic resistance, known as left ventricle hypertrophy (47). Obesity also alters vascular homeostasis by impairing the equilibrium between relaxing and contractile endothelial factors which is a vital component in developing hypertension (48). Obesity is also highly correlated with chronic low-grade inflammation (e.g. C-reactive protein; CRP) and insulin resistance (e.g. HOMA-IR, etc.) (28). Taken together, obesity alters many mechanisms and pathways within the body that directly and indirectly lead to the pathogenesis of multiple comorbidities and mortality.

Although it is well established that obesity is related to increased risk of comorbidities and mortality, there is considerable variability in regards to the severity of health complications and mortality risk presented by each individual with obesity. Even when diagnosed with comorbidities such as cardiovascular disease, heart failure, coronary artery disease, and type 2 diabetes, some individuals with obesity have similar or a better prognosis than those with normal weight (13,49–52). A similar or better prognosis in individuals with obesity may be likely due to their increased muscle mass, less cachexia (53), and less nutritional inadequacy (52) as compared to individuals with lower BMI. In addition, there are individuals with obesity with metabolic profiles that are nearly indistinguishable from healthy normal weight individuals (15,16,54). One of the underlying mechanisms to why individuals with obesity can be metabolically healthy, may also be the contribution of PA engagement and high CRF to improving body composition which in turn improves metabolic markers and reduces mortality (17,18,55,56).

Physical Activity & Cardiorespiratory Fitness

Although physical inactivity is one of the well-known modifiable risk factors for many chronic diseases such as type 2 diabetes, obesity, osteoporosis, depression, hypertension, and coronary artery disease (19,31,57), approximately 54% of the Canadian population remains physically inactive by self-reported data (58). Physical activity is classified as any bodily movement produced by the skeletal system that requires the expenditure of energy (59). Physical activity is beneficial for preventing the onset of chronic conditions (primary prevention), attenuating, managing and potentially reversing established chronic conditions (secondary prevention), but also reducing the risk of mortality.

The Canadian Physical Activity Guidelines recommend a minimum of 150 minutes of moderate to vigorous PA a week for adults between the ages of 18 to 64 years old to reap health benefits. However, research has demonstrated that engaging in amounts of PA that is lower than the recommended levels still results in improvements in health (60). Individual bouts of exercise can have acute effects on lowering plasma glucose levels for up to 48 hours through the increased translocation of GLUT-4 glucose transporters stimulated by muscle contractions (61). Similarly, PA improves lipid metabolism by reducing plasma free fatty acids (32), reducing intramuscular and hepatic lipids (32,61); improves serum concentrations of TG, cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol; and increases overall lipolytic enzymatic activity (62). It is important to note that the appropriate dose of PA to generate health improvements is different for various cardiometabolic risk factors. For example, moderate intensity PA, as opposed to vigorous intensity PA, is recommended for decreases in blood pressure (63). In contrast, increases in the total volume of PA through increases in frequency and/or duration are to be focused on for improvements in HDL cholesterol which can indirectly improve total and LDL cholesterol through clearance of LDL cholesterol (64). Nonetheless, long-term PA is recommended as these transient benefits diminish approximately 48 hours after exercise (65,66). Some chronic adaptations that arise from habitual PA include upregulating the expression of GLUT-4 proteins to improve insulin sensitivity (67), increased arterial compliance and production of nitric oxide to improve blood pressure regulation (61).

Engaging in PA is a very common lifestyle modification recommended for all individuals with obesity. It is typically sought as a means to increase caloric expenditure needed for an overall negative energy balance for weight loss. Research has shown that modest weight loss of 5% to 10% of body weight has been correlated with a beneficial effect on cardiovascular and metabolic risk factors (11,12,68). Exercise intervention studies often result in both a reduction in body weight as well as an improved metabolic profile. Consequently, it is hard to differentiate whether the health improvements were directly from exercise or indirectly from a reduction in body weight. Nonetheless the benefits of PA are not entirely contingent upon weight loss as studies have shown that exercise interventions without weight loss still show improvements in visceral adiposity, liver fat, lipid profile, and insulin sensitivity (32,64,69).

Physical activity engagement is also beneficial for improving physical fitness (70). Although PA and physical fitness are often used interchangeably, PA is the act of expending energy whereas physical fitness is a set of attributes that relates to the ability to perform PA and encompasses aspects such as CRF, musculoskeletal strength, and flexibility (59). In particular, CRF is a measure of the capacity for the cardiovascular and respiratory system to provide oxygen rich blood and eliminate waste products to and from skeletal muscle during sustained exercise (59). Cardiorespiratory fitness is assessed with tests that measures aerobic capacity by either measuring or predicting maximal oxygen consumption (i.e. VO_{2max}). One method used to predict VO_{2max} using a treadmill test is the Bruce protocol which is a graded multistage test where the total time completed on the treadmill is entered into sex-specific predictive equations. Total treadmill test time is highly correlated with VO_{2max} ($r = 0.94$) with the Bruce protocol (71). However, individuals with obesity are more likely to stop prematurely during VO_{2max} testing due to obesity-related joint and mobility problems which may cause their total time and overall predicted VO_{2max} to not reflect their true CRF level (72).

Cardiorespiratory fitness is thought to be a measure of habitual PA behavior (73). However, research suggests that health outcomes are less strongly related to PA than CRF and that CRF is a stronger predictor of overall health (21,22). This may be due to the fact that CRF and PA differ in the method in which the information is collected. Physical activity is often measured through self-administrated questionnaires and self-reported data is subjective and often less reliable as it is more susceptible to recall bias (74,75), social desirability (74), and inconsistency in perceiving of PA intensity (76). This may be the reason why Lakoski et al. (77) found that participants with obesity did not increase their CRF level as compared to individuals with normal weight when reporting to have engaged in similar amounts of PA since inaccuracies in self-reported PA tend to be greater with individuals with obesity as compared to leaner individuals (78,79). Using accelerometers is a more objective measure of PA; however, accelerometers are also prone to inaccuracies in quantifying habitual PA behaviour. For example, intensity thresholds used to assess accelerometer output do not take into account age and gender (80) and most accelerometers do not measure upper-extremity activities or take into consideration load-bearing movements (81). Also, the placement and sensory capacity of accelerometers may lead to inaccurate measures in individuals with obesity with higher amounts of abdominal adipose tissue (82). The assessment of CRF is often considered more objective as it is performed by trained technicians in a laboratory or clinical setting using tested protocols. Further, biological and genetic factors that influence health outcomes may also influence CRF and result in a stronger correlation between CRF and health outcomes. It is reported that ≥ 50% of the variability in CRF can be attributed to heritable factors (83). Nevertheless, many studies have shown that improving CRF is associated with decreased prevalence of obesity, metabolic syndrome, more favourable blood pressure, serum TG, LDL cholesterol, HDL cholesterol, and TG/HDL cholesterol ratios (23,24,84). It is important to note that there is variation within the literature as to what constitutes “low” CRF, as some studies use absolute cutoff points based on metabolic equivalents (25) while others use age- and sex-specific VO_{2max} cut-offs (24,55). Nevertheless, research has shown that the greatest benefit to health arises when CRF improves to the point where individuals are classified within the upper 80% (high CRF) instead of lower 20% (low CRF) using age- and sex-specific VO_{2max} cutoffs (85). Regardless of the classification used, high CRF is often reported to be associated with better health outcomes than low CRF (18,23–25,84).

Fit Fat Paradox

There is increasing evidence within the literature that not all individuals with obesity would benefit from weight loss and it may be due to their CRF status. This overall phenomenon is called the fit-fat paradox whereby some individuals with obesity are not negatively affected by their excess weight and are classified as metabolically healthy because they are normotensive, insulin sensitive, have less visceral adiposity, and have a favorable lipid and inflammatory profile (15,16,54). There are differences in the criteria used to classify metabolically healthy obesity (MHOB). Definitions of MHOB range from having ≤ 1 metabolic risk factors, ≤ 2 metabolic risk factors, or the total absence of clinical or subclinical metabolic risk factors (17,86,87). The prevalence of MHOB within literature ranges from 1.3% to 30% (17,54,87), which may be due to the inconsistency in defining MHOB.

The healthy profile of individuals with MHOB may be in part due to their high CRF level (17). One of the first studies to publish findings on the fit-fat paradox was by Wei et al. (25) using Aerobics Center Longitudinal Study (ACLS) data. They demonstrated that men who were overweight or obese but still fit were at an overall lower risk of cardiovascular disease mortality than men who were normal weight but unfit (25). In regards to metabolic health, having high CRF has been associated with decreased prevalence of metabolic syndrome, more favourable blood pressure, TG, and HDL cholesterol (23), independent of adiposity (24,84). High CRF is also positively correlated with beta cell function and insulin sensitivity and negatively correlated with fasting glucose in women with obesity (88). Longitudinal data has also demonstrated the beneficial effect of improving CRF on mortality and morbidity. Studies have demonstrated that either maintaining or improving CRF over time was associated with a decreased risk of hypertension, metabolic syndrome, hypercholesterolemia, and cardiovascular disease and all-cause mortality as compared to decreases in CRF, independent of any changes in BMI (89,90). Despite these findings, some studies have not shown that having high CRF reduces the negative health consequences and increased risk of mortality associated with obesity (26,61,91). For example, analyses from the Lipid Research Clinics Study reported that individuals with obesity and high CRF were still at a higher risk of all-cause mortality compared to individuals with normal weight and high fitness (91). Moreover, a systemic review found that although individuals with obesity and high fitness still had a lower all-cause and cardiovascular mortality risk, they had an overall increased risk of type 2 diabetes and cardiovascular risk factors as compared to individuals with normal weight and low fitness (61).

The benefits of PA in populations with obesity have also been very well described. Indeed, in populations with obesity, PA is inversely association with the risk of type 2 diabetes

(31), gestational diabetes (92), cancer, osteoporosis and cardiovascular disease (85). However, the joint analysis of adiposity and PA on health still demonstrates that adiposity has a greater association with health even when adjusting for PA (93–95). Nevertheless, PA should be highly recommended to reduce the negative ailments associated with obesity.

Despite the well-established associations between obesity, morbidity, and mortality, it seems promising that increased PA and fitness provides some degree of protection from the obesity-related negative health ailments. However, most of the studies examining the associations between increased PA, high CRF and health outcomes have focused on populations with normal weight, overweight or mild obesity. The underlying mechanism regarding the benefit of high CRF on health outcomes is also not well documented. Some studies hypothesized that a reduction of ectopic fat depots may explain the variance in mortality and morbidity risk at different levels of CRF, independent of BMI (96). However, after adjusting for WC and visceral adipose tissue, the inverse relationship between ectopic liver fat and fitness was not significant (97). Therefore, the beneficial effect of fitness on health may be partly mediated through a reduction of visceral adipose tissue (44). Studies have reported that individuals with a moderate to high CRF had a lower amount of total fat mass, abdominal subcutaneous and visceral adipose tissue for a given BMI and WC value (18,98). However, Wong et al. (18) found that this benefit of fitness on visceral adipose tissue decreases with increasing BMI and seems to be abolished after a BMI of 35 kg/m^2. Therefore, it remains unclear whether high CRF is still beneficial on health outcomes such as metabolic risk factors in populations with moderate to severe obesity as visceral adipose tissue is thought to be a vital mediator of the overall beneficial effect of high CRF.

Summary of Literature

In summary, obesity is associated with increased risk of morbidity and mortality (4,8). Yet there are individuals with obesity who are not negatively affected by their excess weight and are classified as metabolically healthy (13,15). The positive effects of high CRF are thought to explain why metabolically healthy obesity is positively associated with insulin sensitivity, blood pressure and lipid profile (17,73). This beneficial effect of high CRF on reducing health risk is thought to be partly mediated through a reduction in visceral adipose tissue (18). Given the disproportionate increase in the prevalence of upper obesity classes (29), further research is needed to understand if there is a beneficial effect of high fitness within this group. The aim of the present study is to therefore examine if the beneficial effect of having high CRF on metabolic risk factors is observed in a population with mild-to-severe obesity.

3.0 Manuscript

Association between cardiorespiratory fitness and metabolic risk factors in a population with mild to severe obesity

Kathy Do, BSc[1], Ruth E. Brown, PhD[1], Sean Wharton, MD[2], Christopher I, Ardern[1], Jennifer L. Kuk, PhD[1].

[1]Faculty of Kinesiology and Health Science, York University, Toronto, ON;

[2] Wharton Medical Clinic, Hamilton, ON.

Abstract

Background: Cardiorespiratory fitness (CRF) is associated with favourable metabolic risk factors and reduced risk of all-cause mortality, independent of body mass index (BMI) in populations of normal weight, overweight and mild obesity.

Objective: To determine if the beneficial effect of having high CRF is present in a population with mild to severe obesity.

Methods: Individuals from the Wharton Medical Clinic (n = 1102) completed a clinical examination and standardized treadmill test. Participants were categorized into fit and unfit CRF based on age- and sex- cut-off points and BMI class (mild obesity: BMI $\leq$ 34.9 kg/m^2 or moderate/severe obesity: BMI $\geq$ 35kg/m^2).

Results: The unfit moderate/severe obesity group had a higher risk of elevated blood pressure when compared to the fit moderate/severe obesity group (OR, 95% CI = 1.53, 1.1-2.1), but with no effect of fitness within the mild obesity groups. Conversely, for low HDL cholesterol, there was a beneficial effect of fitness in the mild obesity group (OR, 95% CI = 1.94, 1.0-3.6), but not in the moderate/severe obesity groups (OR, 95% CI = 1.25, 0.9-1.8). For elevated waist circumference, both fit – mild obesity and moderate/severe obesity - groups were at a lower odds ratio for elevated waist circumference compared to their respective unfit group. There were no significant associations with CRF and the odds of elevated triglycerides and fasting glucose.

Conclusion: These findings suggest that favourable metabolic adaptations associated with having high levels of CRF are similar in individuals with moderate/severe obesity as compared to mild obesity.

Introduction

The prevalence of obesity has dramatically increased over the past few decades, and in particular, the prevalence of the more severe obesity classes has increased the greatest amount in Canada (29). It is well established that obesity is associated with many chronic conditions such as type 2 diabetes, hypertension, and metabolic syndrome (4,6) as well as an increased risk of mortality (5). Cardiorespiratory fitness (CRF) is associated with lower risk of cardiovascular disease mortality (25), and many obesity-related health conditions (23,24), independent of body mass index (BMI). Surprisingly, some individuals with mild obesity (BMI less than 35 kg/m^2) and a high CRF do not present with negative health factors and may have lower risk of mortality risk than their normal-weight unfit counterpart (25). However, it is unclear if the benefits of having a high CRF also apply to those with severe obesity. The health benefits of having a high CRF are thought to be in part due to reduced visceral obesity for a given BMI (18). However, Wong et al. (18) demonstrate that the decreased abdominal obesity associated with a high CRF may only hold true for those with mild obesity. Given the large increase in prevalence of more severe obesity classes, it is important to understand whether the beneficial effect of having high CRF is also observed in moderate to severe obesity classes. The primary objective of this study is to determine the relationships between CRF and metabolic risk factors in individuals with higher levels of obesity.

Methods

Participants

Participants included an opportunistic sample of 1147 patients who attended the Wharton Medical Clinic between February 2012 to November 2013. The Wharton Medical Clinic is a referral based bariatric clinic for weight and diabetes management. The clinic focuses on long term weight management for patients with overweight and obesity through a multidisciplinary team of internal medicine physicians, dieticians, nutritionists and behavioural therapists. The clinic focuses on educating patients on how to implement effective strategies to improve patient health and wellbeing. The clinic operates within the Ontario Health Insurance Plan and provides patient weight management care free of charge. Participants were included if they underwent measurements of weight, height, blood pressure, general blood work and standardized treadmill test during their first month at the clinic. Participant data was extracted from the Wharton Medical Clinic electronic medical records. Participants who had a BMI below 30 kg/m^2 were excluded (n=45). A total of 1102 patients were included in the final sample for analysis. All participants provided written informed consent knowing their decision to participate would not alter the care provided and that they could withdraw consent at any time with no repercussions on their treatment. The York University Institutional Review Board approved the study protocol used.

Clinical Examination

Blood samples were obtained via venipuncture after at least an eight hour fast to assess metabolic parameters such as triglyceride, glucose, and HDL cholesterol using standard procedures by certified medical laboratories. Blood pressure was measured manually at the clinic by trained technicians. Body weight was measured to the nearest 0.1 kg with a MedWeight, MS-2510 Digital High Capacity Platform Scales (Itin Scale Co, Inc., NY). Height was measured to the nearest 0.1 cm using a tape measure (McArthur Medical Sales, Inc., ON) mounted to the wall. Body mass index was calculated as kilograms per meter squared and waist circumference was measured at the level of the umbilicus.

National Cholesterol Education Program (NCEP) metabolic syndrome criteria were used to categorize individuals as having elevated health risk: triglycerides ≥ 1.7 mmol/L or taking lipid medications; HDL cholesterol <1.03 mmol/L for men or < 1.29 mmol/L for women or taking lipid medication; systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or taking antihypertensive medication; fasting glucose ≥ 5.6 mmol/L or taking diabetic medications. Body mass index category specific waist circumference (WC) cut-offs were used to denote elevated health risk (99). Waist circumference cutoffs used in the metabolic syndrome criteria (33) were not used as 99% of the sample population had elevated WC with these cutoffs.

To assess CRF, maximal oxygen uptake (VO_{2max}) was estimated from a graded multistage Bruce protocol performed on a treadmill. VO_{2max} was predicted using sex-specific equations (100,101). Participants were stratified by fitness based on standard age- and sex-specific VO_{2max} cutoffs: unfit (< 20th percentile) or fit (≥ 20th percentile) (102) and by BMI category: mild obesity (30 – 34.9 kg/m^2) or moderate/severe obesity (≥ 35 kg/m^2) groups.

Statistical Analysis

Differences in the characteristics among each of the four groups (fit or unfit- and mild or moderate/severe obesity groups: fit/class II; unfit/class II; fit/class III, and; unfit/class III) were assessed using one-way analysis of variance for continuous variables and chi-square tests for categorical variables. Logistic regression was used to assess the odds ratio (95% confidence interval) of high risk triglycerides, fasting glucose, HDL cholesterol, and blood pressure in fit or unfit- and mild or moderate/severe obesity groups. The models for each metabolic risk factor were adjusted for age and sex. Statistical significance was established at $p < 0.05$. All analyses were performed using SAS v.4 (SAS Institute, Cary, NC).

Results

Participant characteristics stratified by BMI class and fitness group are shown in **Table 1**. Within the sample, 56% of participants with mild obesity had a high CRF whereas only 24% of the participants with moderate/severe obesity had a high CRF.

Odds ratios for the prevalent elevated health risks are shown in **Figure 1.** Fitness was not significantly associated with the odds of having high glucose or triglycerides in the mild or moderate/severe obesity groups ($P>0.05$). For elevated blood pressure, the unfit moderate/severe obesity group had a higher risk of elevated blood pressure when compared to the fit moderate/severe obesity group (OR, 95% CI = 1.53, 1.1-2.1), but with no effect of fitness within the mild obesity groups. Conversely, for high risk HDL cholesterol, there was a beneficial effect of fitness in the mild obesity group (OR, 95% CI = 1.94, 1.0-3.6), but not in the moderate/severe obesity groups (OR, 95% CI = 1.25, 0.9-1.8). Both unfit – mild and moderate/severe obesity groups were at a higher odds of elevated waist circumference compared to their respective unfit group (OR, 95% CI = 2.01, 1.2-3.4 and OR, 95% CI = 3.0, 1.2-3.2, respectively). However, there was a greater difference in waist circumference between fitness groups in the moderate/severe obesity group than the mild obesity group.

Table 1: Participant characteristics stratified by BMI group and fitness

	Mild Obesity		**Moderate/Severe Obesity**	
Total Sample (n=1102)	**Fit**	**Unfit**	**Fit**	**Unfit**
n (%)	151 (55.9%)	119 (44.1%)	198 (23.8%)	634 (76.2%)
Sex (% male)	21.2	15.1	29.3	27.3
Age (years)	50.5 ± 11.0[bc]	52.9 ± 12.6[bc]	44.9 ± 11.3[a]	47.3 ± 12.6[a]
BMI ($kg \cdot m^{-2}$)	32.5 ± 1.4[bc]	32.8 ± 1.5[bc]	39.4 ± 3.9[ac]	44.2 ± 6.8[ab]
Weight (kg)	90.5 ± 11.5[bc]	90.6 ± 11.5[bc]	110.2 ± 16.1[ac]	124.7 ± 25.3[ab]
VO_{2max} ($mL \cdot kg^{-2} \cdot min^{-1}$)	40.1 ± 23.9[ac]	22.7 ± 5.8[b]	41.6 ± 20.7[ac]	21.4 ± 7.3[b]
High Waist Circumference*	80 (53.7%)	80 (67.8%)	103 (52.3%)	505 (80.2%)
High Triglycerides	26 (17.2%)	26 (21.9%)	32 (16.2%)	127 (20.0%)
Low HDL Cholesterol	22 (14.6%)	30 (25.2%)	45 (16.7%)	172 (27.1%)
High Fasting Glucose	21 (13.9%)	25 (21.0%)	30 (15.2%)	123 (19.4%)
High Blood Pressure	56 (37.1%)	46 (38.7%)	97 (49.0%)	383 (60.4%)

[a] Significantly different compared unfit-mild obesity ($P < 0.05$)

[b] Significantly different compared to fit-moderate/severe obesity ($P < 0.05$)

[c] Significantly different compared to unfit-moderate/severe obesity ($P < 0.05$)

BMI, Body Mass Index; VO_{2max}, maximal oxygen consumption;

*High waist circumference cut points were specific for BMI category (99).

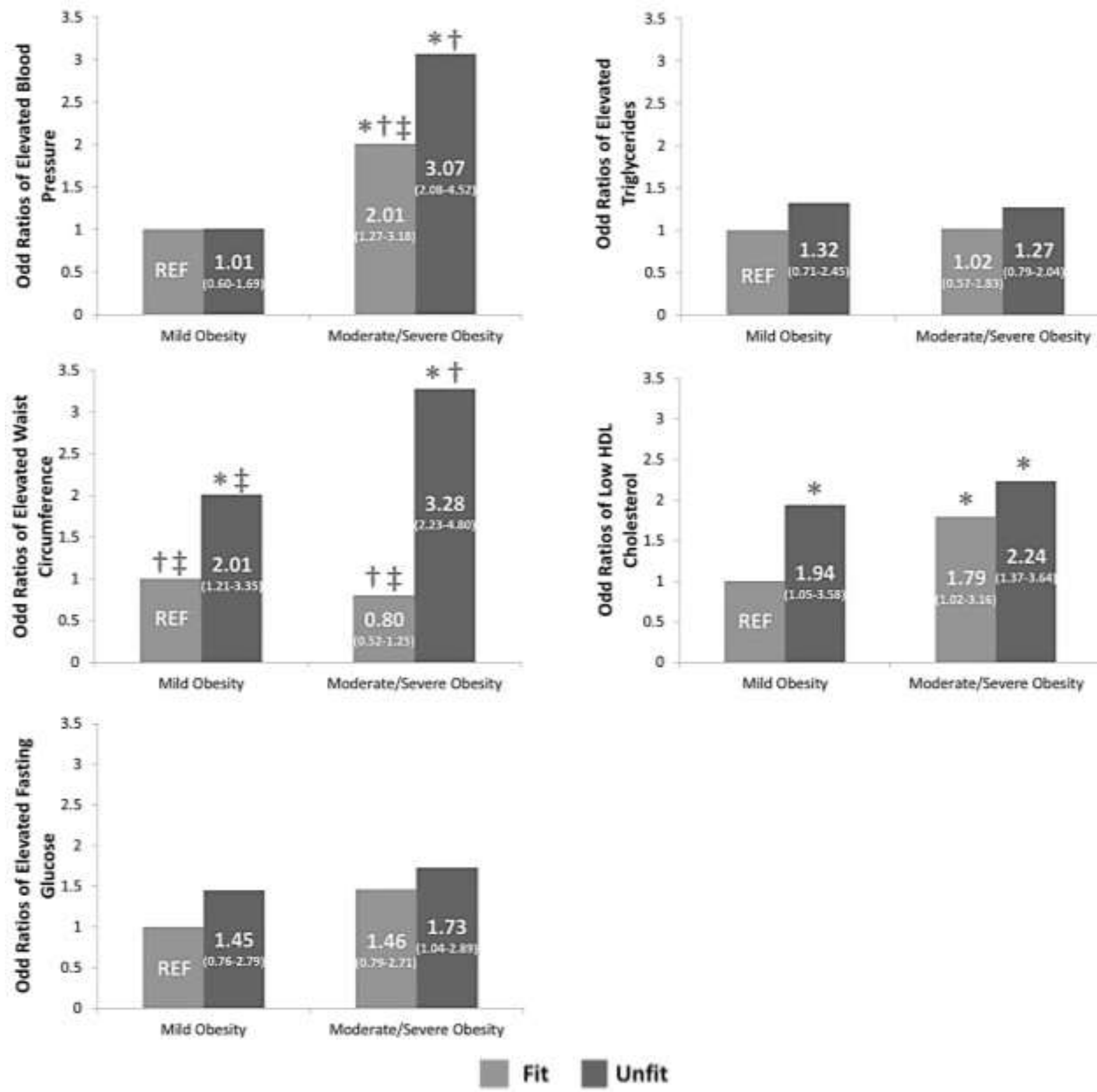

Figure 1: The odds ratios of high risk blood pressure, triglycerides, waist circumference, HDL cholesterol, and fasting glucose in individuals by obesity and cardiorespiratory fitness group.

***** Odds ratios significantly different from fit-mild obesity group ($P < 0.05$).

† Odds ratios significantly different from unfit-mild obesity group ($P < 0.05$).

‡ Odds ratios significantly different from unfit-moderate/severe obesity group ($P < 0.05$).

Figures are adjusted for age and sex.

Discussion

This is the first study to our knowledge that demonstrates that association between CRF and health may be similar in individuals with moderate/severe obesity as compared to mild obesity and extends previous research done in populations with normal weight, overweight and mild obesity.

Several studies have demonstrated an inverse association between CRF and metabolic risk factors such as triglycerides, HDL cholesterol, blood pressure and fasting glucose in populations of normal weight, overweight, and mild obesity (23,24,84,103). We extend these findings to demonstrate that the association of fitness was similar in moderate/severe obesity for fasting glucose and triglycerides. The beneficial health effects of CRF are suggested to be mediated through the positive health benefits of engaging in habitual physical activity (PA) behaviours (24,73). Physical activity has also been shown to improve fasting glucose by increasing the rate of glucose update in skeletal muscle, due to insulin independent increases in GLUT4 protein (67), and improve the lipid profile through increases in intramuscular free-fatty acid metabolism (104) and increase lipoprotein lipase in both skeletal muscle and adipose tissue (62).

However, many studies have shown that CRF is often more strongly associated with health risk factors than self-reported PA (21,22). This may be attributed to the fact that CRF is an objective measure that is not subject to self-report bias that tends to increase proportionally with the individual’s weight (78,79). This may help explain why it appears that CRF and PA are not as strongly linked in obesity. Physical activity engagement in leaner populations is clearly associated with CRF, but the same may not be true for individuals with obesity who engage in similar amounts of PA (77). Thus, differences in CRF levels may be more strongly linked with genetic factors associated with better functioning of the cardiovascular and respiratory systems. Genetic influences can account for up to 50% of the variability in CRF and may also be related to variations in metabolic risk factors (83). This is not to discredit the transient benefits of acute bouts of PA such as improved mood (105,106) and quality of life (107), enhanced endothelial function (108), improved glucose metabolism (67), and enhanced sleep quality (109) but its effect on CRF may not be as beneficial in populations with obesity (77).

Our results show that there was a greater difference in waist circumference between fitness groups in the moderate/severe obesity group than the mild obesity group. Waist circumference reflects the accumulation of both visceral adipose tissue (VAT) and subcutaneous adipose tissue, of which VAT is considered to be more detrimental for health (41,42). Visceral adipose tissue secretes cytokines, free fatty acids and pro-inflammatory markers into circulation that can cause adverse metabolic consequences (41–43). Wong et al. (18) showed that the positive difference in VAT between CRF groups decrease with increasing BMI and are completely abolished at a BMI of 35 kg/m^2 and up. This may be why we only observed the beneficial effect of fitness on HDL cholesterol in the mild obesity group and not the moderate/severe obesity. Further, the moderate to vigorous aerobic physical activity that is necessary to attain health benefits for HDL cholesterol may be more attainable for individuals with mild obesity than moderate/severe obesity.

Borodulin et al. (84) and Lee et al. (24) demonstrated that there was a stronger association between CRF and systolic blood pressure (SBP) with increasing levels of adiposity and conclude that fitness had a greater beneficial effect on SBP in those with abdominal obesity as compared to their lean counterparts. Similarly, we demonstrate that there is a greater beneficial effect of fitness on blood pressure in those with moderate/severe obesity as compared to mild obesity. These differences may be associated with greater improvements in endothelial function and reduction of sympathetic activity allowing for improved vasodilatory response and overall vascular compliance (110).

Within the present study, CRF was predicted using symptom-limited treadmill testing. This means that some individuals may have been unable to complete the test until cardiovascular fatigue but instead may have stopped early after experiencing joint pain. Hulen et al (72) demonstrate that women with obesity were more likely to prematurely stop their treadmill test due to musculoskeletal pain rather than from cardiovascular fatigue. Also, certain medications that are more prevalent in populations with obesity, such as beta blockers, can influence heart rate and blood pressure and increase the likelihood of experiencing early cardiovascular fatigue during exercise (111). Given that our sample comprised individuals with higher levels of obesity who are likely to have more health problems, our ability to accurately measure CRF is reduced as compared to leaner populations. Incorrectly classifying CRF group could have decreased our ability to observe significant effects of fitness within our study. Nonetheless, errors in accessing CRF are more likely to be bias towards the null and therefore the true association between CRF and health may be even greater than what is reported in this study.

The strengths and limitations of our study warrant mention. This study used a sample with greater number of individuals with higher levels of obesity than previous studies which allowed us to stratify and analyze those with mild obesity as compared to moderate/severe obesity. Another strength of our study is that we have a sample of patients attending a weight management clinic that is covered under the provincial health care plan who represent a broad range of cultures and socio-economic statuses with a range of motivations regarding their health goals. The cross sectional design of our study does not allow us to infer causality. Also, we were unable to adjust for other factors such as physical activity, ethnicity, smoking status, and education as these variables were not consistently reported within our clinical population.

The rise in the prevalence of more severe obesity classes is a very alarming public health issue faced in the world today. While the evidence that the association between CRF and metabolic health observed in higher levels of obesity is similar to that of lower levels of obesity, it is still important to promote physical activity and fitness behaviours to this increasingly prevalent group of individuals in order to see benefits in their metabolic health.

4.0 General Discussion

Societal changes such as the adoption of sedentary behaviours and consumption of readily available calorically dense food are two of many possible factors that have contributed to the shocking rise in obesity (3). In 2005, 396 million people worldwide were classified with obesity and it is projected that by 2030 that number will reach close to 1 billion people worldwide (2). Even more alarming is that there is a disproportionally larger increase in moderate to severe obesity as compared to mild obesity for adults within Canada (29). Obesity is well documented to be related to an increased risk of morbidity and mortality (4,8,9,28,61) which is even more exaggerated in moderate to severe obesity (112). Taken together, the burden on the health care system associated with obesity and obesity related ailments are larger than ever before (113).

Obesity is a multifactorial condition and therefore many strategies and interventions are needed to help prevent and manage this complex issue. Engaging in PA and improving CRF is often readily suggested to individuals with obesity as both PA and CRF are positively associated with overall health (19,73). However, the scientific literature on the effects of CRF on health is not fully conclusive. While some studies have shown that high CRF is often associated with decreased risk of metabolic abnormalities independent of adiposity (23,24,84), other studies found that CRF was not able to reduce the adverse health consequences and increased mortality risks associated with obesity (26,61,91).This may be attributed to the possibility that the response of different metabolic risk factors is different depending on the amounts and types of PA as well as the individual’s initial health and training period (104,114). For example, some researchers demonstrate that men who have initially low levels of HDL cholesterol are unable to increase their HDL cholesterol levels with exercise training as compared to men with initially normal

HDL level (104). Further, these differences may be attributed to the differential effects of CRF in severe obesity.

Physical activity confers a variety of physiological and psychological health benefits, with or without weight loss. There is much evidence within the literature that increased PA lowers the risk of developing cancer, types 2 diabetes, cardiovascular disease, osteoporosis, hypertension and a variety of other chronic conditions and diseases (85,115). It is also linked with improvements in quality of life (107) and overall reduction in the incidence of depression and anxiety (105,106). Moreover, physical activity has been shown to help treat and reverse established diseases by improving glucose metabolism in individuals with type 2 diabetes (67), reducing blood pressure for those with hypertension (116) and decreasing the risk of cardiac mortality for individuals with established coronary heart disease engaging in exercise rehabilitation programs (117).

It can be generally accepted that engaging in physical activity is beneficial for health, however most of the Canadian population is sedentary (58,118). Based on objectively measured PA data, only 17% of men and 14% of women accumulate the recommended ≥ 150 minutes of moderate to vigorous PA a week (118). Further, more than a third of the Canadian population do not even accumulate 15 minutes of moderate to vigorous PA at least one day a week (118). Similar to other health behaviours, physical activity is episodic as a lot of people start and stop engaging in physical activity throughout their lifetime. Although there are studies that have shown some success in the adoption of short-term physical activity (119), long term compliance to PA programs and free-living PA is often low (120). In a study on a community over a 1-year period, 26% of men and 34% of women adopted moderate PA while 11% of men and 5% of women adopted vigorous PA (120). However, within months attrition rates were about 25-35%

and 50% for moderate and vigorous PA, respectively (120). Individuals who arguably would benefit the most from physical activity interventions (ie. those with poor fitness levels and with comorbidities) often have an increased likelihood of dropout from exercise programs (121). Maintaining an active lifestyle is important to sustain health benefits as the acute effects of PA typically last 48-72 hours after a bout of exercise (61,122) and chronic effects of PA will diminish with detraining (123).

Physical activity can also affect major aspects of energy expenditure to contribute to weight loss. Simply stated, weight loss is a result from a net negative energy balance where more energy is expended than consumed. Modest weight loss of 5% to 10% of body weight has been reported to improve cardiovascular risk factors and metabolic function (11,68). Traditional PA programs often suggest participating in approximately 30-45 minutes of moderate intensity PA 5-7 days a week which can result in an increase of 1,500-2,100 kilocalories expended per week (19). Physical activity can also potentially result in increases in resting metabolic rate which accounts for the greatest amount of energy expenditure in the body (19,124). Studies have shown that after an exercise session, resting metabolic rate is elevated for several hours (19,124). Some individuals who regularly participate in PA have an overall higher resting metabolic rate and this can be attributed to the increase in lean muscle mass (124), which can be up to 70 times more metabolically active than fat (19).

It is estimated that 65% of males and 68% of females with obesity are attempting to lose weight in the US (125). The American College of Sports Medicine recommend 200 – 300 minutes of moderate intensity PA for long-term weight loss (126). On the other hand, the PA guidelines for health benefits recommend only 150 minutes but only 15% of the Canadian adult population meet these guidelines (118). Thus, the guidelines for weight loss may be discouraging for individuals trying to lose weight. Even when short term weight loss can be achieved, long term weight management is often rare as the odds of regaining weight increases with time (127). As individuals regain weight, there is a greater likelihood of regaining more body fat as compared to before the initial weight loss (19). Weight cycling is associated with cardiometabolic dysfunction and may even increase the risk of developing type 2 diabetes or cardiovascular disease as compared to remaining weight stable for individuals with obesity (127).

Other methods of weight loss include the use of pharmacotherapy and bariatric surgery. Pharmacotherapy often has high attrition rates which may be due to the adverse effects and drug interactions as well as the low efficacy of successful weight loss (128). Bariatric surgery has been shown to be one of the most effect strategies to provide drastic weight loss for individuals with severe obesity in order to reduce negative obesity-related ailments and reduce mortality risk (129,130). Individuals with a BMI $\geq$ 40 kg/m^2 who are unsuccessful with other forms of weight loss as well as individuals with a BMI $\geq$ 35 kg/m^2 with comorbidities qualify for bariatric surgery (131). However, the interest (132) and accessibility (133) for bariatric surgery among those qualified is low.

Interestingly, many studies have demonstrated that participation in PA is inversely associated with cardiometabolic abnormalities, independent of changes in weight (32,64,69). Moreover, some individuals with obesity are better off focusing on maintaining their weight while increasing their PA participation and CRF level as this may result in similar or better health outcomes than normal weight individuals (25,50,53).

In conclusion, the observations within this study demonstrate that the association between high CRF and metabolic risk factors is similar in the moderate/severe obesity group as compared to the mild obesity group. Thus, these findings strengthen the benefit of engaging in physical activity and maintaining high CRF for individuals of all weights for health.

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