The Role of an Addictive Tendency Towards Food and Patterns of Body Fat Distribution in Obesity and Metabolic Health

By

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ABSTRACT

Food addiction (FA) is a contributing factor to obesity. Individuals with similar total body fat (BF) %, exhibit a large amount of heterogeneity in how BF is distributed. Certain BF distribution (BFD) patterns produce different outcomes regarding metabolic health. Little is known about how FA influences BFD and metabolic profiles.

The study was designed to evaluate the correlation between FA symptom counts and metabolic characteristics, the correlation between FA symptoms and BFD patterns with emphasis on central obesity and Visceral fat (VF), and the role of android fat (AF) in women's metabolic health. Data from the CODING study was used for analysis.

FA symptoms are correlated with HOMA-β, triglycerides (TG), inversely correlated with high-density lipoprotein (HDL) in men and are correlated with TG in post-menopausal women. FA symptom counts were also associated with central obesity markers in men and women, including trunk fat (TF) and VF. Women exhibited slightly stronger correlations for all BFD measures except for VF and AF than in men. AF to GF ratio (AGR) affected metabolic characteristics and metabolic syndrome (MetS) risk in women. When separated into AGR tertiles, women in each tertile differed significantly in levels of insulin, glucose, TG, HDL, low-density lipoprotein (LDL), total cholesterol (TC), blood pressure (BP), and waist circumference (WC). Women in the top tertile exhibited higher levels of HOMA-IR and HOMA-β. When women in the top AGR quartile, matched by age and body mass index (BMI) with a control group while controlling for VF, were 2.4x more likely to have MetS.

In conclusion, FA symptoms exhibit correlations with markers of metabolic disturbance in men and to a smaller degree in women. FA symptoms are also correlated with central obesity in men and women. Women with high levels of AF are at increased risk of developing MetS when compared to women of similar age and BMI.

Acknowledgments

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Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

AF-Android Fat

AGR-Android to Gynoid Ratio

ATPIII-Adult Treatment Panel III

BDNF-Brain Derived Neurotrophic Factor

BF-Body Fat

BFD-Body Fat Distribution

BIA-Bioelectrical Impedance

BMI-Body Mass Index

BP-Blood Pressure

CODING-Complex Diseases in a Newfoundland Population: Environment and Genetics

CT-Computed Tomography

CVD-Cardiovascular Disease

DSM-IV TR-Diagnostics and Statistical Manual IV Text Revision

DXA-Dual Energy X-Ray Absorptiometry

FA-Food Addiction

FAIM2-Fas Apoptotic Inhibitory Molecule

FAO-Food Addicted Obese

FFA-Free Fatty Acid

FFQ-Food Frequency Questionnaire

fMRI-Functional Magnetic Resonance Imaging

FTO-Fat Mass and Obesity Associated Protein

GF-Gynoid Fat

GNPDA2-Glucosamine-6-Phosphate Deaminase 2

GWAS-Genome Wide Association Study

HDL-High Density Lipoprotein

HOMA-IR-Homeostatic Model of Assessment Insulin Resistance

HOMA-β-Homeostatic Model of Assessment Beta Cell

HREA-Human Research Ethics Authority

IR-Insulin Resistance

LDL-Low Density Lipoprotein

LEP-Leptin

LEPR-Leptin Receptor

LF/TF-Leg Fat/Trunk Fat

MC4R—Melanocortin-4-Receptor

MetS-Metabolic Syndrome

MI-Myocardial Infarction

MRI-Magnetic Resonance Imaging

NCEP-National Cholesterol Education Program

NFA-Non-Food Addicted

NL-Newfoundland and Labrador

SD-Standard Deviation

SEC16B-SEC 16 Homologue B

SES-Socioeconomic Status

T2D-Type 2 Diabetes

TC-Total Cholesterol

TF-Trunk Fat

TG-Triglyceride

TMEM18-Transmembrane Protein 18

TNF-α-Tumor Necrotic Factor Alpha

TSH-Thyroid Stimulating Hormone

Visceral fat-VF

WC-Waist Circumference

WHO-World Health Organization

WHR-Waist to Hip Ratio

WHR_{BMIadj}-Waist to Hip Ratio Adjusted for Body Mass Index

YFAS-Yale Food Addiction Scale

Co-Author Statement and Thesis Overview

This thesis is written in manuscript format and is divided into five chapters. Chapter 1 consists of an overarching introduction and literature review which serves to introduce the theme of the research presented in chapter 2-4. Chapters 2-4 are three standalone research chapters that have an individual introduction, methods, results, and conclusion followed by a final summary which is chapter 5. Chapters 2-4 represent published work (chapter 2) and manuscripts in preparation (chapter 3-4) with individual co-author statements, to identify my role in the work and the contributions of other members of the research teams. For each manuscript, I participated in participant recruitment, data analysis, data collection, and acted as the primary manuscript writer. Participant recruitment involved my making advertising materials and assisting in scheduling participants. Data collection consisted of meeting between 1 and 3 participants 5 days a week year-round to complete laboratory visits. I would make sure all forms had been completed and then I would take each participant's blood pressure, temperature as well as measure waist and hip circumference, height, and weight. I would then complete all DXA scans and retrieve the nurse for blood collection. After blood collection, I would discuss DXA results with each participant. I also had a role in laboratory work including the processing of blood for plasma/serum isolation. Blood processing duties were split with our laboratory tech. I independently performed all data analyses for each manuscript. After Dr. Sun's laboratory had acquired the technology to measure visceral fat in 2015, 3000+ DXA scans had to be re-analyzed to ensure visceral fat was measurement was as accurate as possible. Hongwei Zhang and I would take several hours each day for months to re-analyze thousands of DXA scans. I participated in the interpretation of all findings. For published work, I was also responsible for submitting and revising the manuscript for the final publication. Hongwei Zhang played a major role in data collection and data entry. Dr. Farrell Cahill is credited in some of my manuscripts because, while he was not regularly present in the laboratory at any point in my master's, he also contributed a lot in the way of participant recruitment and data collection during his Ph.D. which completed before my arrival. The CODING study has been an ongoing effort since 2003 and I wished to acknowledge Dr. Cahill, who immediately preceded me, for his efforts. He also played an important role in training me on how to use our laboratory equipment. Dr. Wayne Gulliver and Dr. Zhai assisted in editing the manuscripts in chapters 2 and 3. Dr. Weiping Teng and Dr. Zhongyan Shan also assisted in revising the manuscripts in chapters 2 and 3. Dr. Michael Wahl is listed as a co-author for the chapter 3 manuscript as he provided essential tools for measuring body composition which made this study possible. Dr. Guang Sun acted as my supervisor, designed the research, and was responsible for the final content of all manuscripts as Principal Investigator.

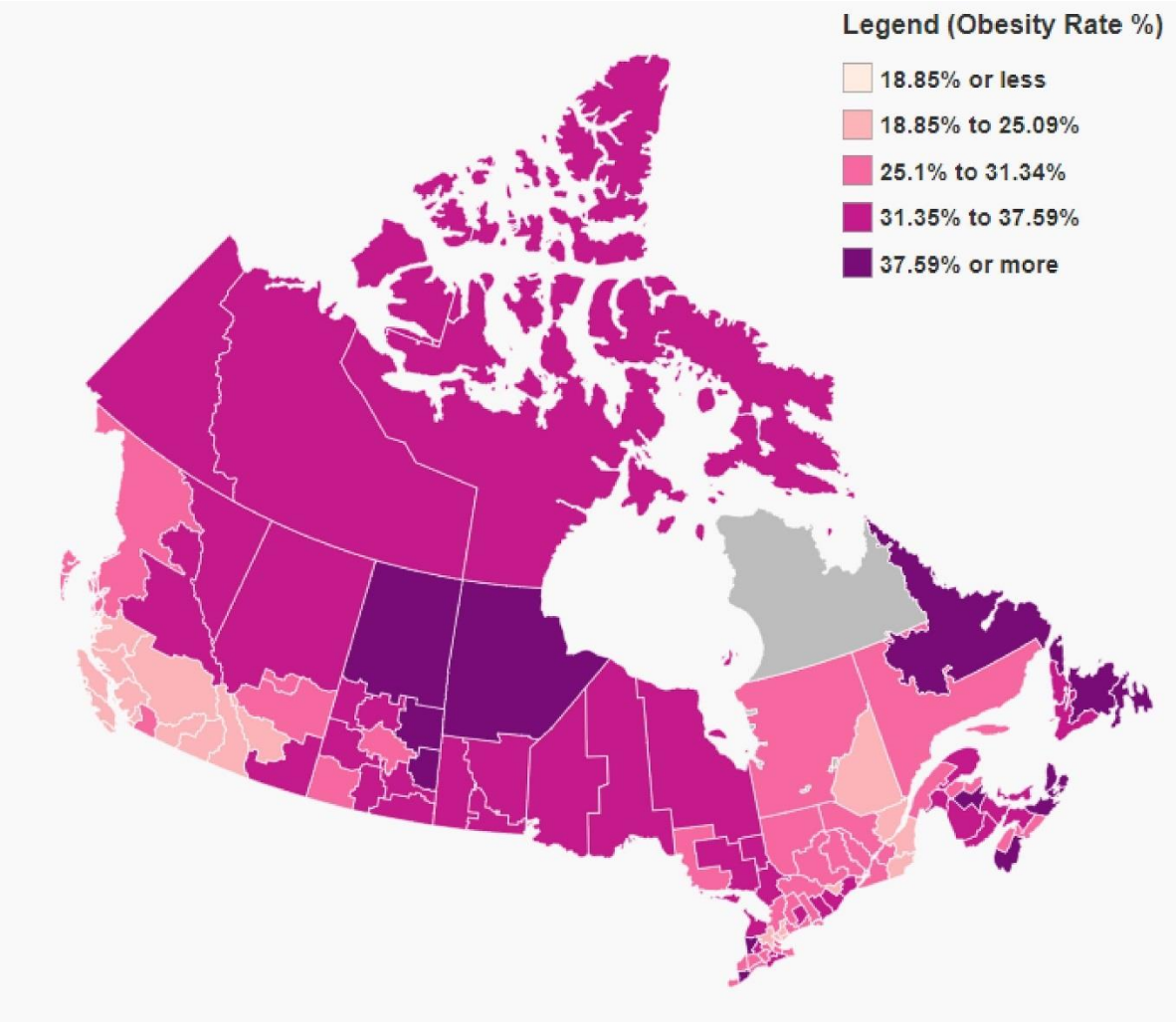
1

Chapter 1. Introduction

1.1 Prevalence of Obesity and Comorbidities

Obesity is a multifactorial disorder characterized by the excessive accumulation of adipose tissue and is defined by the World Health Organization (WHO) as having a body mass index (BMI) of 30.0 or higher [1, 2]. The severity of obesity ranges from class I obesity to class III obesity with class 1 being a BMI of 30.0-34.9, class II is a BMI of 35.0 to 39.9 and class III is a BMI of 40 or greater [3]. It is associated with the development of a number of health issues such as hypertension and high blood sugar. It is also considered a risk factor for other illnesses including but not limited to cardiovascular disease, type 2 diabetes (T2D), and some forms of cancer such as breast and prostate [4-10]. The worldwide rate of obesity has been climbing rapidly for the past 3 decades and Canada is no exception to this trend. The WHO reported that the prevalence of obesity globally, tripled between 1975 and 2016 with the global prevalence of obesity now at 13% [2, 11]. Between 1985 and 2011 the prevalence of obesity amongst Canadian adults increased from 6.1% to 18.3% [12]. As of 2018, the prevalence of obesity among Canadian adults is 18.7% for those ages 18-34, 30.3% for those ages 35-49, 31.3% for those ages 50-64, and 28.1% for those ages 65 and over [13]. The obesity trend has been accompanied by a similar increase in other chronic diseases such as diabetes and cardiovascular disease [14-16]. This is precisely why obesity is considered one of the greatest public health issues facing the world today accompanied by the fact that it is a significant economic burden and is often associated with a lower quality of life [17, 18]. The financial cost of obesity in Canada, according to a 2011 report from the Public Health Agency of Canada was estimated to be approximately $7 billion annually [19]. This is

due to both the direct cost of obesity such as surgery and medication as well as the indirect cost such as lost working hours and premature death. The population of Newfoundland and Labrador (NL) suffer from a high prevalence of obesity unmatched by the rest of Canada. Recent reports put the prevalence of adults living with obesity in NL at 39.9% [13]. The prevalence of obesity is reported to be as high as 38.94% along NL's East Coast and 42.46% in the region along the Northern Peninsula and Labrador (**Fig.1-1**) with the prevalence of those living with obesity in Canada as a whole at 28.2% [20]. Due to the high prevalence of obesity in NL, obesity research is of particular importance to this Province's population. One reason is new information on the causes and consequences of obesity may inform health practitioners how to best treat those affected by obesity in the future, whether it be through therapy, medication, surgery or a combination of all three. Another reason being, information generated by obesity research may also help shape public health initiatives as it can reveal information about trends, risk factors, the outcomes of previous interventions and patterns of care. Research on the underlying causes of obesity may also assist in informing the most economical means of tackling the obesity issue.



Source: Public Health Agency of Canada: Obesity in Canadian Adults: It's About More than Just Weight, 2017

Figure 1-1 Map of the Prevalence of Obesity in Canadian Adults

1.2 Etiology of Obesity

Obesity is a multi-factorial condition with many genetic, environmental, physiological, and behavioural factors to be considered and it is important not to overlook how these factors affect one another. There are 75 and counting obesity susceptibility loci that have been discovered since the employment of genome-wide association studies (GWAS) [21, 22]. One notable example would be the minor allele of the fat mass and obesity-associated (*FTO*) gene which is associated with a 1130g increase in body weight and increases the risk of obesity 1.2x [23]. Additionally, a 2009 study confirmed that variants of several genes associated with obesity in a Caucasian population such as SEC 16 homologue B (*SEC16B*), transmembrane protein 18 (*TMEM18*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), brain-derived neurotrophic factor (*BDNF*), fas apoptotic inhibitory molecule 2 (*FAIM2*) and melanocortin-4-receptor (*MC4R*) were also significantly associated with obesity in a Japanese population [24].

Many of the aforementioned genetic variants which are associated with obesity, code for proteins, and hormones essential to the maintenance and performance of energy regulation pathways which is why the physiological aspects of obesity and how they affect appetite and metabolism must also be considered. Ghrelin, for example, is an orexigenic hormone that is reduced in individuals living with obesity and is dependent upon body mass and food intake patterns and diet-induced obesity may lead to ghrelin resistance [25, 26]. A study from our lab revealed that a 7-day overfeeding challenge in young men increased circulating levels of PYY, an appetite inhibiting hormone which acts directly on the hypothalamus [27]. Adipokines, which are cell-signaling proteins

secreted primarily by white adipose tissue also play an important role in energy regulation and obesity. The discovery of adipokines was quite a milestone in obesity research as white adipose tissue was long thought to merely be a site of storage. Visfatin, an adipokine which is upregulated by hyperglycemia and downregulated by insulin, was found to be significantly higher in a sample of 21 obese women when compared to a sample of 16 lean women. Lean, in this case, referred to women with a BMI of 24.9 or less. The women chosen for this study had an average age of 29. Visfatin exhibited a significant correlation with glucose in obese women and a significant correlation with insulin in the lean group. It was concluded that the increase of visfatin in those living with obesity may have a counter-regulatory effect to prevent increasing glucose levels. and other adipokines such as IL-6, RBP4, and resistin increase inflammation and insulin resistance [28].

Various environmental factors have also been found to correlate with the development and maintenance of the obese state. For example, convenient access to calorie-dense fast foods has been shown to correlate with obesity [29]. A 2014 study by Slack and colleagues identified several environmental and socioeconomic correlations with obesity. The correlations that were observed include a positive correlation between obesity and unemployment as well as an inverse correlation with the number of physicians per 1000 people, education level, and the number of recreational/natural amenities in an area [30]. A study by Cooksey-Stowers and colleagues investigated the role of "food swamps" in obesity. A "food swamp" is an area where there is a high density of convenience stores

and other fast food establishments. The researchers analyzed 211 food environment indicators from 3141 United States counties and the “food swamp” measures that were used were the traditional Retail Food Environment Index as well as two expanded forms of the Retail Food Environment Index. BMI measurements were calculated from the self reported height and weight of over 500,000 respondents aged 20 years or older. The Retail Food Environment Index is the ratio of convenience stores and fast food establishments to grocery stores and supermarkets. The expanded forms include additional food outlets such as farmer markets and super centres. It was reported that “food swamps” are indeed significantly associated with obesity in adults. This correlation remained significant after controlling for indicators of physical activity such as the number of recreational facilities, natural amenities, and means of transportation to work in a given county, socio-economic factors such as level of education and income, and other variables such as race, age, and gender [31]. Some limitations worth noting in this study are the fact that weight and height were self-reported. For example, participants were simply asked “About how much do you weigh without shoes?”. Also, one of the main measurements, the Retail Food Environment Index, relied on the categorization of food as “healthy” or “unhealthy” with the latter being described as foods with high amounts of saturated fat, added sugar/sodium, or those that contribute little to meeting daily dietary recommendations. This definition is open to some subjectivity and it is not made clear if unhealthy food must simultaneously be high in saturated fat, added sugar/sodium, and do little to meet dietary recommendations or if a food is categorized as unhealthy if it meets just one of those three criteria. Also, the ratio of the cost of low-fat

milk to soda was used as a proxy for the relative cost of healthy food compared to unhealthy food. Why those specific food items (low-fat milk and soda) were chosen is not made entirely clear or why that cost ratio made for the best proxy. Another environmental factor contributing to obesity may be where an individual works, as certain occupations are associated with a higher incidence of obesity. While it has been found that employed individuals tend to have lower BMIs than those who are not employed across different populations and age groups [32-34], certain occupations may have a higher prevalence of obesity when compared to other occupations. One study of 125,992 working adults (aged 18 years and over) in the United States which collected data on 23 broad occupational groups and 93 minor occupational groups found that the highest prevalence of obesity among non-Hispanic white males was among those working in health care support (36.3%), protective services (34.3%) and transportation and material moving (33.7%). In the 2 periods between 2004-2007 and 2008-2011, obesity significantly increased among males working in computers, mathematics, legal areas, and protective services. Among all individuals, the highest prevalence of obesity was observed for those working as motor vehicle operators, construction or construction-related workers, law enforcement, home health aides, psychiatric workers, or nurses. The lowest prevalence of obesity was observed among those working in health diagnostics and treatment, certain military careers, art/design, and post-secondary teachers. Among non-Hispanic white females, the highest prevalence of obesity was observed in those working in farming/fishing/forestry, transport workers, and production. The lowest prevalence of obesity in this group was among those females working in life/physical/social science, legal areas,

art/design/entertainment/sports/media, and life/physical/social sciences. Among Non-Hispanic black females, those working in health care support, transportation, protective services, personal care, community/social services, food preparation/serving, and health care practitioners/technicians had an age-adjusted prevalence of obesity above 40%. Non-Hispanic black females tended to have a high prevalence of obesity with the exception of those working in computers, mathematics, and legal areas. In non-Hispanic black males, those working in protective services, community/social services, production, and transportation had the highest prevalence of obesity. Out of the 93 minor occupations observed, non-Hispanic black males working in law enforcement and motor vehicle operation had the highest prevalence of obesity among that group. Hispanic males working in protective services, community/social services, life/physical/social sciences, computers, and mathematics had the highest prevalence of obesity. Hispanic males working in farming/fishing/forestry, food preparation/serving, building, and ground cleaning/maintenance had the lowest rate of obesity among males of this group. Hispanic females working in transportation, community/social services, and health care support had the highest prevalence of obesity among the minor occupation groups, and Hispanic females working in motor vehicle operation had the highest prevalence of obesity within that group [35]. While age was adjusted for in this analysis there are several limitations present in this study. Height and weight were self-reported which may have affected the accuracy of these measurements and there are many other potentially confounding variables not accounted for such as physical activity, chronic illnesses, or other

socioeconomic factors. These variables could potentially explain some of the variations observed among certain ethnic groups, sexes, and occupations.

While physiological mechanisms are partly responsible for driving eating behaviour as previously noted, the reciprocity of eating behaviour on physiology and obesity must also be acknowledged because should an individual go on to develop potentially harmful eating behaviours, such as binge eating or addictive eating tendencies, obesity and obesity-related issues can be far more difficult to manage [36-38]. A study consisting of 638 healthy, non-smoking women ages 55-65 years examined the relationship between eating behaviours with weight and BMI. Eating behaviour was quantified using the Eating Inventory questionnaire which quantifies 3 constructs termed restraint and disinhibition as it pertains to eating, as well as hunger. Disinhibition, defined as the tendency to overeat in the presence of palatable foods or stimuli such as emotional distress, was found to be a strong predictor of both current BMI and weight gain. Restraint which was described as a tendency to consciously restrict food intake, while not a strong independent predictor of BMI did appear to moderate the association of disinhibition with weight gain [39]. An important note about this study is that current and past weight was self-reported for all participants so it is of course possible that reporting may have been incorrect, especially for past weight. The researchers took care to exclude smokers and individuals who reported health or eating disorders but there is always the possibility of some individuals failing to report health issues as they had not been diagnosed at the time of answering the questionnaire. A study on the relationship between

food addiction (FA) symptoms, as defined by the Yale Food Addiction Scale (YFAS) Questionnaire which will be covered in much greater detail in later sections, and weight loss as well as other behavioural factors was conducted among adults seeking weight loss treatment. This study included 57 participants (68.4% female) with an average age of 47.4 years who were enrolled in an 18-week behavioural weight loss intervention. Behavioural and psychological measures included psychological distress, maladaptive eating behaviours, weight bias attitudes, and body image/satisfaction. It was reported that higher YFAS scores were significantly correlated with higher levels of psychological distress as measured by the Center for Epidemiological Studies Depression Scale. YFAS scores also exhibited a significant correlation with body image and weight bias. There was a significant correlation between YFAS scores and maladaptive eating behaviours such as binge eating, emotional eating, and difficulty controlling eating. These behaviours were measured using the Binge Eating Scale, the Dutch Eating Behaviour Questionnaire, and the Eating Self-Efficacy Scale, respectively. The researchers performed Cronbach's alpha calculations on each of these questionnaires to test internal consistency and each of the three maladaptive eating behaviour questionnaires yielded acceptable alpha scores which ranged from 0,84 to 0.98. What is most relevant for the purpose of this thesis are the correlations observed between YFAS scores and body weight. YFAS scores displayed a significant negative correlation with the percentage of weight lost at week 7 of the study. It was found that individuals with more FA symptoms lost less weight than those with fewer symptoms [40]. While this study helped demonstrate how eating behaviour can influence body weight there are several limitations to these findings. This study was

conducted in a small sample of largely white, female participants actively seeking to lose weight so it is difficult to say whether these findings could be applied to a large general population. This study is also unable to predict how these eating behaviours might affect long term weight loss or weight gain. It was also determined that YFAS scores were no better at predicting weight loss than binge eating behaviours. There is some overlap between FA and binge eating which makes it difficult to say which of these issues accounted for more of the variance in weight loss so it would be premature to conclude that FA is the primary reason for lack of weight loss in some of the participants.

The etiology of obesity is often reduced to simply being a matter of long term, positive caloric balance caused by the ingestion of too many calorie-dense foods and lack of physical activity, however, as evidenced by the previous examples, the behaviours and physiological components that contribute to and sustain an obesogenic environment and the maintenance of body fat, are quite intricate. FA and its relationship to endocrine function and adiposity are an excellent example of the intricacy of obesity etiology. There is a substantial gap in knowledge concerning FA and its relationship to adiposity and metabolism which is why we chose to focus on this topic for my graduate work. This research made use of the CODING study which consists of over 3000 individuals of the general NL population. Our unique cohort has been screened to make sure all participants are at least third-generation Newfoundlanders above the age of 19 and not pregnant or experiencing serious metabolic disease at the time of taking part in the study. Many studies on obesity make use of BMI classifications which lack accuracy when trying to

assess body composition and how body fat is distributed. We chose to make use of dual-energy x-ray absorptiometry (DXA) scanning technology which is a far superior measure of body fat percentage and body fat distribution compared to BMI as demonstrated by previous research and shares a good concordance with other imaging technologies such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) [41-47]. A study in 2009 found that the adiposity status of approximately 1/3 of men and women of the NL population was misclassified when relying on BMI [48, 49]. Studies that have been performed on several vastly different populations also reported on the accuracy of DXA for body composition measurement. These studies range from study populations such as the elderly, division 1college athletes, and underweight to individuals with chronic intestinal disease [42, 44, 45, 50]. When discussing BFD, the precise definition of terms such as upper body fat, lower body fat, central fat, and others can vary greatly from group to group depending on the tools of measurement available and/or the personal preferences of certain researchers. Due to this variability, I will first define the terms of BFD employed by Dr. Sun's laboratory and the precise definition and anatomical locations of these BFD measurements in the following section.

1.3 Body Fat Distribution Terms and Definitions

All measures of body fat distribution and body composition, as previously noted, were measured using DXA scanning technology. The terms described below are per the definitions of the factory pre-sets of our DXA scanner. The principles of DXA scanning

and technical specifications of our DXA scanner are explained in greater detail in section **1.4**

Total Body Fat (BF) – This includes all subcutaneous fat storage sites throughout the entire body, head to toe, and all extremities, as well as all visceral fat.

Trunk Fat (TF) - The trunk consists of the area between the lowest boundary of the pelvis to the highest boundary of the neck, just below the chin. It includes the chest, abdominal and pelvic areas with perimeters set at the middle of the femoral necks while avoiding cutting out the edge of the pelvis.

Android Fat (AF) – The android area is located within the trunk of the body. This area is between the ribs and the pelvis. The chest, neck, head, and arms are all excluded from the AF measurement. It is the area ranging from the iliac crest to 20% of the height between the iliac crest and the base of the skull (**Figure 1-2**).

Visceral fat (VF) – VF refers to the fat depot located behind the abdominal wall within a fold of the peritoneum. This area is called the omentum. It also includes the area of the mesentery and surrounds organs in that space which include the liver and intestines. This area is a 5cm wide region that runs across the entire abdomen just above the iliac crest at a level that approximately coincides with the 4th lumbar vertebrae (**Figure 1-3**).

Gynoid Fat (GF) – This area includes the hips, upper thighs, and buttocks. It slightly overlaps with the leg and trunk region. It is approximately located between the superior and inferior trochanter major or from the lower boundary of the umbilicus to a line equal

to twice the height of the AF area. The upper boundary of the gynoid area is located below the top of the iliac crest at a distance of 1.5x the height of the android region and the total height of this region is 2x that of the android region (**Figure 1-2**).

DXA technology allowed a more accurate calculation of specific patterns of body fat distribution, including VF deposits, however, DXA is just one of several different methods by which BFD and body composition can be measured.

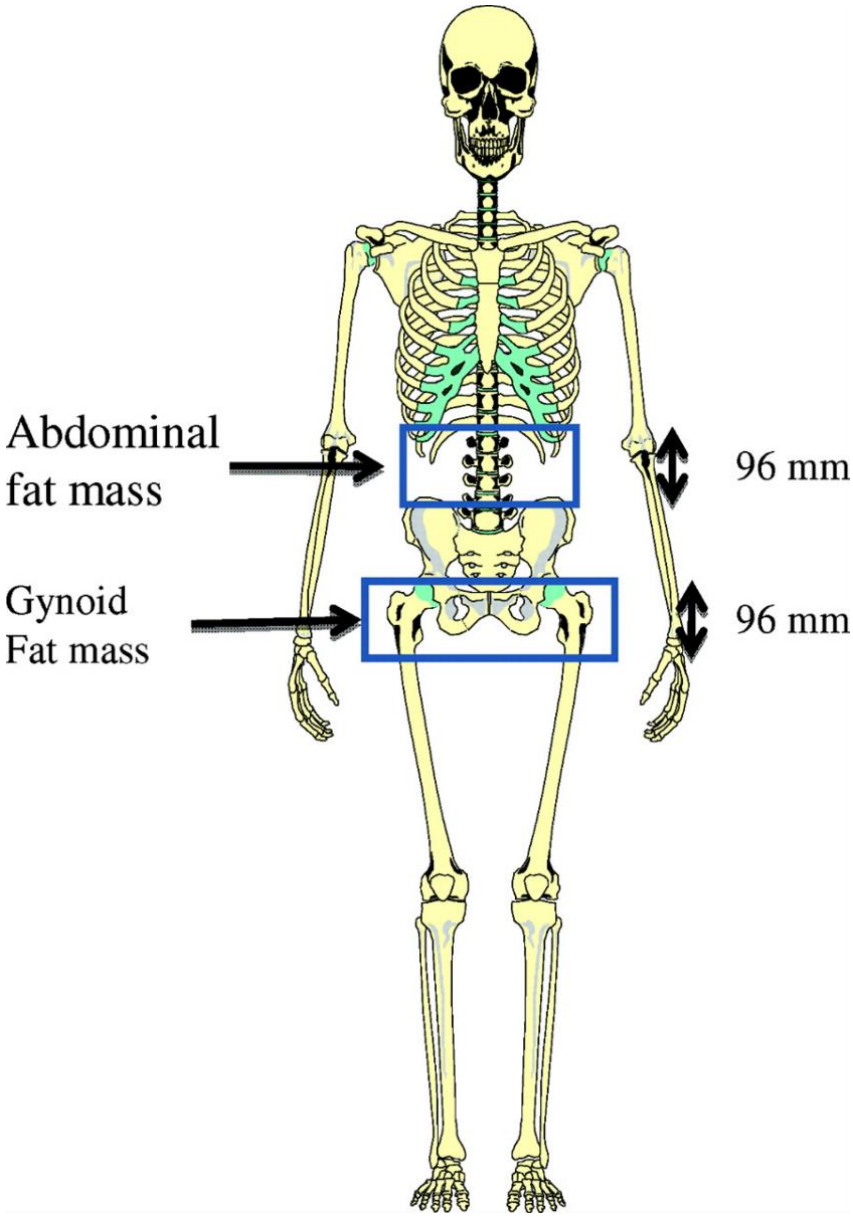


Figure 1-2 Estimates of Abdominal and Gynoid Region According to DXA

Wiklund, Peter; Toss, Fredrik, Abdominal and Gynoid Fat Mass Are Associated with Cardiovascular Risk Factors in Men and Women, The Journal of Clinical Endocrinology & Metabolism, 2008, 93, 4360-4366, by permission of Oxford University Press

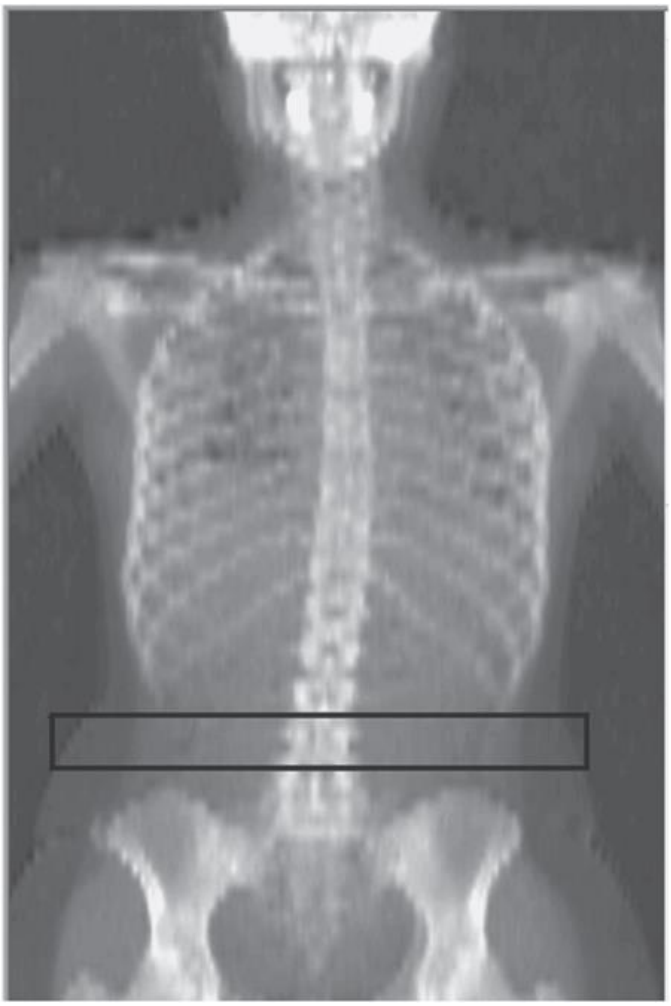


Figure 1-3 Visceral Fat Region as Determined by DXA

Kelly, Thomas L. Wilson, Kevin E. Punyanitya, Mark. Et al. Dual-Energy X-Ray Performs as Well as Clinical Computed Tomography for the Measurement of Visceral Fat. Obesity 2012.20 by permission of John Wiley and Sons

1.4 Measurements of Body Fat Distribution

When discussing the health implications of BFD, it is important to consider how certain body fat depots or body regions are measured and defined. Upper body fat or central obesity is described in many different ways depending on the study in question and the tools available to the respective research teams. Some researchers may opt to define upper body or central obesity using only waist circumference (WC) or waist to hip ratio (WHR) [51-53]. This is perhaps the simplest and most cost-effective method as it only requires a measuring tape and takes only seconds to perform. However, one should be aware that there is no universally accepted method for the measurement of WC which means there will always be a degree of uncertainty with this measurement until it is standardized. One study attempted to shine some light on this issue. 528 participants aged 6-78 were recruited. Prepubertal children had a BMI range of 12.3-25.7, pubertal children had a BMI range of 13.8-38.6 and adults had a BMI range of 16.8-40.2. Weight and height were measured using an electronic scale and stadiometer. Individuals who were pregnant, lactating, smoking, using anti-hypertensives, lipid-lowering, or hypoglycemic medication were excluded as was anyone using drugs that may influence body composition. WC was measured at three different points, below the lowest rib, above the iliac crest, and midway between both these areas using a non-elastic plastic measuring tape. Measurements were taken with the tape parallel to the floor with participants standing erect and those taking the measurement avoided compressing the skin with the measuring tape. Visceral and subcutaneous fat was measured using MRI. When the measurements at each of the three sites were compared, the discrepancy between circumference ranged from 10%-20% in

women and 6%-10% in men. Participants were also stratified by sex and BMI class and partial correlation analysis between WC, subcutaneous abdominal fat, and VF, adjusted for age, was performed. The highest significant correlation observed between any measure of WC and VF was 0.67 which was observed in normal-weight women when measuring WC from below the lowest rib. Obese women exhibited a similar correlation coefficient of 0.66 when WC was measured from the same site. In men, the strongest correlation with VF was observed in the normal weight group when WC was measured at the midpoint of the lowest rib and iliac crest with a correlation coefficient of 0.61. In obese men, no significant correlation was observed between any measure of WC and VF and all other significant correlations between WC and VF in men ranged from a coefficient of 0.52-0.58. In normal-weight and obese women, the correlation coefficient between WC and subcutaneous abdominal fat ranged from 0.70-0.77. The group of overweight women exhibited the lowest correlations of all groups with the correlation between WC and subcutaneous abdominal fat ranging from 0.30-0.51 depending on which of the three WC measurement sites were chosen. In men, the strongest correlation between WC and subcutaneous abdominal fat was 0.74 which was observed in overweight men when WC was measured from the iliac crest. The lowest correlation between WC and subcutaneous abdominal fat was 0.40 when measured in normal weight men from the bottom of the lowest rib. In all but two measurements, the correlation between WC measured at any site and subcutaneous abdominal fat was higher than the correlation observed between WC and VF. The only exceptions were in overweight women (VF: r=0.32, subcutaneous abdominal fat: r=0.30) when WC was measured from

the bottom of the lowest rib and in normal weight men (VF: r=0.52, subcutaneous abdominal fat: r=0.40), also when WC was measured from the bottom of the lowest rib. Based on these correlation coefficients, the authors concluded that, while WC can be a moderately decent indicator of subcutaneous adipose tissue, it is not as reliable for the quantification of visceral adipose tissue [54]. This study highlights the shortcomings of using WC as a measurement of upper body fat. Depending on sex, precisely where WC is measured, the BMI of the individual, and the fat depot of interest (VF stores versus subcutaneous abdominal fat stores), WC may exhibit either no significant correlation at all or it may yield a significant, moderately good correlation. There is a high degree of variability so caution should always be exercised when drawing conclusions from studies that employ WC as their only method of upper body fat measurement. Another study examined the concordance of WHR with DXA measured central and peripheral fat mass. This study was performed in 376 adults, 200 of whom were women, with a mean age of 36 years. These participants were part of an ongoing longitudinal study that began in 1976 and participants were recruited from two secondary schools. The average BMI of the participants was 24.8. The authors of this paper concluded that WC and skinfolds may offer a reliable alternative measurement of fat distribution in a cheap non-invasive manner, but WHR does not. WHR was measured using a flexible steel tape. WC was measured at the umbilicus and hip circumference was measured at the widest point of the buttocks. Central fat mass in this particular study refers to the trunk as defined by the factory pre-sets of the DXA machine used. The trunk area, according to this paper, started at the neck and descended down the entire length of the participant's torso and also

included the hips with cut-off points where the shoulder meets the scapula and at the femoral necks. Peripheral fat mass included the subcutaneous fat stores of the arms and legs. Skinfolds were measured using Harpenden calipers at several sites which include the subscapular, suprailiacal, biceps, triceps, and upper leg. It was concluded that in both men and women skinfolds and WC offer a reliable alternative for the measurement of fat distribution in a cheap non-invasive manner based on the correlations observed with DXA scanning ($r \geq 0.80$), however, WHR does not [55]. It should be stated that the current study consisted of mostly lean individuals so the accuracy of the method used may vary in a mostly overweight or obese sample. Also, all participants were Caucasian and as acknowledged by the authors, results are most applicable to a Caucasian population-based on previously reported ethnic variations in BFD and body composition. Bioelectrical impedance (BIA) is another relatively cost-effective method of measuring body composition, however, it is saddled with many limitations when it comes to measuring BFD and exhibits variations in accuracy depending on the level of adiposity of the individual. Accuracy can also be affected by things such as having recently eaten before measurement, exercising, or the environment the measurement is conducted in. This is because all these things can affect electrolyte concentration in the body or on the skin which can influence the rate at which the current passes through the person being measured. BIA works by emitting a very low-level electrical current through the body, in most cases, about 50kHz. The current moves faster through hydrated lean body tissues and is impeded by the presence of adipose tissue. This allows BIA to calculate body fat based on the differential rate at which the current moves through the body along with the

use of specific equations [56]. A study from Dr. Sun's research team in 2005 on a group of healthy adults revealed that the mean body fat percentage when measured by BIA, was consistently lower than when it was measured by DXA. Body fat was overestimated by 3%-4% in men with less than 15% body fat and women with less than 25%. Conversely, body fat was underestimated by 4.32% in men with over 25% body fat and underestimated by 2.71% in women with over 33% body fat [57]. Another BIA study was performed using a group of 35 men and 37 women aged 60-83 years who were screened for dehydration, edema and use of drugs that may alter the body's electrolyte balance. It was found that BIA measurements of fat free mass that were thought to be accurate according to an earlier study by this same group in a younger population of men and women aged 20-40 years which employed similar methods, overestimated fat free mass in an elderly population by approximately 6kg [58]. BIA lacks the precision of DXA and other imaging technologies when it comes to measuring actual BFD but can be a quick and easy method of measuring whole body composition at the cost of some accuracy. Upper body obesity may also sometimes be defined as excessive adipose tissue within the trunk of the body [59]. What is known as the "trunk" area consists of the area between the lowest boundary of the pelvis to the highest boundary of the neck, which is the operating TF definition [60] for the projects this team has completed on BFD. However, this does not always account for adipose tissue in the arms, though some researchers have chosen to include arm fat in their upper body definition [61]. The term, upper body, has also been used to refer to the android region which encompasses an area slightly smaller than what would be considered the trunk of the body, primarily concentrated around the abdomen.

The android area consists of the region near the waist, between the middle of the lumbar spine and the upper-most part of the pelvis [62]. This area ranges from the iliac crest to 20% of the height between the iliac crest and the base of the skull [47]. This is definition that has been employed for the purposes of these projects as well. It is an accumulation of adipose tissue in this area that results in the “apple” shape, more common among men [63]. In studies concerning lower body fat, the lower body region is often referred to as the gynoid or gluteo-femoral area. This area consists of the hips, buttocks, and thighs. The more precise definition, as described in section **1.3**, is the area between the superior and inferior trochanter major or from the lower boundary of the umbilicus to a line equal to twice the height of the AF area. Accumulation of adipose tissue in this area of the body creates the “pear” shape, often seen in women who present with smaller upper bodies with most of their body fat being concentrated in the hips and thighs [64]. More detailed measurements of the mass and area of upper body adipose tissue, whether subcutaneous or visceral adipose stores, usually requires advanced imaging technologies. MRI scanning is often used for this purpose. This is due to its ability to distinguish between tissue types. MRI also provides great resolution and lacks the ionizing radiation associated with x-ray technology [65, 66]. MRI scanning relies on the use of extremely strong magnetic fields, usually between 1.5-3.0 Tesla (T), for the sake of comparison, the earth's magnetic field is about 0.00005T. So how exactly are magnetic fields used to produce images? The human body is largely composed of water, approximately 70%. Water also happens to be rich in hydrogen nuclei and these nuclei spin on an axis. The axis on which hydrogen nuclei spin within the body is randomly aligned. When these nuclei are subject to

extremely powerful magnets like those found in MRI machines, they align along the axis of the MRI scanner, parallel to the magnetic field, creating a magnetic vector. MRI machines consist of a primary magnetic field, radiofrequency coils, receiver coils, gradient coils and of course a computer system to store and present the images that are produced. The primary magnetic field is responsible for emitting the strong magnetic field which forces hydrogen nuclei to align along its axis creating the magnetic vector. The radio frequency coils emit a secondary magnetic field in a short pulse which disturbs the hydrogen proton alignment. When the radio frequency pulse ends, protons will return to their position parallel to the magnetic field emitted by the primary magnet. Based on the tissue these protons are in, they will return to their former parallel state at different rates. When protons are parallel with the primary magnetic field, they are in what is known as the relaxed state. When the radio frequency pulse ends, the time it takes these protons to completely relax is measured by 1) how long it takes for the magnetic vector to return to its relaxed state and 2) how long the axial spin takes to return to its relaxed state. This is known as T1 and T2 relaxation, respectively. Due to different tissues having different relaxation times, this can be used to distinguish one type of tissue from another. The signal, which is a radio wave, that is emitted upon protons returning to the relaxed state is picked up by receiver signals which surround the body part of interest. It is these radio waves that are actually responsible for producing the image. The signal is plotted along a grey scale and from this, cross sectional images can be constructed. Gradient coils are arranged in opposition to each other to produce negative and positive poles. These allow the MRI machine to image along the Z, Y and X axis. The Z gradient runs along the

long axis to produce axial images, the Y gradient runs along the vertical axis to produce coronal images and the X gradient runs along the horizontal axis, producing sagittal images. These gradient magnets can alter the strength of the primary magnetic field in small increments which helps with spatial encoding of the image as different slices of the body resonate at different frequencies. The radio wave signals undergo an analog to digital conversion which are then converted to the final image using a mathematical process known as Fourier Transformation [67, 68]. MRI technology is among the most advanced available for assessing body composition but due to high cost not just to purchase and run the equipment but to simply house it as well, it is not practical to use MRI for body composition studies on large numbers of people. Also, due to the use of high-powered magnets, it may be unsafe for individuals with metal implants or metal prosthetics, especially if they are not secured and anchored into bone. Computed Tomography (CT) scans are another method which is sometimes used to assess BFD [69-71]. CT scans provide excellent contrast and allow for the visualization of the body through multiple cross-sectional images. However, like MRI, CT scanning can be quite expensive. The other issue with CT scanning, particularly when it used on volunteers for research as opposed to diagnostic purposes, is that it emits a high level of ionizing radiation the research participant otherwise wouldn't have been subjected to, which can increase an individuals risk of developing cancer [72]. CT makes use of x-ray technology. An x-ray being a form of electromagnetic radiation with wavelengths measuring from 0.01 to 10 nanometers. To put that in perspective, visible light ranges from 400-700 nanometers. X-rays are produced when the kinetic energy of electrons is converted into

electromagnetic energy when the electrons are decelerated by interacting with a target material which is, in this case, an anode. The x-ray tube, the equipment necessary for x-ray production, consists of several key components. This is a vacuum tube which houses a cathode, an anode and is attached to high voltage cables at the cathode and anode which are connected to a generator. The cathode, which is the source of electrons, is heated to a temperature as high as ~2200 degrees Celsius, which causes it to release electrons in a process known as thermionic emission. These electrons are then accelerated to the positively charged anode which is assisted by the large electrical potential difference between the cathode and anode (~20,000-150,000 volts). When the electrons collide with the target atom, the kinetic energy of the electrons is converted into other forms of energy. Most interactions with the target atom simply give rise to heat but a small fraction of electrons (about 1%) come within close proximity of the positively charged nucleus of the target atom. These electrons will then decelerate and change direction resulting in a loss of kinetic energy which is converted into x-ray photons. This is termed bremsstrahlung radiation. The energy level of the x-ray is expressed in kiloelectronvolts (keV). The energy level is dependent upon how close to the nucleus the electron was before slowing down and being redirected. Electrons that reach the *K* shell, the electron shell closest to the nucleus, will eject a *K* shell electron due to strong repulsive forces between the two negatively charged particles. An electron from the neighboring *L* shell will then fill its place and an x-ray photon is emitted whose energy is equal to the difference in the binding energies of the two electron shells. The greater the distance between the incoming electron and the nucleus, the lower the energy of the resulting x-

ray. This is because electrons in the *K* shell, closest to the positively charged nucleus will experience the greatest binding energy due to their proximity to the attractive force exerted by oppositely charged proton particles. Tungsten is commonly used as the anode in the x-ray tube assembly as the x-ray energy is proportional to the charge on the nucleus which is proportional to the atomic number. Tungsten has a high atomic number at 72 and it can also withstand incredibly high temperatures before melting [73-75]. CT relies on the fact that the density of the tissue being passed through by the x-ray beam can be measured using what is known as the attenuation coefficient, which represents how easily a material is penetrated by the x-ray beam. Modern CT scanners have an x-ray tube, as described above, which rotates around the patient at a high speed while emitting a wedge-shaped x-ray beam. Directly across from the tube, on the opposite side of the patient, is a detector which rotates synchronously with the x-ray tube, although some CT scanners have a stationary ring of detectors that surround the patient on all sides. The detector measures attenuated and unattenuated x-ray intensity. Attenuated intensity (I) is equal to

$$N \cdot h\nu / S \cdot t$$

where N is the amount of photon energy passing through a unit of area (*S*) in a unit of time (*t*), *h* is Planck's constant, and *v* is the frequency of the photon of the radiation emitted. The relationship between attenuated x-ray intensity and unattenuated x-ray intensity (I_0) is expressed by the equation

$$\ln(I/I_0) = u \cdot x$$

where *u* is the linear attenuation coefficient and x is the thickness of the biological tissue. Attenuation exhibits a linear relation with the density of the tissue being scanned. This

equation is used in the CT reconstruction algorithm in a pre-processing step before image reconstruction [74]. Detectors often use either a high-pressure inert gas, most often xenon, or a scintillator paired with photodiodes. A scintillator is a material that exhibits luminescence when excited by ionizing radiation. In a xenon-based detector, the detector is made up of thin tungsten plates with an electrical current applied to every other plate (~500 V) while the other plates have no voltage. When an x-ray photon hits the detector, the xenon gas is ionized and releases a photoelectron which then ionizes more xenon gas ions. The ionized xenon nuclei are drawn to the zero-voltage plate and the free electrons are collected by the 500V plate. The quantity of xenon gas that has been ionized is proportional to the intensity of the x-ray and as I have previously noted, it is this intensity data that is used to construct the image [76]. In scintillator-based detectors, the x-ray photon undergoes a photoelectric interaction with the scintillator material. A photoelectron is released which then excites electrons in other atoms. When these excited electrons return to their ground state, they release light on the spectrum of visible light and ultraviolet [76]. The light is then guided to a photocathode of a photomultiplier tube which then emits an electron, creating an electric current. Within the photomultiplier tube are dynodes that are coated with a material that will create secondary electrons upon interacting with the initial electron. The electrons are then directed to a series of dynodes that will amplify the electric signal. An electric pulse is emitted at the end of the photomultiplier tube whose intensity is proportional to the absorbed energy [77]. Images are then constructed from the resulting intensity signals which are proportional to the energy absorbed by the detector which in turn are affected by the amount of radiation

attenuated by the body's tissues and organs. Each of our research endeavours concerning BFD makes use of DXA scanning technology as mentioned in a previous section. DXA has been chosen for several reasons. It is far more cost-effective and less time consuming than MRI or CT scanning. It can reliably distinguish between bone, lean body mass, and fat mass. DXA has often been used clinically for the diagnosis of osteoporosis [41, 78, 79]. DXA also provides the added advantage of producing highly accurate VF mass and area measurements comparable to those produced by CT scanning (r^2=0.957) [43]. This particular function was crucial to these projects. DXA scanning, like CT, make use of x-ray technology. I have described above how x-ray radiation is generated and the generation of x-rays in a DXA scanner is no different. Our model of DXA scanner makes use of the scintillation-based detectors which have also been described, however, several features make DXA uniquely suited for a research effort like the CODING study. The DXA scanner is only 205cm in length, 109cm in width, 128cm in height, and requires just a small desk and a standard consumer brand computer with a minimum of an i3 processor, 2GB of ram, and 1GB of free space for the accompanying software [80]. This makes it not only cost-efficient but size efficient as well. DXA also subjects participants to significantly less radiation than a CT scan. A CT scan can expose an individual to as little as 2.1mSv for a head and neck scan to as much as 31mSv for an abdomen-pelvic scan [81]. Our Lunar Prodigy scanner, made by General Electric [60, 82] exposes participants to approximately 0.004mSv for a whole-body scan [83]. Smaller doses of radiation are received because DXA scanners use a K-edge filter which is a material used to block the majority of x-ray photons, exposing the participant only to x-rays of two

specific x-ray energies. This is where the term dual-energy is derived. The K-edge filter is usually an element such as gadolinium, samarium cerium, or others that block x-ray photons of a particular energy level. The filtration material used depends on the energy range you wish to block and the voltage of the x-ray tube. The K-edge refers to the energy required to eject a *K* shell electron [73, 84, 85]. The remaining x-rays are an energy that is optimal for absorption by bone and soft tissue. The Lunar Prodigy, for example, produces x-rays at two distinct energy peaks of approximately 38keV and 70keV [83]. DXA scanning relies on the fact that bone will absorb more x-ray photons than the bodies soft tissues and the difference in the attenuation of the x-ray photons is linearly related to the proportion of fat in the soft tissues [86]. Another important feature of the DXA scanner is the way the x-ray beam is dispersed. There is pencil beam, fan beam and narrow fan beam DXA scanners. The DXA scanner used for our projects makes use a narrow fan beam scanner. Pencil beam scanners, while limiting radiation exposure, can take quite some time to complete a scan (5-10 minutes). Pencil beam detectors used a thin beam with a single detector which scans the individual in a rectilinear fashion. Fan beams are much faster (about 1 minute per scan) as they scan the entire individual in a single sweep but expose individuals to more radiation and have issues with magnifying parts of the body closer to the x-ray source. The narrow fan beam is compromise between these two methods. This is the beam utilized by the Lunar Prodigy DXA scanner. Narrow fan beam technology scans in a rectilinear fashion while using a broader fan beam which decreases scan time but still narrower than the original fan beams which reduces the magnification effect and exposes the participant to less radiation. Each pass of the narrow fan beam over

laps with the previous pass and these overlapping images are reconstructed resulting in more accurate estimations of bone depth [80, 86]. This concludes the review of available technologies for the measurement of BFD. Reliable measurements of BFD are incredibly valuable to obesity research as simple indexes of obesity such as BMI do not provide information on adiposity which can present issues.

1.5 Body Fat Distribution and BMI

Many people with similar BMI, the traditional index, or surrogate measure by which obesity is diagnosed, may have drastically different levels of BF. BMI is not a measure of BF and it cannot assess an individual's adiposity [48, 87]. BMI is body weight as measured in kg divided by height in m^2 ($BMI=kg/m^2$) [88]. Again, for reference, the BMI classifications are as follows:

Normal Weight – 18.5-24.9

Overweight – 25.0-29.9

Class 1 Obesity – 30.0-34.9

Class 2 Obesity – 35.0-39.9

Class 3 Obesity – 40.0 and above

At a population level, BMI shares strong correlations with several health indices. For example, a study on men and women from 12 European countries found that each 5 unit increase in BMI was associated with a 34% increased risk of CVD in men and a 29% increased risk of CVD in women.[89]. McLaughlin et al studied the relationship between BMI and insulin resistance in 465 healthy adult volunteers. Those who participated in the

study had to be in good general health which was determined using medical history and a physical examination. Participants could not be diabetic nor could they be taking any medications for the treatment of BP, hyperglycemia, or dyslipidemia. Participants were also subjected to a chemical screening battery. Blood samples were taken following an overnight fast. It was reported that 36% of individuals in the highest tertile for insulin resistance were BMI defined obese [90]. Another large study of 3981 men and 3099 women showed that BMI defined overweight and obese individuals experienced far worse physical well-being defined by measures such as bodily pain, fatigue, and physical functioning, among others. These measures were evaluated using the 12 Item Health Status Questionnaire. This questionnaire subjectively evaluates physical, social and mental well-being over the past 4 weeks. Participants were asked to rank how severe they perceive their bodily pain to be on a scale of 1 (none) to 6 (very severe). They were also asked questions regarding fatigue and physical functioning. Physical functioning was defined by the participants perceived ability to handle basic daily tasks such as carrying groceries, climbing stairs, or walking several blocks, ranked on a scale of 1 (limited a lot) to 3 (not limited at all) while fatigue was assessed by asking participants how often they feel as though they have "a lot of energy" on a scale of 1 (all the time) to 6 (none of the time) [91]. In this study, BMI was calculated from self-reported weight and height so it is important to note that some participants may have misreported one or both of those measures, possibly resulting in BMI misclassification. Misclassification of adiposity can also be quite persistent. A study of 27,000 individuals from 52 countries found that, while higher BMI was associated with an increased risk of experiencing a myocardial infarction

(MI), this relationship became substantially weaker after controlling for central adiposity which was defined in this study using WHR. The risk of MI when comparing the top BMI quintile to the lowest, was 44% higher but upon adjusting for WHR the risk was only found to be 12% higher [92]. The concern with BMI misclassification in athletic individuals or simply those with higher levels of lean body mass was the topic of a study by Lambert et al. in 2012. The BMI, fat mass, and fat-free mass of division 1 college American football athletes were compared to a group of gender and age-matched volunteers. It was concluded that the athletic group was far more like to be classified as overweight based on BMI despite having more fat-free mass than the comparison group [50]. While this particular study is not representative of the general population, as only an incredibly small fraction of individuals will ever compete in Division 1 collegiate sports, it does serve to highlight how BMI can at times be an unreliable measure of overall health. To further highlight the shortcomings of BMI, a massive study of 15,184 adults, published in *Annals of Internal Medicine,* examined the relationship between common anthropometric markers and BMI concerning their relationship with mortality. The study consisted of 7249 men and 7935 women with a mean age of 45 years old. WHR was used as an index of upper body obesity and was calculated by measuring the WC at the height of the iliac crest and hip circumference at the widest point around the buttocks. Women with a WHR of 0.85 or greater and men with a WHR of 0.90 or greater were considered to have central obesity. There were 3222 deaths, 1413 of which were women in an average follow up time of 14.3 years. 1404 were cardiovascular related deaths. The analysis revealed that normal weight, central obesity, defined only by WHR, exhibited a

greater association with mortality, largely due to cardiovascular related disease, than BMI defined obesity in both men and women [93]. As noted in section **1.4**, while WHR is a cheap, quick way to assess BFD, it comes a large degree of variability depending on the expertise of the person taking the measurement and the exact position of the measuring tape [54]. Also, while this analysis revealed that normal-weight central obesity shares a greater association with mortality than BMI defined obesity, it is important to remember that there are levels to the severity of obesity and we cannot conclude that normal-weight central obesity may be a greater health risk when compared to individuals living with morbid obesity which is a BMI of 40 or greater. As previously noted, many individual's adiposity status is often misclassified when relying only on BMI measurements [48] and it appears their true risk of any number of health issues may easily be under or overestimated as well.

Furthermore, BMI does provide any information on the heterogeneity of obesity. Individuals with similar adiposity levels can exhibit a high degree of heterogeneity in how that adipose tissue is distributed throughout their body which in turn can have very different metabolic outcomes. For example, individuals who tend to carry the majority of their adipose tissue in the trunk or android region of their body are at a significantly higher risk of CVD and other metabolic issues than those who are predisposed to carry more adipose tissue in the gynoid region of their body. A study on the commingling effects of AF and GF on metabolic dysregulation was performed on 1802 adults with normal BMI (<25.0) and an average age of 34.9 years. AF and GF were measured using

DXA and all metabolic markers were measured in serum which was obtained from a blood sample following an 8 hour fast. The markers that were chosen for this study included TG, HDL, LDL, and blood glucose. Height and weight were measured using a fixed stadiometer and digital scale while WC was measured using non-elastic tape at the height of the right iliac crest at the mid-axillary line. After adjusting for age, sex, smoking status, and alcohol intake, it was found that in the full sample of participants android to gynoid percent fat ratio exhibited stronger correlations with several cardiometabolic risk factors compared to BMI and AF or GF percent alone. This included significant positive correlations with systolic/diastolic BP, fasting plasma glucose, TG, LDL, and total cholesterol (TC). In men, android to gynoid percent fat ratio exhibited a significant negative correlation with HDL and significant positive correlation with systolic/diastolic BP, TG, LDL, and TC. In women, android to gynoid percent fat ratio exhibited a significant positive correlation with TG and fasting plasma glucose and a significant negative correlation with HDL [94]. Odds ratios were also calculated for cardiometabolic risk factors of individuals in the highest tertile of android percent fat to gynoid percent ratio. While these odds ratios suggested that those in the top tertile were more likely to have elevated glucose, BP, TG, LDL, TC and low levels of HDL, the selection of the top tertile as the cut-off is an arbitrary designation and there is no clinically defined ideal percentage of AF or GF for the maintenance of good health. This was a cross-sectional study so the exact cause or directionality of these correlations cannot be concluded. Another important factor that is missed when solely relying on BMI without considering BFD, is VF. Seidell and colleagues assessed the correlation between VF and various

anthropometric measurements of subcutaneous abdominal fat in a group of 71 men and 34 women with an average age of 51.5 years and 52.4 years, respectively. Research subjects underwent routine abdominal CT scans at a local hospital for diagnosis and monitoring of malignancies. Anyone under the age of 19 or anyone presenting with an abnormality such as an enlarged liver, that would influence body fat measurements were excluded. The subcutaneous fat measurements that were used include waist, hip, and thigh circumferences as well as skinfold thickness near the supra-iliac and para-umbilical areas. WC was measured at the height of the umbilicus and hip circumference was measured at the height of the anterior superior iliac spine. Some of the key findings observed in women include a significant correlation between abdominal subcutaneous fat and VF (r=0.73) as well as a significant correlation between skinfold measurements and VF (r=0.73). In men, abdominal subcutaneous fat and VF also exhibited a significant positive correlation (r=0.72) as did WHR and VF (r=0.75). An important note about this study is that some of the participants were there to obtain CT scans to monitor disease progression so it is possible that either the illness or medication use may have influenced the amount of body fat [95]. There are several important differences between abdominal subcutaneous and VF depots. First, the anatomical difference between VF and abdominal subcutaneous fat is that VF, sometimes called intra-abdominal fat, refers to the adipose tissue located behind the abdominal wall within a fold of the peritoneum, known as the omentum as well as the area of the mesentery and surrounds organs in the same space such as the liver and intestines (**Figure 1-4**). Abdominal subcutaneous fat is in reference to fat just beneath the skin of the abdominal area which extends from the subcutaneous

fascia to the dermis as well a deeper layer of fat composed of more loosely packed fat lobules as described by Markman and Barton following 36 hemidissections of 8 fresh and 10 preserved cadavers [96]. While the anatomical location is just one distinction, it is an important one as VF that accumulates near the liver will undergo lipolysis resulting in free fatty acids (FFA) entering hepatic circulation via the hepatic vein. This was demonstrated by Nielsen and colleagues. This group investigated whether a larger amount of VF would result in more hepatic FFA delivery. The participants consisted of 12 non-obese men and women, 20 men living with obesity, and 24 women living with obesity. Participants were taken off medication for hypertension and lipid-lowering medications 1 month before the study while diabetic patients were withdrawn from hypoglycemic therapy 2 weeks before the study. All meals were consumed at the research centre 3 days before the study to ensure that caloric and macronutrient intake were consistent among participants. Hepatic FFA delivery from the VF depot was measured using isotope dilution to label FFA and catheterization of the hepatic vein. The evening before the procedure participants were admitted to the research centre and were intravenously administered a 0.45% NaCl saline solution and resting energy expenditure was measured using indirect calorimetry. Sheaths were inserted in the right femoral artery and a catheter was inserted through the sheath with the tip in the common iliac artery for arterial blood sampling and infusion of the medical dye, indocyanine green. A sheath was then inserted into the right femoral vein with the distal tip in the external iliac vein. A catheter was then inserted with the tip placed in the right hepatic vein. When all catheters were in place [9, 10-3H] palmitate or [1-14C] palmitate (used in an obese subgroup for additional analysis

not reported in this study) and indocyanine green infusions began 30 minutes before blood sampling. Arterial, femoral, and hepatic vein samples were taken at 10-minute intervals over 30 minutes. Regional body fat was measured using DXA and a CT scan between the L2 and L3 vertebrae to measure VF. Plasma FFA concentration was significantly greater in men and women of the obese group (663umol/L and 709umol/L, respectively) than men and women of the lean group (487umol/L and 587umol/L, respectively). VF area was positively correlated with the percent of hepatic FFA delivery from VF stores in men and women with correlation coefficients of 0.52 and 0.49, respectively. The authors also reported that this effect was more accentuated in women than in men. Generally, among lean individuals, 5-10% of hepatic FFA delivery is from VF and in obese individuals, over 30% of hepatic FFA delivery is from VF [97]. Several of the participants in the obese group were hypertensive, diabetic, or dyslipidemic. While this was intentional as the authors wanted to be sure those with obesity-related complications were represented, there could be any number of underlying metabolic issues that could skew results in a manner not representative of those living with obesity yet remain healthy. Those with metabolic disorders were not separated from the otherwise healthy obese group though the research team did appear to take measures to account for variance due to medication or diet as best they could. There are also important biochemical differences between subcutaneous fat and VF. For example, one study that analyzed 2 independent cohorts investigated whether there was differential macrophage infiltration between subcutaneous and VF samples and see if these differences were present among two vastly different populations with a wide range of BMIs. One cohort

consisted of 20 lean men and women, 20 subcutaneously obese men and women, and 20 viscerally or intra-abdominally obese men and women. Each group consisted of 10 men and women. Obesity status was determined using BMI, total fat percent was measured using DXA, and VF was measured using CT with images taken between the L3 and L4 vertebrae. Those with a VF to subcutaneous fat ratio above 0.5 were in the intra-abdominally obese group while those with a ratio below 0.5 were in the subcutaneously obese group. Blood samples were taken after an overnight fast and insulin resistance was determined using the euglycemic hyperinsulinemic clamp. The second cohort consisted of 27 severely obese women (BMI >40) who were divided according to whether they had normal glucose homeostasis or impaired glucose homeostasis which was determined using fasting glucose levels. Insulin resistance in cohort 2 was determined using the homeostatic model of assessment-insulin resistance (HOMA-IR) equation. The second cohort did not undergo CT or DXA scanning as cohort 1 had. WC was measured in both groups either at the point between the iliac crest and lowest rib or, among those living with severe obesity, at the point of the largest trunk circumference. Cohort 1 included individuals who did not have any acute or chronic inflammatory disease, glycated hemoglobin levels below 7.5% and fasting glucose below 180mg/dl, systolic BP below 160mmHg and diastolic BP below 95mmHg, less 1han 100mg/dl LDL and more than 35mg/dl HDL, no evidence of CVD or peripheral arterial disease, no medication usage with the exception of metformin for the ten type 2 diabetics in the obese groups, no history of alcohol or drug abuse and no pregnancy at the time of the study. Cohort 2 was established with the intent of examining biochemical differences between the

subcutaneous and VF depots. Adipose tissue samples were obtained from both groups during various abdominal surgical procedures which ranged from exploratory surgeries (if findings were negative), weight reduction surgery, or most commonly, gastric banding surgery. Expression of chemoattractant protein-1, an inflammatory cytokine, and colony-stimulating factor-1, which stimulates macrophage colony formation among other inflammatory effects, were measured using real-time polymerase chain reaction. When compared to abdominal subcutaneous fat tissue samples, VF taken from the omental area displayed significantly more macrophage infiltration in all cohort 1 groups, lean controls included. Macrophage infiltration was higher among the intra-abdominally obese group compared to the subcutaneously obese group. Also, macrophage infiltration demonstrated a significant positive correlation with visceral obesity but displayed no significant relationship with subcutaneous obesity. The cohort 1 analysis also revealed that macrophage infiltration, whether it was in subcutaneous or VF, had a positive correlation with BMI, WC, fasting insulin, and systolic BP. Increased macrophage infiltration was also significantly associated with mRNA levels of colony-stimulating factor-1 in cohort 1. Cohort 2 also exhibited more macrophage infiltration in VF compared to subcutaneous fat, in fact, it was 2.5-fold more. Cohort 2 also displayed higher levels of chemoattractant protein-1 and colony-stimulating factor-1 in VF samples. A positive correlation was also demonstrated between the number of MetS factors as defined by the adult treatment panel III (ATPIII) criteria and VF macrophage infiltration but not subcutaneous fat macrophage infiltration [98]. An ambitious study such as this one makes it difficult to standardize the experimental procedures across cohorts and make it quite difficult to properly control for

any number of confounding variables as both cohorts consisted of vastly different people. One example of this is the different method of measuring insulin resistance in each cohort, one used the highly reliable gold standard euglycemic hyperinsulinemic clamp while the other relied upon the HOMA model. HOMA-IR also has limitations that should be acknowledged. The first thing to note is the HOMA-IR equation which is

Glucose (mmol/L) x Insulin (mmol/L)/22.5

HOMA-IR has a moderately good correlation with insulin resistance as measured by a euglycemic hyperinsulinemic clamp which is the gold standard for measuring insulin resistance but it is less reliable in some people including older individuals with impaired glucose tolerance and older men and women with diabetes [99, 100]. Also, HOMA-IR does not distinguish between hepatic or peripheral insulin resistance. This study did, however, demonstrate that, in 2 very different cohorts consisting of healthy individuals and those with metabolic disorders with a wide range of obesity phenotypes, VF is distinct from subcutaneous fat in the way that it is susceptible to macrophage infiltration which can result in inflammation. Additionally, macrophage infiltration, specifically in VF, is associated with a higher number of MetS components. However, there is slight controversy surrounding the degree to which VF contributes to metabolic disorders due to the finding that upper body subcutaneous fat stores contribute between 60%-78% of FFA to systemic circulation, lower body subcutaneous fat stores contribute 16%-20% of FFA to systemic circulation while VF store contributes 5%-20% of the FFA in systemic circulation, depending on the abdominal adiposity of the individual, plus VF often only

makes up, at most, approximately 10% of total fat mass [97, 101]. BFD is an important factor in the development of obesity related comorbidities and a shortcoming of BMI is that it simply cannot account for this variation. The relationship between BFD and obesity related comorbidities is explored in the next section.

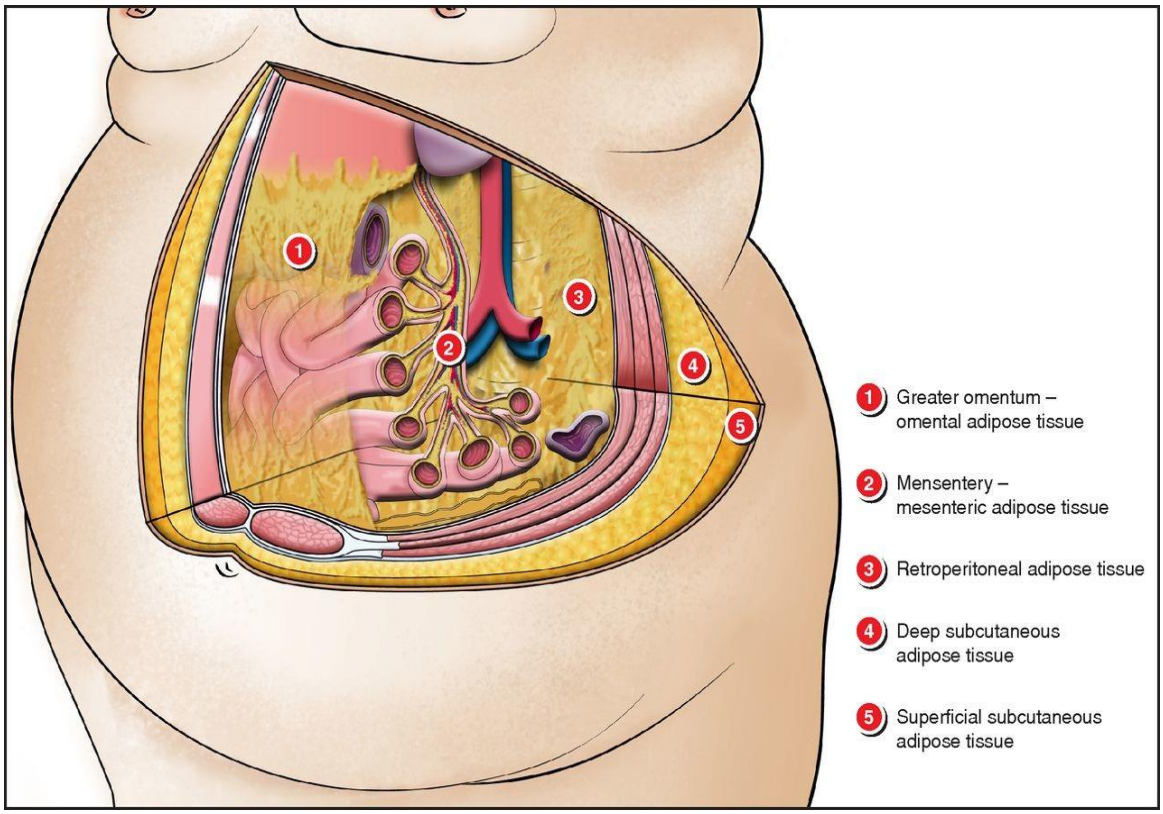


Figure 1-4 Visceral Fat Anatomical Location

Tchernof, Andre. Despres, Jean-Pierre Pathophysiology of Human Visceral Obesity: An Update. Physiological Reviews. 93. By permission of The American Physiological Society

1.6 Body Fat Distribution and Obesity Related Comorbidities

Obesity, which is a multifaceted disorder, has recently been classified as a "disease" by both the American Medical Association and the Canadian Medical Association. However, this classification is not without criticism. There are several reasons for this skepticism and fair questions have been raised such as the concern of possible financial incentives [102]. One primary reason for the hesitancy of some to label obesity as a disease is due to the fact that some individuals living with obesity experience no comorbidities or negative health effects. This is, in part, because obesity is often diagnosed using BMI which, as described above, may be a reliable index at the population level but says nothing of actual adiposity. It is understandably difficult to label something a disease when some individuals who meet the criteria for said disease are otherwise healthy. This is why the matter of BFD and adiposity is so important when discussing obesity as it pertains to health outcomes and certain BFD patterns are of unique concern due to the heightened risk of developing obesity related comorbidities. The studies reviewed below support this claim.

A study published in 2017 by Han and colleagues investigated the relationship between BFD and CVD risk in a sample of 15,686 (6761 men, 8925 women) adults aged 20 years and older with no previous diagnosis of CVD. Many variables were used in this study as it is quite comprehensive (ex. muscle distribution kidney disease, albuminuria) but I will focus on the measurements relevant to this thesis. BFD was measured using DXA and the ratio of leg fat to TF was used as an index of BFD. The metabolic components that were measured include BP which was taken 3 times in a seated position, plasma glucose,

insulin, HDL, LDL and TG were all measured following an 8 hour overnight fast. CVD risk was assessed using several different criteria which included the atherosclerotic CVD risk score from the American College of Cardiology and the American Heart Association, the Framingham 10-year CVD risk score, and the Korean coronary heart disease prediction model. The atherosclerotic CVD risk score calculates risk based on age, ethnicity, TC, HDL, systolic and diastolic BP, and whether not an individual is a diabetic or a smoker [103]. The Framingham risk score calculates risk using age, TC, HDL, Systolic BP, whether an individual is receiving treatment for high BP, whether they are a diabetic or a smoker and how many CVD incidents they've had in their lifetime [104]. The Korean coronary heart disease prediction model calculates risk using the same variables as the Framingham risk score but includes LDL, TG and expands on smoking status by asking whether an individual is a former smoker [105]. Individuals were separated into sex specific tertiles based on CVD risk score and leg fat to total fat ratio. They were also separated by obese or non-obese and then each group was further stratified by leg fat to total fat ratio tertiles for analysis. In both the obese and non-obese groups, those in the highest tertile of to total BF ratio fat exhibited the lowest prevalence of hypertension, diabetes, and MetS. The prevalence of hypertension, diabetes, and MetS in the highest leg fat to total fat ratio tertile in the non-obese group was 7.0%, 1.1%, and 2.4%, respectively. The prevalence of hypertension, diabetes, and MetS in the lowest tertile within the same group was 37.5%, 15.2%, and 37.6% respectively. The prevalence of hypertension, diabetes, and MetS in the obese group, among those in the highest tertile of leg fat to total fat ratio was 24.0%, 4.3%, and 35.0% respectively. The prevalence of

hypertension, diabetes, and MetS in the lowest tertile within the obese group was 53.8%, 26.4%, and 72.4% respectively. Higher leg fat to total fat ratio was also associated with more favorable levels of glucose, insulin, HOMA-IR, LDL, TG, and HDL. Those with higher leg fat, after separating by sex, had lower CVD risk scores even when they had higher amounts of total fat. Also, a logistic regression analysis which controlled for age, sex, obesity, smoking status, alcohol intake, BP, serum glucose, dyslipidemia BMI, menopausal status, and kidney function revealed those with the lowest leg fat to total fat ratio had significantly higher CVD risk, using the atherosclerotic CVD risk score from the American Heart Association, with an adjusted odds ratio of 1.85%. Other risk scores showed similar results [106]. One notable limitation of this study, as with any cross-sectional study, is that the directionality of the association could be not concluded. The authors also note that they did not have all the information on medication usage available to confirm whether certain medications may have influenced the results. Also, it is important to note that, in the Korean population, the BMI cut-off point for obesity is a lower than western populations as East Asian populations tend to have more body fat and experience obesity related comorbidities at a lower BMI than western populations, however, this is a large general population study which demonstrates the important role of BFD in obesity related comorbidity, also, many of the criteria used to assess CVD risk are the same as those used in western populations. There is some controversy regarding the beneficial relationship between measures of metabolic health and GF as other studies have found that GF still shares an association with worsening metabolic characteristics. In one study, odds ratios were calculated for DXA measured GF and it was reported that it

was significantly correlated with impaired glucose tolerance (OR=2,07), hypertriglyceridemia (OR=2.10), and hypertension (OR=2.15) in 175 men with an average age of 45.3 and an average BMI of 25.7, whereas the ratio of GF to BF mass exhibited a protective effect against hypertriglyceridemia (OR=0.42) and hypertension (OR=0.61) while controlling for age, physical activity, and smoking status. Among the 417 female participants with an average age of 46.8 and an average BMI of 24.8, GF was associated with an increased risk of hypertension (OR=1.57) while gynoid to total fat ratio decreased the risk of hypertriglyceridemia (OR=0.49) and hypertension (OR=0.62), emphasizing the importance of fat distribution as opposed to fat accumulation in any one region [107]. Other studies highlight the role of sex on BFD. Wiklund et al performed a longitudinal study on 3258 individuals with a follow-up period of approximately 8 years that found in women, abdominal to GF ratio was the best predictor of MI while the ratio of gynoid to total fat mass was protective after adjustment for age and smoking status. There was no significant difference in total fat mass between women who did or did not experience a MI (26.2kg vs 27.5kg, respectively) and there was no significant difference in BMI (25.5 vs 26.4). However, there was a significant difference with respect to abdominal to GF mass (0.56 vs 0.66) and GF to total fat mass ratio (0.11 vs 0.01). In men, no significant results were observed suggesting higher gynoid to total fat mass ratio offered any protective effects against MI [108].

Another study that highlights the importance of BFD as it pertains to obesity related comorbidities was performed by Grundy and colleagues. In this study, 1449 women and

1138 men aged 30-65 years sought to assess the relative contribution of BF and BFD to the components of MetS. The sample population consisted of individuals enrolled in the Dallas Heart Study. Those with diabetes mellitus were excluded from the analysis. Body fat and BFD were measured using DXA and the authors used the ratio of TF to lower body fat as their BFD measurement. The authors defined lower body fat as all fat below the oblique lines. The components of MetS that were measured include TG, HDL, HOMA-IR which is a measure of insulin resistance and systolic BP. Participants were separated into tertiles based on their ratio of TF to lower body fat and grouped by sex. In men, BFD exhibited a stronger correlation with TG than BF percent, but BF had a stronger correlation with HOMA-IR. There was not a significant difference in the correlation coefficients for systolic BP or HDL. In women, BFD had a stronger correlation with TG and a stronger negative correlation with HDL. There was not a significant difference between correlation coefficients for systolic BP or HOMA-IR. Based on this study, it appears that markers of insulin resistance were more attributable to BF while markers of dyslipidemia and higher TG levels were more attributable to the ratio of TF to what the authors defined as lower body fat. One thing to note about this study is that it was composed of individuals of Caucasian, African American, and Hispanic ethnicity proportional to the population of the city in which it took place and while there were differences among these ethnicities in regards to BFD and BF, the level of association between these variables and components of MetS were consistent among these groups which is why the authors pooled them together. As this study was meant to properly represent the demographics of an ethnically diverse North American population,

it is possible that the strength of these correlations may differ in a more homogenous population. While this study was chosen for this review because it highlights how BFD and total BF may differentially affect different obesity related comorbidities in a wide age range of men and women from a general population, it is important to note the factor of ethnicity that may make it less generalizable to some populations [109]. Another large general population study that highlights the role of BFD in the development of obesity related comorbidities was published in *BMC Public Health* by Lukacs. This study examines the relationship between BFD and metabolic risk factors in a sample of non-obese participants. 2082 men and 3146 women aged 18 years and older with no history of diabetes, hypertension, ischemic heart disease, or chronic obstructive pulmonary disease. All measurements were performed on-site by a community nurse and a public health practitioner. The metabolic variables that were measured include blood glucose, TC, LDL, HDL, and TG. WC was used as an index of abdominal obesity and this measurement was made at the halfway point between the lowest rib and iliac crest. Participants were divided into a high WC group and a normal WC group with a high WC being defined as having a WC above 102cm in men and above 88cm in women. Those in the high WC group had a significantly higher occurrence of high systolic BP, high fasting blood glucose, high cholesterol, and high TG based on the cut-off points set by the ATPIII criteria of MetS. A subsequent logistic regression analysis adjusted for age and gender showed that the high WC group had a significantly higher risk of having high BP, low HDL, and high TG as the odds ratios were 1.53, 2.06, and 1.65, respectively. The authors also reported that participants ages 45-74 were more likely to have high TG

compared to those ages 20-31 [110]. This study demonstrates the impact specific BFD patterns can have on health even in a normal weight, general population, however, there are some limitations to note in this study. The issue of using WC as an index of adiposity has been mentioned before. It can vary quite a bit and is dependent on the skill of the individual taking the measurement. It is also important to note that the sample population also skews a little younger with the majority of participants between the ages of 18-44. Another limitation is that information on medication usage is not provided or adjusted for. It is possible that some participants may have been using medications that may have affected the outcomes of this study, especially among older participants, and of course, as this is a cross-sectional study, cause and effect cannot be discerned. It is apparent BFD patterns are important for determining the risk of obesity related comorbidities, it is imperative that the factors which influence BFD patterns are thoroughly researched and well understood. The factors that contribute to BFD patterns are no less complex than the factors that contribute to obesity as a whole. There are a plethora of aspects to be weighed and considered. The next section explores these factors beginning with a review of the underlying genetic factors and building outwards to physiological, environmental factors, and behavioural factors.

1.7 Factors Influencing Body Fat Distribution

1.7.1 Genetics and Body Fat Distribution

There are a large number of genetic factors that have been shown to influence BFD and with the advances in GWAS, more are being found. A large collaborative effort to identify the interaction of age and sex with genetic loci associated with obesity and BFD

found 44 loci associated with WHR adjusted for BMI (WHR_{adjBMI}). Of the 44 loci identified, 17 were novel. 28 of the 44 showed larger effects in women while only 5 exhibited a larger effect in men and perhaps most interestingly, 11 showed opposite effects between sexes. The genes exhibiting sex-dependent opposite effects were *CECR2, PTPRD, RXRA, TTN, IRS1, SLC2A3, IQGAP2, SGCZ, GNPNAT1*, *SIM1*, and *NMU*. These genes control a very diverse role of functions ranging from chromatin remodeling, to lean muscle development, insulin receptor substrates, and hypothalamic mediators of stress [111]. Another study concerning WHR_{adjBMI} conducted a GWAS meta-analysis of 224,459 individuals. This revealed 49 loci, 33 of which were new, associated with WHR, and 19 novel loci associated with waist or hip circumference alone. 20 loci displayed sex-dependent effects, 19 of which appeared to be much more pronounced in women. Additional pathway analysis identified many possible physiological mechanisms by which these genes operate including adipogenesis, angiogenesis, and insulin resistance [112]. Follow up studies to further investigate the functionality of these genetic loci as they pertain to BFD could offer great insight into potential therapies in the future and it would also be beneficial to better understand the underlying mechanism of the sex-dependent effects that were observed as sex is an important BFD factor

1.7.2 Sex and Body Fat Distribution

Another more noticeable observation concerning BFD patterns is the stark difference between many men and women. In men, the accumulation of truncal or android and visceral adipose tissue is far more common than gynoid adipose tissue accumulation. While women can also display android type obesity, gynoid adipose tissue accumulation

is far more common in women than men. This sexual dimorphism of BFD has long been observed [113-115]. The BFD differences between men and women may largely be influenced by sex hormones. Estrogens have been repeatedly shown to decrease appetite and therefore caloric intake. Animal studies on estrogens have been shown to decrease appetite by potentiating the effects of anorectic hormones such as cholecystokinin and leptin while decreasing the effects of orexigenic hormones such as ghrelin [116-118]. Studies on women have also found that energy intake tends to be at its lowest during the late ovulation phase of the menstrual cycle when estradiol levels are at their peak [119, 120]. However, the effects of sex hormones on BFD go well beyond appetite control. Testosterone, growth hormone, and estrogen are thought to combat central fat accumulation by mobilizing fat stores while hormones such as cortisol and insulin promote fat accumulation. Furthermore, visceral adipose tissue tends to have more cortisol and androgen receptors than adipose tissue elsewhere in the body which explains why these hormones appear to wield so much influence over the deposition of VF while estrogen receptors do not appear to be present on this particular type of adipose tissue [121, 122]. A study aimed to better elucidate the role of estrogen in fat accumulation by obtaining subcutaneous abdominal adipose tissue samples from two groups of women via liposuction. One group of women were an average age of 55.8 years, had an average BMI of 25.5, and were reported to be healthy and not receiving any hormone replacement therapy treatment. The other group of women were an average age of 53.7 years, had an average BMI of 24.8, and were receiving hormone replacement therapy but were reported to be otherwise healthy. The drugs that were used for hormone therapy consisted of 12

days of taking a tablet containing 2mg of estradiol, 10 days of taking a tablet containing 2mg of estradiol and 1mg norethisteronacetate, and 6 days of taking a tablet containing 1mg of estradiol. The authors defined the *in vivo* portion of their study as the research that was performed on the isolated adipocytes of this group of women. The authors described the *in vitro* portion of the study at the research that was performed on cultured adipocytes. All liposuction procedures were for cosmetic reasons and all women had received hormone replacement therapy for 3 years. In addition to this, samples of subcutaneous abdominal and visceral adipose tissue were obtained from 5 women living with obesity with an average BMI of 45.2 who underwent gastric banding surgery for severe obesity. This is a procedure that involves placing an adjustable, inflatable band around the upper portion of the stomach which induces feelings of fullness without consuming as much food as the patient would have previously consumed. The purpose of this procedure is to achieve weight-loss via caloric restriction [123]. Lipolysis, lipoprotein lipase, hormone-sensitive lipase, α2-adrenergic receptor mRNA, and α2-adrenergic receptor activity were measured from isolated adipocytes as well as cultured adipocyte samples. It was found that estradiol directly increases the number of antilipolytic α2A-adrenergic receptors in subcutaneous adipocytes thereby lowering the subcutaneous lipolytic response whereas estradiol appeared to exhibit no control over intra-abdominal or VF adipocytes. This would suggest that the typically female BFD pattern is maintained by way of female sex hormones, specifically estradiol, inhibiting lipolysis in certain subcutaneous fat regions thereby favoring subcutaneous fat accumulation rather than VF accumulation [124]. Testosterone has been shown to decrease VF accumulation as it promotes the growth of

lean muscle mass and mobilizes fat stores in this area [125, 126]. This section concerns the differences in BFD attributable to sex and as the previous research explored the role of female sex hormones the next study that is cited will explore the role of male sex hormones. A study published in 2006 by Derby and colleagues investigated the association between BMI, BFD and changes in sex hormones in a group of 942 men who were randomly recruited to take part in the Massachusetts Male Ageing Study. All men were between the ages of 40 and 70 at the time of recruitment between 1987-1989 and follow up measurements were completed in 1995-1997. The anthropometric measurements included height, weight, and WHR. BP was also measured. Height and weight were measured by a trained interviewer while participants were in socks and light clothing. A non-fasting blood sample was obtained by a trained phlebotomist for the measurement of sex hormones between 9am and 11am. Two blood samples were taken 30 minutes apart to account for episodic hormone secretion. WC and WHR were used as an index of abdominal adiposity which was defined as a WC above 100cm or a WHR above 0.95. Men who were diagnosed with prostate cancer or had outlying hormone concentrations were excluded. The hormonal measurements that were taken included total testosterone, free testosterone, Dehydroepiandrosterone, and sex hormone-binding globulin. Covariates included age, follow up levels of smoking, alcohol intake, diabetes, heart disease, cancer, physical activity levels, and general health status. The baseline levels of all measured hormone concentrations were inversely correlated with WC. Baseline levels of total testosterone, dehydroepiandrosterone, and sex hormone-binding globulin concentration were all inversely correlated with WHR and all baseline hormone

concentrations with the exception of dehydroepiandrosterone were inversely correlated with BMI. Free testosterone, total testosterone, and sex hormone-binding globulin concentrations were all lowest among men who were classified as obese at baseline and follow up and those who became obese at follow up. Levels of total testosterone at follow up were highest among men who were never obese by any of the 3 indices used and the lowest follow up concentrations were reported for men who were obese at both baseline and follow up. It should be noted that the use of waist and hip measurements and as an index of abdominal adiposity is subject to error and can vary based on the exact location of the measurement. Also, this study was completed in a group of men ranging in age from 40-70 so it is best to be cautious if generalizing these results to much younger men. While this study demonstrates a relationship between sex hormones and BFD, the design of the study does not allow one to conclude the directionality of the correlations between BFD and sex hormones. While the sex-related variation of BFD is well researched and easily observed, another sex-related aspect that should not be overlooked when researching BFD and obesity is that of menopausal status in women.

1.7.3 Menopause and Body Fat Distribution

In women, reproductive stages may also influence BFD. Before menopause, subcutaneous fat stores tend to build in the gynoid area as opposed to the abdominal area while this balance seems to shift to store more abdominal fat after menopause [127]. This was demonstrated in a study that examined 12 perimenopausal women and 12 post-menopausal women. Perimenopause describes the 2 to 8 year period before menopause as well as the first year after the final menses. Women were matched for BMI, body fat, and

race. All women were described as sedentary meaning no more than 20 minutes of exercise weekly, had stable weight meaning less than 2 kg in weight change over the last year and none reported smoking within the last 5 years. Women were also screened to be sure no participants were using birth control, hormone replacement therapy, or drugs that could influence lipid metabolism. Several measurements of body composition were taken including waist and hip circumference, DXA scanning, and a single slice abdominal CT scan taken between the L4 and L5 vertebrae of the spine. Follicle-stimulating hormone, estradiol, free testosterone, and sex hormone-binding globulin were measured from serum samples. Adipose tissue samples were obtained for measurement of lipoprotein lipase activity from the abdominal and gluteal regions by aspiration using a 16-gauge needle following an overnight fast. Participants were also put on a controlled diet for 2 days before the study which consisted of 50-55% carbohydrates, 15-20% protein, 30% fat, 200-400mg cholesterol, and polyunsaturated to saturated fat ratio of 0.6-0.8. Basal lipolysis in adipose tissue cells from the gynoid region, referred to in this paper as the gluteal region, was significantly higher in perimenopausal women. Adipose tissue lipoprotein lipase activity was reported to be significantly lower in perimenopausal women in samples obtained from both the gluteal and abdominal area. This was expressed as the nanomoles of FFA produced per gram of tissue in 1 min. In perimenopausal women, this number was 2.0 nmol FFA/g.min and 1.3 nmol FFA/g.min in the gluteal and abdominal region, respectively. In postmenopausal women, lipoprotein lipase activity was reported to be 4.9 nmol FFA/g.min and 3.2 nmol FFA/g.min in the gluteal and abdominal area, respectively. Lipoprotein lipase activity was reported to be

significantly higher in the gluteal region compared to the abdominal region in both groups. When lipoprotein lipase activity was expressed per 1 million cells, it was reported to be significantly lower in the abdominal region of the perimenopausal group but was not significantly different for the gluteal region [127]. The strength of this study lies in the fact that the researchers managed to obtain adipose tissue samples from living subjects in two groups of women matched for BMI and body fat percentage. It was also wise to control the women's diet leading up to the sampling. It would've been helpful to know if all blood samples were taken at approximately the same time as some hormone's concentrations can vary throughout the day. It is, of course, difficult to say how strictly each participant adhered to the controlled diet as well. Abdominal fat accumulation may increase after menopause as a result of the change in lipoprotein lipase activity explored in the previously described study and this is preceded by lowering estrogen levels, but it has been shown that estrogen substitution via hormone replacement therapy can reduce abdominal fat storage in postmenopausal women [128, 129].

To clarify, it appears that estrogen promotes fat storage in the lower body while testosterone systemically combats any fat accumulation and uniquely influences VF accumulation. It is when estrogen and testosterone are diminished in women and men respectively, that central or VF accumulation may begin to increase. This is further substantiated by studies that have shown that in pre-menopausal women when estrogen levels are higher, body fat tends to accrue around the hips, buttocks, and thighs but as estrogen levels decrease after menopause, it appears as though fat accumulation shifts

towards abdominal fat storage [130, 131]. While the underlying cellular mechanisms for these effects are not well understood and there is still much to be learned, here is what is currently known of the sexual dimorphism of BFD at the cellular level. Visceral and subcutaneous adipose tissue contains both estrogen and androgen receptors, however, VF tends to have more androgen receptors as noted above in section **1.7.2**. Androgens such as testosterone inhibit preadipocyte differentiation and maturation. The presence of androgen receptors in adipocytes appears to be upregulated in the presence of testosterone. When bound, androgen receptors interact with co-activators which may up or down-regulate transcription of genes that contain androgen response elements. It has been proposed that β-catenin nuclear translocation is triggered by the androgen receptor which is a downstream effector of the Wnt signaling pathway, Wnt proteins then inactivate glycoprotein kinase 3β which represses phosphorylation of β-catenin, an important pathway for cellular differentiation and proliferation. Also, in preadipocytes, expression of Wnt protein represses adipogenesis via the inhibition of PPARγ transcription factors [132]. Androgens may also upregulate adrenoceptors which are g-protein-coupled receptors for catecholamines such as norepinephrine and are important for the activation of lipolysis. Lipolytic effects on adipose tissue are mediated through the activation of β-adrenoceptors which subsequently activates adenylyl cyclase, signaling an increase in intracellular cAMP levels. cAMP then phosphorylates Protein-Kinase A which in turn phosphorylates hormone-sensitive lipase and lipid droplet binding proteins. Fatty acids are then released, bound by chaperone proteins, and transported out of the cell by fatty acid transport proteins [133]. Estrogen effects on adipose tissue are regulated

through various estrogen receptors (ER), for example, ERβ4 and ERβ5 expression are higher in gynoid adipose tissue than subcutaneous abdominal adipose tissue [134]. Also, activation of ERα increases the expression of anti-lipolytic α2 adrenergic receptors in subcutaneous but not VF stores. The activation of α2 adrenergic receptors inhibits adenylyl cyclase activity which decreases cAMP levels resulting in a decrease in the rate of lipolysis [135].

Sexual and menopausal factors account for a great deal of the variability in BFD, however, other factors have been shown to have an association with BFD that should not be overlooked. This includes ethnicity, environmental factors, and dietary behaviour which are explored in the subsequent sections.

1.7.4 Ethnicity and Body Fat Distribution

Ethnicity is yet another factor that may also play a role in body composition and BFD patterns. Slight variations among different ethnicities within the same geographical area have been observed and used as reference data [136]. Differences in body composition and BFD have even been observed in young children in various stages of life ranging from infancy, childhood, and puberty [137]. Ethnic differences in BFD are explored in the studies cited below in several different age groups to support the previous claim that ethnic differences in body composition and BFD are observable at different life stages.

A study of 332 term infants recruited within 1-3 days of birth investigated the relationship between race and body composition. The race of the infants was based on the report of the mother that all 4 grandparents of that child were of that particular race. Infants with

congenital disorders, infections, or non-singleton birth were excluded. Infants were also excluded if the mother was diabetic, had pre-eclampsia, or were admitted to the neonatal ICU. Infant length and crown to rump length were measured using an infant length board. Weight was measured using an electronic scale. Fat mass was calculated using air displacement plethysmography. To sum this method up briefly, an individual is placed in a chamber, and body volume is calculated based on pressure changes that occur between the testing chamber and reference chamber with corrections made for thoracic gas volume. This is calculated using Boyles Law ($P_1V_1=P_2V_2$) [138]. Body density is calculated by dividing body mass by body volume and fat mass is calculated using Siri's equation (% Body Fat=[(4.95/body density-4.50)x100] [139]. The authors reported that African American and Caucasian females had higher fat mass than African American and Caucasian males, however, Caucasian males had less fat mass than Asian and Hispanic males but there was no significant difference observed between Caucasian and African American males [140]. Air displacement plethysmography is a reliable means of measuring fat mass in infants [141], results can be affected by the hydration levels of the participant and it does not provide regional body composition data the way other measures of body composition could. It should also be mentioned that the researchers had no information on maternal nutrition or access to nutrition so they are unable to correct for these variables that could influence birthweight and infant body composition. This study, though not without some limitations, demonstrates that there are possible ethnic differences in body composition from birth, but how do these differences extend to BFD in childhood and adulthood? The next study described explores similar factors (body

composition and BFD) among 176 girls and 182 boys ages 5-12 years who were either Caucasian (n=120), African American (n=95), or Asian (n=143). The ethnicity of all four grandparents was used to confirm the ethnicity of the child and medical history along with a physical examination was used to confirm normal health status. This study measured body composition and BFD using skin-fold thickness measured by calipers and DXA. Skin-fold measurements were taken at the tricep, bicep, chest, subscapular, abdomen, suprailiac, calf and thigh area. Among male participants, according to skin-fold measurements, Asian children had significantly more GF than African Americans but did not differ significantly in extremity fat from either African American or Caucasian children. According to DXA based BFD measurements, Asian boys had significantly less extremity fat than Caucasian boys. Among female participants, Asians had significantly less extremity fat and GF than Caucasians when using skin-fold measurements. According to DXA based measurements, Asians had significantly less extremity fat than both Caucasians and African Americans. Asian girls also significantly less GF than African American girls [142]. One possible issue with this study is that pubertal status was not confirmed biochemically in all children, just a small sample of them, which could have affected body composition among some of the older children. It is also important to note that information on socioeconomic status (SES), diet or exercise was not available for this analysis. Each of the previously described studies examined BFD differences among several ethnicities early in life and demonstrated that some differences among ethnicities may be present from birth. However, these results would carry more weight had dietary information and SES been accounted for. Another study that examined BFD

variations among different ethnicities was performed by Stults-Kolehmainen and colleagues. This study consisted of 852 men between the ages of 18 and 30. The participants were 50.7% Caucasian, 17.7% Hispanic, 23.7% Asian, and 7.9% African American. Height and weight were measured using a stadiometer and physician scale. BFD was measured using DXA. Individuals were excluded if they had any metal or rods in their bodies or if they were unable to fit their entire body in the DXA scanner. All participants filled out health questionnaires and were reported to be free of any chronic disease before taking part in the study. Hispanics had a higher fat percentage than Caucasians for every region and a higher fat percentage than African Americans in every region but the arms. Hispanics had more fat in the trunk and android region than Asians, though Asians had higher TF and AF than African Americans. Asians also had more TF than Caucasians [143]. Some important notes about this study are that participants were recruited from an exercise class and while none of the participants were college-level athletes at any point, they may be much more active than the average person. Also, the average BMI among each group ranged from 23.9 to 26.5 meaning the majority of participants were not obese so it cannot be assumed that similar ethnic BFD differences would be observed among those living with obesity. Though there were no significant BFD differences between African American and Caucasian men in the study, other studies have found that Caucasian men of a similar BMI have a greater amount of VF than African American men and women after controlling for age, sex hormone levels and total BF [144]. There have been many reported observations of differences in BFD and body composition between members of different ethnicities but factors such as SES, diet

and access to nutrition are important factors that should be considered as environmental aspects could be potential confounders.

1.7.5 The Environment and Body Fat Distribution

Living in environments of lower SES can affect dietary behaviours which have been shown to be largely mediated by the food environment in low SES areas [145]. Additionally, lack of fruit/vegetable consumption in low SES areas and the consuming of certain foods that are eaten more frequently in low SES areas such as soft drinks, processed meats, pizza, chips, table sugar, and other savory snack foods [146] have been shown to increase central adiposity [147, 148] whereas healthier diets such as the Mediterranean diet have been shown to decrease central adiposity. A study of 25 males and 34 females living with obesity and MetS investigated the benefits of dietary intervention, using a hypocaloric Mediterranean diet, on body composition and cardiometabolic health. Patients were followed for 6 months and had assessments every 4 weeks. Those who did not comply with the dietary regimen were excluded. Other exclusion criteria included T2D, coronary or peripheral artery disease, heart failure, renal or hepatic disease, and smoking. None of the participants reported using any lipid-lowering, anti-diabetic, insulin, nitro derivatives, or systemic corticosteroid medications at the time of the study. The total caloric intake recommended for each participant was calculated individually with resting metabolic rate accounted for. The mean energy value was around 1500 kcal. Height and weight were reported to have been performed according to the standard procedure after a 12 hour fast without clothes or shoes. WC was measured at the narrowest point between the lowest rib and iliac crest and hip

circumference was measured at the widest point. Body composition was determined using DXA. Blood samples were taken following a 12 hour fast between 7:00 am and 9:00 am and used to measure glucose, TC, HDL, LDL, and TG. It was reported that adherence to the Mediterranean diet resulted in a significant decrease in WC, total BF, TF, and AF. Adherence to the diet also resulted in a 56% decrease in MetS for men and a 47% decrease in MetS for women [149]. While the outcomes for participants were great, this study was conducted with consistent support from nutritional experts so it is hard to say how likely someone would be to adopt and adhere to this diet long-term without access to such guidance. Additionally, while the Mediterranean diet is a healthy, nutrient-dense diet, this study intentionally decreased daily caloric intake for each participant by about 500 calories a day. It is difficult to say, to what extent the promising results are attributable to the content of the diet as opposed to merely decreasing caloric intake. This finding has been mirrored in other studies as well [150, 151]. While there are dietary factors to be considered such as whether a meal induces satiety thereby decreasing the need to consume more or the glycemic index of a food which will influence the insulin response, ultimately, weight-loss requires creating a calorie deficit. Some disordered eating behaviours such as BED or FA may make it much more difficult for individuals to even attempt creating a calorie deficit with the goal of losing weight. However, before the role of FA, as defined by the YFAS, in BFD patterns can be discussed, a foundational understanding of FA and how it is measured must first be understood.

1.8 Food Addiction

Simply overeating is not necessarily indicative of disordered eating however, some individuals may begin compulsively eating to an obsessive degree. This type of behaviour goes well beyond normal indulgence or homeostatic eating and self-reported food addicts display behaviours consistent with the criteria for substance abuse disorders as described in the DSM-IV TR [152]. Food addicted individuals will continue to eat certain foods far beyond the appropriate amount required to merely maintain health. Individuals who display these addictive eating behaviours have been found to display less impulse control, higher emotional reactivity, significantly greater food cravings, and the tendency to self-soothe with food [153].

Several overlaps have been identified between addictive eating behaviour and other forms of substance addiction. Highly palatable foods have been found to share many similarities with nicotine regarding how the brain's reward pathways, such as the mesolimbic dopamine system, are activated and behavioural overlaps have been observed as well [154]. Another example of this overlap was demonstrated by a study that examined the relationship between maternal nicotine exposure, food preferences, and dopaminergic pathways in rats. It was reported that adult rats that were subjected to maternal nicotine exposure had lower dopamine receptors and dopaminergic transporters in the nucleus accumbens and lower dopamine receptors in the arcuate nucleus, which coincided with a higher *ad libitum* intake of the provided high sugar diet [155]. The relationship between lower dopamine receptor content, binge eating, and increased sugar intake has also been noted by Avena and colleagues [156]. Many of the findings concerning the similarities

between abusing addictive substances such as nicotine and the consumption of highly palatable foods such as those rich in sugar and fat have also been observed using rodent models. Studies have found that rats have exhibited signs of tolerance, sensitization and even withdrawal symptoms such as anxiety, teeth chattering, forepaw tremors and head shakes in several studies concerning FA and binge eating behaviours [157, 158]. Further evidence of the neurobiological overlap between FA and substance abuse and how FA symptoms fit into the criteria for other substance abuse disorders are explored in sections **1.8.1** and **1.8.2**

1.8.1 Neurobiological Correlates of Food Addiction and Substance Abuse

Both highly palatable foods and nicotine have been found to evoke similar reward pathway activation patterns, as noted in the previous section. The similarities between FA and substance abuse are further illustrated by the following study. A study of 48 young women with an average age of 20.8 years, ranging from lean to obese were subjected to a between-subject functional magnetic resonance imaging (fMRI) study. Lean or obese status was determined using BMI classification and height and weight were directly measured by researchers using a digital scale and stadiometer. Participants were asked not to ingest any food or beverages 4-6 hours before the imaging session which allowed researchers to assess the participants in the state of hunger experienced as individuals approach their next meal. This is also the time when differences in behaviour as it pertains to food reward would be most pronounced. Most participants completed the paradigm between 10:00 am and 1:00 pm, though some completed it between 2:00 pm and 4:00 pm. All participants were given the opportunity to practice and familiarize

themselves with the fMRI paradigm on a separate computer. FA was measured using the YFAS. Patients were divided into two groups, a high FA group with 3 or more FA symptoms and a low FA group with 1 or no symptoms. The researchers excluded those with only 2 FA symptoms to make sure there was an adequate separation between the two groups. Participants were randomly presented with an image of either a chocolate milkshake or a glass of water which was followed by the administration of either the milkshake or a solution designed to mimic the taste of saliva as actual water can also activate the taste cortex. In 40% of the trials, the taste was not delivered as anticipated to avoid confounding the neural response to the anticipation with the response to ingesting the substance in question. It was found that FA scores correlated with increased activation in the anterior cingulate cortex, the medial orbitofrontal cortex, and the left amygdala, all of which are involved in the brain's reward pathways, and those women with higher FA scores exhibited greater activation in areas associated with reward circuitry when they anticipated that they would be receiving food [159]. One limitation of this study was that it was performed in a small group of young women so the conclusions should not be carelessly generalized to men or a large general population. Also, only two participants met the criteria for FA “diagnosis” so individuals with severe FA are not necessarily well represented in this study. Also, hunger was not measured in this study. A measurement of the participant's hunger may have been helpful here as this may also affect the response to the presentation and administration of the milkshake. Neuroimaging studies have also revealed differential activity in the brain based on obesity status in response to highly palatable foods. For example, one study investigated the association between blood

oxygenation level-dependent activation in the dorsal striatum, an area related to reward circuitry, dopamine receptors, and BMI. BMI was calculated by measuring height and weight using a mechanical scale. Blood oxygenation level-dependent response was measured in 29 individuals aged 19-39 years. All participants were screened for any serious medical conditions, psychiatric disorders, neurological disorders as well as any history of head trauma or loss of consciousness. Participants were asked to arrive feeling neither hungry nor full and to avoid eating 1 hour before the session. They were also asked to rate their hunger upon arrival by selecting a number from visual analog scales ranging from -100 (“I am not hungry at all” or “I am not full at all”) to +100 (“I have never been more hungry” or “I have never been more full”) with 0 being “neutral”. Participants were also allowed to participate in a mock trial to familiarize themselves with the procedure. The training and scanning sessions were performed on different days and all scans took place between 11:00 am and 3:00 pm. Blood oxygenation level-dependent response was measured using susceptibility-weighted single-shot echoplanar imaging. Susceptibility-weighted imaging is a neuroimaging technique that makes use of a tissue magnetic susceptibility to enhance contrast in MRIs, magnetic susceptibility being the degree of magnetization of a material when a magnetic field is applied. A single-shot echoplanar image is a very fast MRI technique capable of capturing an entire image in only a fraction of a second using only a single radio-frequency excitation [160]. Dopamine receptor availability was measured using positron emission tomography. During the fMRI, participants were administered either a tasteless solution or a Nestle chocolate milkshake for 4 seconds. They were asked to hold the substance in their mouth

until it was fully administered, and a tasteless rinse was administered 3-10 seconds after the milkshake. It was found that there was an inverse relationship between the blood oxygenation level dependent response in the dorsal striatum to the milkshake and BMI. The availability of the dopamine receptors, D2R and D3R, exhibited a positive correlation with BMI, however, there was no clear connection observed between the blood oxygenation level-dependent response to palatable food and dopamine receptor availability [161]. The echoplanar imaging techniques used in this study allowed the researchers to collect highly detailed information on how the brain's reward systems respond to palatable food. A limitation of this study is the small sample size (n=29). The authors of the paper acknowledge that this may have contributed to a false negative regarding the relationship between dopamine receptor availability and the blood oxygenation level dependent response. The authors of the paper also note that the availability of dopamine receptors appeared to decrease as age increased which may suggest one be cautious if trying to generalize these results to a senior population. Many of these same brain areas, including the anterior cingulate cortex and the orbitofrontal cortex, are associated with cravings in individuals with substance abuse disorders such as those addicted to cocaine [162]. Some of these areas show increased activation by simply recalling past experiences with drug use [163]. It was demonstrated quite some time ago that food elicits a short term increase in dopamine in the nucleus accumbens, which connects multiple components of the brain's reward pathways, in a way similar to other addictive substances [164]. It has also been found that consuming food items such as chocolate can activate the nucleus accumbens in ways that mirror addictive substances

[165]. It has been reported that not only drugs but also drug-related stimuli can produce increased activation in the mesolimbic dopamine system which plays a role in cravings and eventual relapse and more recently, an fMRI study by Rothemund and colleagues found that images of highly palatable, high-calorie food can have the same effect in a sample of obese patients. This study was conducted with 13 obese female subjects and 13 normal-weight female subjects with an average age of 31 and 29 years, respectively. Each participant was screened for neurological and psychiatric illness as well as diabetes, stroke, a history of substance abuse, or eating disorders. Obesity status was defined as a BMI of 31.0 or greater. All participants also had normal or corrected to normal vision which was important in this particular study as participants are subjected to a series of visual stimuli. Participants were also excluded if they reported being hungry before testing as this study aimed to measure an individual's response to food-related visual cues and hunger would of course influence this response. No subject had been eating within 1.5 hours of fMRI scanning. Mean calorie intake was also reported before taking part in the study. Participants were hooked up to an fMRI scanner with a vacuum pad to minimize head movement and shown 40 images for 3 seconds at a time. The images consisted of high-calorie foods (ex. Hamburgers), low-calorie foods (ex. vegetables), eating-related utensils (ex. Forks, spoons, etc.), and neutral images such as flowers and rocks. It was reported that visual cue-induced food motivation resulted in differential activation of the dorsal striatum in women living with obesity compared with normal-weight women. A proportional increase between BMI and activity in the dorsal striatum during the high-calorie food image presentation was also reported [166]. The authors of

this paper acknowledge that the handedness of 3 of the control group participants may have affected stimulus processing and that differences in the educational background may have also influenced food preferences. Another limitation of this study is of course the fact that this was conducted on a small group of women so we cannot conclude that we would reliably see similar results in men. Participants are said to not have eaten 1.5 hours before testing but it is not made clear if they also abstained from drinking any beverages. This would have been helpful to know as consumption of beverages, especially sugar-sweetened or fatty beverages may have influenced response to visual food cues. Participants were reported to have been screened for addictions but confirming that individuals abstained from smoking anything prior to testing would have been ideal as substances such as nicotine may also influence response to food related stimuli since nicotine can affect appetite. Also, it is not made entirely clear if weight and height are self reported or if the research team weighed participants at the study site. The numerous similarities between food and addictive substances as it pertains to activation in the brains reward and motivation centres lend to the development of the idea of FA and tools by which to measure or diagnose FA.

1.8.2 Diagnosis of Food Addiction

The YFAS is a validated tool that is used to diagnose FA and measure the severity of FA in an individual. In addition to the brain imaging research described in the previous section, there were other keen observations made by various researchers that preceded the development of the YFAS. One such observation was in 2003 when Gold and colleagues

noted that there were similarities between the diagnostic criteria for substance dependence and the diagnostic criteria for binge eating disorder (BED). The symptoms that Gold and colleagues noted specifically are 1) tolerance or the need for an increased amount to achieve the desired effect, 2) substance is taken in larger amounts of or over a larger period than intended 3) persistent desire of unsuccessful attempts to cut down or control use 4) a great deal of time is spent obtaining, using or recovering from the substance, 5) important activities are reduced or given up because of the substance and 6) continued use despite adverse consequences. Gold and colleagues go on to note other similarities between those living with BED and those with substance abuse disorders such as compulsive thoughts and obsession. They also note that much like alcohol or tobacco addicts, an individual with BED cannot merely "take it or leave it" [167]. This particular article is not original research nor is any formal experiment conducted, however the creators of the YFAS mention this piece of work as a notable contribution to the larger body of work that preceded the creation of the YFAS [168]. Another paper that lent to the rationale behind the YFAS comes from Volkow and O'Brien who noted similarities between symptoms of substance abuse and the broader issue of obesity rather than BED. They reported that these corresponding obesity-related behaviours were

-tolerance: increasing amounts of food to maintain satiety

-distress and dysphoria during dieting

-larger amounts of food being eaten than intended

-persistent desires for food and unsuccessful attempt to curtail the amount eaten

-a great deal of time is spent eating

-activities are given up for fear of rejection because of obesity

-overeating is maintained despite knowledge of adverse physical and psychological consequences [169]

One symptom of substance abuse for which there is little evidence of a corresponding behaviour in FA is that of withdrawal. There is one case study reported by Ehrenreich in 2006 where a woman with a previously controlled panic disorder experienced the return of her symptoms after starting a high protein low carbohydrate diet. The symptoms upon diagnosis of the panic disorder at age 37 included chest pain, dizziness, and an overwhelming sense of fear without depression, among others. This was largely under control until she began her low carbohydrate diet at the age of 47 in an effort to lose weight as she weighed 252 pounds at the time. One day after starting this diet she experienced shakiness which turned into full-blown panic attacks that reportedly improved within the first day of resuming carbohydrate consumption and resolved within several days [170]. Of course, this is a case study so there are a number of factors that may be unaccounted for and withdrawal-like symptoms would have to be observed in a larger number of people before any conclusions could be made. It is also possible that this withdrawal-like behaviour was unique to this woman as her panic disorder was a pre-existing condition. The very idea that certain foods may have addictive properties goes back as far as 1956 when Randolph suggested that frequently consumed foods such as maize, wheat, potatoes, and several others, relieve symptoms of "malaise" and that this may result in sensitization to these foods, leading to obesity [171]. Earlier research on addictive eating tendencies focused on chocolate. In 1993, Hetherington and Macdiarmid

recruited 50 participants who were self-described “chocoholics”. The aim was to quantify chocolate intake and investigate their beliefs, feelings, and attitudes about their supposed addiction to chocolate using the Dutch Eating Behaviours Questionnaire, the Eating Attitudes Test, the Eating Inventory, the Body Shape Questionnaire and the Beck Depression Inventory. These questionnaires assess disordered eating, restrained eating, body dissatisfaction and depression. The average age of participants was 39.8 years and 92% were women with a mean BMI of 25.3. The mean number of self-reported chocolate cravings per month was 24.2 times with an average consumption of 12.5 bars of chocolate a week (1 bar=60g). Other foods that were commonly craved included confections, cake, ice cream, bread, pasta, and pizza. 86% of participants said they indulged their food cravings 75% of the time and of those who reported giving in to these cravings, 49% reported that it made them feel guilty, dissatisfied, and unattractive. When trying to reduce chocolate consumption 66% reported feelings of irritation while most participants (86%) reported feeling positive while eating chocolate. 76% reported being unable to resist urges to eat chocolate while 72% said that even the sensory features of chocolate caused cravings. There are several important limitations to note in this study. First, the majority of participants were women and of these women, 58% reported increased cravings during pre-menstruation. This is an important sex-specific effect that makes it difficult to say how applicable these findings are to men. Second, they mentioned the age range is 14-83 years old. Questions on body image and guilt related to eating may be perceived very differently by such a young individual and eating habits may be very different than that of the older participants as a child’s parents may be largely dictating

what and when they eat. Due to a lack of information, we cannot be absolutely sure there aren't other young teens included in this study. It also appears as though height and weight were self-reported in this study so the BMI calculation may also be inaccurate, and it is not clear exactly how many of the participants were obese, merely overweight or normal weight. Lastly, according to the Beck Depression Inventory 84% of participants reported mild depression and 30% reported moderate depression. With so many participants experiencing depressive symptoms it also makes it difficult to say how representative this sample is of the average population. While there has been some solid research on the neurobiological correlates of the addictive potential of food as described in **section 1.8.1**, early research on addictive eating behaviours had many limitations such as those noted in the above study. Before the YFAS there were tools that measured disordered eating such as the Dutch Eating Behaviour Questionnaire which measures emotional eating, external eating (eating simply due to the sight or smell of food), and restrained eating [172]. There was also the Eating Self-Efficacy Scale which measures difficulty controlling eating in various social situations or when experiencing feelings such as depression, anxiousness, or nervousness [173], however, there was no dedicated tool to assess specifically addictive eating. The YFAS is a tool for diagnosing FA and providing a means of measuring the severity of FA in an individual [168]. It has been employed as a method of measuring FA in studies of several different populations including but not limited to adults seeking weight loss treatment [40], obese individuals with BED [174], and bariatric surgery patients [175]. The YFAS is a 25-item questionnaire that is meant to assess the last 12 months of eating habits. Together, these

25 questions make up the 7 possible symptoms of FA. Some of these questions ask about the frequency of a specific behaviour. For example, the first item on the YFAS states "I find that when I start eating certain foods, I end up eating much more than planned" and asks how often this behaviour has occurred over the last year with the options being "never", "once a month", "2-4 times a month", "2-3 times a week", or "4 or more times or daily". Other questions simply require the individual to answer yes or no. An example of this type of question would be "My food consumption has caused significant physical problems or made a physical problem worse" [168, 176]. If an individual answers affirmatively to certain questions or indicate a problematic degree of frequency of certain behaviours, they are said to have the symptom corresponding to that collection of questions. There are two methods of scoring with the YFAS.

The first method is simply dichotomous and is used to make a diagnosis of FA. In order for an individual to be diagnosed with FA, they must have 3 or more of the 7 possible symptoms and answer affirmatively to one or both of the questions indicating clinically significant impairment or distress. These questions are as follows;

- "My behavior with respect to food and eating causes significant distress"

- "I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of food and eating"

The 7 symptoms of FA as described by the YFAS are;

1. Substance taken in larger amount and for longer period than intended

2. Persistent desire or repeated unsuccessful attempts to quit

3. Much time/activity to obtain, use, recover

4. Important social, occupational, or recreational activities given up or reduced

5. Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)

6. Tolerance

7. Characteristic withdrawal symptoms; substance taken to relieve withdrawal.

The second method of scoring using the YFAS is the Likert scoring method which counts how many symptoms (from 0 to 7) are present in any one person, in order to assess the severity of an addictive tendency towards food [176].

1.8.3 Eating Behaviours and Body Fat Distribution

Highly processed foods, especially those high in fat with a high glycemic load such as soft drinks, potato chips, and refined grains, tend to be among the foods most commonly referred to as addictive [148, 177, 178]. Research in animal models supports the notion that high sugar, high-fat foods can produce addictive-like behaviours [156, 158, 179, 180]. Fascinatingly, these same types of foods consistently show a relationship with abdominal obesity while food items lower in saturated fats and with higher fiber content show just the inverse of this relationship [181]. Individuals who tend to adhere to a more

western-style diet high in processed meat and refined grains also tend to have higher WHR and overall waist girth suggesting increased abdominal or central obesity [182]. Given what we know about the metabolic implications of high amounts of abdominal fat, coupled with the knowledge that the food items that contribute to abdominal obesity may elicit addictive eating patterns is especially concerning. However, to date, the research on addictive eating patterns and fat distribution, particularly VF, is scarce. Dr. Pedram and colleagues of Dr. Sun's laboratory published a paper in 2013 which demonstrated the relationship between YFAS symptom counts with obesity, BF percent, and TF percent in a general population [183]. However, at that time, the laboratory did not possess the necessary tools to accurately measure VF. Dr. Sun's laboratory would not gain the ability to perform research on VF until 2015. At the time of writing, only one study besides our own (**Chapter 3)** had investigated the relationship between FA, as defined by YFAS, and VF. The sample that was used in that study, unfortunately, does not compare very well to the general NL population so results are poorly generalized to our population. The sample used in this study was largely Caucasian but that is where the similarities end. That study was performed on only 93 young adult females from Australia between the ages of 18 and 35 with an average of 24.3 years. This is generally, much younger and leaner than the general NL population. The authors of that paper mention that the reason for studying exclusively females was to eliminate any variation attributable to sex hormones that may influence BFD and described the participants as a "convenience sample". The only noted exclusion criteria was pregnancy or living outside of Australia. The YFAS and other questionnaires were administered online and at a later date, 93 of those participants

reported to a physical testing location to measure height, weight, body composition and BFD. Height was measured using a stadiometer. Weight, body composition, and BFD were measured using BIA. It was found that YFAS symptom counts were positively associated with VF area and that YFAS symptom scores predicted an increase in VF area (β=1.17, $p<.001$) [184]. While this study was the first to demonstrate that the number of YFAS symptoms were associated with increased visceral adiposity, there are several limitations to address. First, this study consisted of a small sample size from a narrow demographic. It was exclusively young women who were, for the most part, normal weight according to BMI (72%). This makes it difficult to say how applicable these results are to men, individuals living with obesity or a general population. Furthermore, there are a number of potentially confounding variables not accounted for such as caloric intake, physical activity, eating disorders, or medication usage. Also, BIA is not quite as accurate as other methods of BFD measurement. While this may be a good starting point for this research, it leaves many gaps to be filled on the matter of FA and visceral adiposity. Dr. Pedram previously demonstrated 1) the prevalence of FA, as defined by YFAS, in a general population 2) those who met the YFAS criteria for FA are more obese than those that are non-food addicted, and 3) YFAS symptom scores are associated with several adiposity measures that are often used as an index of visceral adiposity and share a good correlation with visceral adiposity such as WC, WHR, and TF. One objective of ours, now that Dr. Sun's laboratory had the requisite technology, was to investigate whether YFAS symptom scores shared a correlation with VF. We hypothesized that, given the previously reported correlation between YFAS symptom scores with WC and

TF in our population, VF would also display a correlation with YFAS symptom scores. Both men and women had similar correlation coefficients for each of these BFD measures except for GF mass and percent which was understandably higher in women (r=0.30, r=0.23, and r=0.24, r=0.15, respectively) and AF percent (r=0.31, r=0.25) which was also higher in women, although AF mass exhibited a similar correlation coefficient among sexes. The main finding of our study was the significant association observed between symptoms of FA and VF mass and percent in men and women. As VF tends to increase the risk of many metabolic issues, the finding that addictive eating symptoms contribute to visceral adiposity may suggest that an individual's eating patterns should be factored into any efforts to make lifestyle modifications to reduce the risk of obesity, T2D, or CVD.

1.8.4 Disordered Eating Behaviour and Metabolic Characteristics

Eating disorders are broadly defined by irregular eating habits that result in either an insufficient caloric intake or excessive caloric intake [185]. The more pervasive and commonly known disorders include anorexia nervosa, bulimia nervosa, and BED. Anorexia nervosa is defined as a preoccupation with maintaining low body weight, possibly due to a fear of "fatness" or an unhealthy obsession with "thinness". Bulimia nervosa is characterized by episodic binge eating followed by compensatory behaviour such as self-induced vomiting to restrict weight gain. There is also BED which is similar to bulimia in that there are episodes of uncontrollable binge eating, but there is a lack of

compensatory behaviours [186]. BED is defined as the presence of three or more of the following symptoms as described by the DSM-IV

-eating much more rapidly than normal

-eating until feeling uncomfortably full

-eating large amounts of food when not physically hungry

-eating alone through embarrassment at the amount one is eating

-feeling disgust or extreme guilt after overeating

The consequences of these disordered eating behaviours go well beyond an individual's weight. There is ample evidence that there are significant metabolic consequences for individuals who suffer from eating disorders. A research effort consisting of 2342 eating disorder patients and 9368 matched controls compared these two groups at three stages. Those three stages were before entering the treatment for an eating disorder, after the entrance until the end of the study period, combining any time before or during, and after the treatment. The aim was to examine the prevalence of T2D in a patient cohort being treated for BED, bulimia nervosa, and anorexia nervosa. T2D was diagnosed by linking the study population with the oral TSD medication data of 17 years from The Medical Reimbursement Register. The first incidence of a participant redeeming a TSD medication was used as a proxy for T2D. The time of the onset of T2D was based on the date of the first time a medication was redeemed. Men and women with BED or bulimia nervosa were far more likely to develop T2D with men exhibiting a higher risk than

women. The prevalence of T2D in patients was 5.2% and only 1.7% in controls. Approximately every third individual with BED went on to develop T2D by the end of the study period, while 4.4% of bulimia nervosa patients would go on to develop T2D. Among women living with BED, the lifetime prevalence of T2D was 30.9% and among men living with BED, it was 54.5%. Among women living with bulimia nervosa, there was no significant difference in lifetime T2D prevalence compared with controls. Among those treated for anorexia, the prevalence of T2D barely differed from the control group (0.8% vs 0.9%) [187]. One limitation of this study is the lack of information on the BMI of the patients. Obesity and T2D often go hand in hand and the ability to control for BMI would've been quite helpful in understanding how much of a factor disordered eating was in the development of T2D. Another limitation is that there was a lack of information on possible comorbidities that may have influenced some of the observations made during this study. Another study by Barnes et al revealed that 43% of obese BED patients (66% of men and 35% of women) collected from 2 primary care facilities in a large urban setting also met the criteria for MetS. There was no significant difference observed in BED patients with and without MetS in terms of ethnicity, BMI, the severity of eating disorder, or depression. Patients were recruited from physician referrals in a primary care clinic and by flyers posted in primary care clinics targeted at individuals who wished to stop binge eating and lose weight. Participants were excluded if they were experiencing significant psychiatric diagnoses such as bipolar disorder or schizophrenia. Other exclusion criteria included uncontrolled hypertension, cardiac issues, neurologic history, the definition of which is not clearly defined in the paper as well as purging behaviours

and use of medication such as selective serotonin reuptake inhibitors that are contraindicated with sibutramine. The diagnosis of MetS was based on the ATPIII definition of MetS [188]. It is important to note that due to this being a cross-sectional study no conclusions can be made regarding cause and effect or the directionality of the findings. The authors also acknowledge potential sampling bias as the participants were actively seeking treatment and do not, as stated in the paper represent "a consecutive series of primary care patients". The average age of participants was 43.2 years and given that some of the markers that were measured using this particular MetS diagnosis criteria tend to increase with age (ex. Cholesterol) it is difficult to say if these conclusions can be generalized to younger BED patients. A 2015 study compared the metabolic and inflammatory profiles of 30 individuals living with both obesity and BED (8 men, 22 women) to 85 individuals (32 men, 53 women) living with obesity who do not have BED. The average age of the BED group was 36.8, the average age of the non-BED group was 41.8 and the average BMI of these groups was 43.7 and 37.2, respectively. All research participants were between the ages of 20 and 65. Patients were excluded if they were pregnant, have recently given birth, had a history of diabetes mellitus, inflammatory disease, malignant disease or pathologies, or using any drugs that alter glucose metabolism. No significant difference in age or sex between the two groups was reported. After a 12 hour fast, patients underwent a 75g oral glucose test with blood draws at baseline, 30, 60, 90, and 120 minutes. Height and weight were measured using a portable stadiometer and balance scale while participants wore light clothing with shoes removed. The obese individuals with BED were reported to have higher BMI, higher percent fat

mass, lower percent lean mass, higher HDL, higher glycated hemoglobin, higher C-reactive protein, higher fasting insulin, and increased insulin resistance, when measured using HOMA-IR, than those in the obese group without BED. Initially, no significant difference was seen between the two groups for fasting or 2-hour glucose levels, however after adjustments were made for BMI, this too became significant [36]. This was a cross-sectional study which means any conclusion on the long-term relationship between BED and markers of inflammation and insulin resistance cannot be made. The research team also noted that they measured fat mass using BIA. While BIA has its limitations, adjusting for fat mass either in place of or along with BMI would have been ideal as they are looking at several markers that have been demonstrated to have correlations with fat mass. Also, as noted earlier, there are limitations to be mindful of when using HOMA-IR to measure insulin resistance, one of which is the lack of accuracy when used for older individuals. Since this study does include individuals as old as 65, this is a limitation is worth noting.

While BED has been the subject of many research efforts, there has been little research into the association and implications of FA in metabolic characteristics and obesity. It should be noted that BED has previously been shown to share overlap with addictive eating behaviours as defined by the YFAS. One such study by Gearhardt and colleagues found that the prevalence of FA in obese patients with BED was reported as 57% [174]. This particular study consisted of participants ages 28-64 (average age of 47.5 years), 70.1% of participants were female and 79.3% were Caucasian. Participants were recruited

via newspaper advertisements aimed at individuals living with obesity who felt as though their eating was out of control and who wanted to lose weight. Another study by this same group of researchers consisted of a more racially diverse group of 96 BMI defined obese BED patients ages 19-65 years (average age of 44.9 years), 75.8% were female and only 45.3% were Caucasian while the rest were 32.6% African America, 12.6% Hispanic, 7.4% other and 2.1% Asian. This time, it was reported that the prevalence of FA was 41.5% [189]. Each of the aforementioned studies reported quite a large difference in the prevalence of FA (57% vs. 41.5%). The authors note that age, race, sex, and education status did not differ significantly among those who were classified as having FA. One thing noted in the methodology that might account for this difference is that the second took extra steps to screen out all individuals who reported having severe psychiatric problems or substance dependence. Those with severe medical issues such as cardiac disease, liver disease, uncontrolled hypertension, thyroid conditions, or diabetes were also excluded in the second study. The enforcement of stricter screening requirements, particularly those concerning issues with addiction, may have accounted for the large drop off in the prevalence of FA reported in the second group. As noted earlier in this section, BED has been associated with T2D, components of MetS and shares a sizeable overlap with FA, however, there has been little research into the association and implications of FA in metabolic characteristics and obesity.

1.8.5 Food Addiction, Obesity, and Metabolic Characteristics

FA, like other disordered eating behaviours, can have serious implications in one's health and contribute to the development and maintenance of the obese state. A study by Dr. Sun's research team revealed that the prevalence of FA in the general NL population was 5.4% (6.7% in women and 3.0% in men). In the same study, the total number of FA symptoms an individual had, as defined by the YFAS, were found to share a significant association with all the obesity and body composition measurements used. When compared to a control group, those diagnosed with FA were on average 11.7 kg heavier, 4.6 BMI units higher, had 8.2% more body fat, and 8.5% more TF [183]. While a significant correlation between the number of FA symptoms and obesity was demonstrated, this study did not investigate exactly which FA symptom(s) correlated with obesity or body composition measurements or if certain symptoms exhibit stronger correlations with measures of obesity and body composition than other symptoms. The author of this paper proposed that "food addiction may represent a distinct etiology of human obesity in the general population". However, such a claim would at the very least require a demonstration that there were measurable differences between those who were food addicted and living with obesity and those living with obesity who are not food addicted. Another paper published by Dr. Pedram and colleagues of Dr. Sun's Laboratory compared a group of twenty-nine food addicts living with obesity (FAO), as defined by the YFAS, to a group of non-food addicted individuals living with obesity (NFO). These two groups were matched for age, sex, physical activity, and BMI. This comprehensive examination measured 34 neuropeptides, gut hormones, adipokines, and pituitary

polypeptides. Glucose, TC, TG, HDL, LDL, and insulin were also measured following a 12 hour fast but there was no significant difference observed between the FAO and NFO group for any of the six aforementioned metabolic factors. The FAO group had lower levels of thyroid stimulation hormone (TSH), tumour necrosis factor-alpha (TNF-α), and amylin but higher levels of prolactin. The FAO group also consumed more dietary fat per g/kg of body weight. Macronutrient consumption was presented as g/kg in this study as Dr. Pedram and colleagues had previously demonstrated that those with FA consume a higher percentage of calories in the form of fat [183], however, as this group is BMI matched and a goal of the study was to investigate differences in diet among the FAO and NFO group, g/kg is more informative of just how much the consumption of each macronutrient is related to a unit of body weight. Expressing as only a percentage of total calories can result in very different absolute amounts of each macronutrient depending on how many calories each participant consumes in a day whereas expressing in only grams isn't as helpful at drawing distinctions between the FAO and NFO group as those in the FAO group may simply consume more calories on average and by extension consume more of every macronutrient compared to the NFO group. Another reason for the use of g/kg is that fat and lean tissue differ in how they affect metabolism. The FAO group also consumed a higher percentage of their calories from fat and carbohydrate sources [190]. The first of my three manuscripts, which is currently published in *Frontiers in Endocrinology*, examined the association between FA symptom counts and a panel of metabolic variables including glucose, insulin, HOMA-IR, HOMA-β, TC, TG, HDL, and LDL. My colleagues and I investigated the association between FA symptoms, as defined

by the YFAS, with lipid profiles and markers of insulin resistance in 739 participants from a general NL population. Much of the existing FA research is in specific subgroups of the population such as individuals with T2D, bariatric surgery patients, or individuals with eating disorders. Furthermore, even fewer research efforts explore the metabolic effects of FA. We know, from previous reports that FA is much more prevalent among those living with obesity and those living with T2D, both of which are known to have strong associations with lipid profiles and insulin resistance but we did not know if FA symptom scores have any correlation whatsoever with lipid profiles or insulin resistance in an otherwise healthy general population. We sought to address this gap in knowledge and though the body of FA research is still quite sparse, we hypothesized that, given the previously reported relationship between FA as measured by YFAS with obesity and adiposity, that YFAS symptom scores would exhibit a correlation with markers commonly associated with obesity comorbidity in the general population. We took care to control for confounding variables such as age, sex, menopausal status, physical activity, caloric intake, body fat percentage and excluded any individuals who reported to be using anti-dyslipidemic or anti-hyperglycemic medications. We showed that there were several modest but significant correlations between FA symptom counts and several metabolic characteristics in men and post-menopausal women. In men, FA symptoms were significantly correlated with HOMA-β, Triglycerides, and inversely correlated with HDL cholesterol. In post-menopausal women, FA symptoms were found to be significantly correlated with triglycerides [191]. One research group investigated the prevalence of FA among individuals with T2D. They found that, in their sample of 334 T2D patients, 70%

met the criteria for FA. They also reported that FA, according to the YFAS criteria accounted for greater BMI variance than measures of depression, anxiety, or stress [192]. The authors reported good internal consistency for the YFAS (α=0.86). This study, however, relied only on surveys administered online which means that BMI was self-reported and subject to error. Another limitation is that there does not appear to be any information regarding the ethnicity or medication usage of participants. Medications meant to treat mood or anxiety disorders could have affected some of the variables measured in this study, as would medications that may result in weight gain or weight loss. In 2017, another research group also examined the prevalence of FA in, who they described as, "newly diagnosed" T2D patients, meaning individuals who were outpatients at a local hospital who received T2D diagnosis between February 2014 and January 2015. The prevalence of FA in T2D patients was 8.6% compared to only 1.3% in a BMI and age-matched control group. T2D patients with and without FA were also compared. Despite being on average 11 years younger than the non-food addicted T2D patient group, T2D patients with FA had significantly higher BMI, WHR, fasting blood glucose, HOMA-IR, and uric acid levels than T2D patients who did not meet the YFAS criteria for FA [193]. , Also, as noted earlier, HOMA-IR may be less reliable in some people including older individuals with impaired glucose tolerance and older men and women with diabetes While the prevalence of FA among T2D is quite high, it's not nearly as high as the 70% that was reported in the previously mentioned 2015 study. This may be due in part to much better screening to control for possible confounders. The 2017 study excluded individuals who had past diagnosis of diabetes, impaired glucose tolerance,

hyperthyroidism, hypothyroidism, eating disorders, psychiatric disorders, those who were required to adhere to certain eating patterns due to pregnancy or operations and anyone with what the authors described as a major disease that affects quality of life. Also, while the 2017 study was performed on a single population, the 2015 study collected surveys from individuals primarily living in Australia, the UK, USA, New Zealand, and other living in Germany, Ireland, Norway, Spain and Malaysia. Such as widespread, multinational survey-based research effort is sure to have a number of confounding variables that are difficult to control for. While our findings and the findings of other research groups suggest that addictive eating behaviours can play a role in metabolic disorders, research in this area is still quite limited and of course it is only one piece of a complex issue.

1.9 Rationale

Due to the complexities surrounding the causes and consequences of obesity and by extension BFD, coupled with evidence supporting the role of FA in the obesity phenotype, this thesis attempts to address questions surrounding these complexities and better understand to what degree FA plays a role in obesity and obesity-related comorbidities from a behavioural and endocrinological standpoint. Furthermore, we aimed to elucidate the impact of central adiposity on women as it relates to a host of metabolic characteristics and incidence of MetS.

FA research in humans remains relatively sparse, particularly as it pertains to the metabolic implications of FA. Previously, a paper published by Dr. Sun's team reported

that obesity is more prevalent among those with FA. Given this, we sought to explore the role of addictive eating tendencies in metabolic markers commonly associated with obesity related comorbidities in 710 individuals (435 women, 275 men) from the general population recruited through the CODING study.

Research participants who had previously been diagnosed with FA were excluded from analysis so we could capture the extent of the relationship between symptoms of FA and metabolic health in a general population. Our cohort was subdivided into men and women. Women were then further subdivided into pre-menopausal and post-menopausal status, given the role of sex and menopausal status on a number of metabolic markers. Furthermore, to identify potential differences between FA and non-FA individuals, we also performed a comparative analysis between these two groups in the total population, as well as in men and women independently of one another. The objectives of the study detailed in **chapter 2** were to 1) assess the impact of FA symptom counts, as defined by the YFAS, on metabolic characteristics 2) assess sex-specific effects of FA symptoms counts on metabolic characteristics 3) compare the metabolic characteristics of FA and non-FA individuals. We hypothesized that there would be a positive correlation between the number of YFAS symptoms and markers of metabolic disturbance. We also hypothesized that those with FA would have a less healthy lipid profile and more insulin resistance when compared to those who do not have FA.

The study in **chapter 3** examined the correlation between FA symptom counts and various measures of central adiposity, VF, and gynoid adiposity as measured by DXA.

The purpose of this study was to understand the role of addictive eating behaviours on specific BFD patterns shown to be associated with metabolic disturbance. As previously mentioned, individuals with similar adiposity can vary in how their body fat is distributed which can greatly affect metabolic health, therefore, it is essential to understand how certain eating behaviours, specifically addictive eating behaviours, might influence BFD. We analyzed the relationship between FA symptom counts with total, truncal, android, gynoid, and VF in terms of both total fat mass and percentage fat mass.

We examined this relationship in our total cohort, as well as men and women separately. The goals of this study were to 1) evaluate the correlation between FA symptom counts and measures central adiposity and VF 2) evaluate the correlation between FA symptoms counts and gynoid adiposity 3) note any differences between men and women regarding how FA symptom counts influence BFD. We hypothesized that a significant correlation would be observed between YFAS symptoms and measures of central adiposity, particularly VF and that this relationship would be more pronounced in women given that women tend to have more body fat.

Given the important role of BFD as it pertains to metabolic health, understanding the metabolic implications of different BFD patterns and how one's sex may mediate these effects, was another effort of Dr. Sun's research team. Previously, I have discussed the role of sexual dimorphism in BFD and obesity related comorbidities, noting that women tend to accumulate body fat in the lower body or gynoid area while men tend to accumulate body fat in the upper body or android area. While upper body obesity may be

more common in men, it is far from exclusive to men. Other studies have produced evidence that not only have the increases in obesity been more prevalent in women, but increases in abdominal obesity have been more prevalent in women as well [194, 195]. Furthermore, MetS and its correlation with visceral adiposity has been found to be higher in women in other populations [196-198]. It is not at all uncommon for women to exhibit upper body obesity along with the accumulation of VF [199-201]. Women with upper body obesity still experience a host of metabolic issues as a result of this. A study published by Wolhfahrt et al investigated the difference in the association between long term changes in weight, abdominal obesity, and ventricular-arterial health. A group of 375 men and 413 women aged 45 years or older with an average age of 60 were used in the analysis. All measurements were taken at baseline and 4 years later at follow up. Height and weight were measured using a wall-mounted stadiometer and electronic scale, respectively. WC was measured using non-elastic tape at the top of the umbilicus and hip circumference was measured at the area of the maximal circumference. WHR, WC, neck circumference, and neck to height ratio were used as indices of abdominal obesity. Left ventricular structure and function were assessed using echocardiography. Echocardiographs were performed by the same 3 sonographers at baseline and follow up. The echocardiographs were then reviewed by 2 cardiologists. BP was measured using a sphygmomanometer. The analysis revealed, after controlling for age. arterial elastance and sex, that all measures of abdominal obesity were associated with age related increases in ventricular stiffness in women but not men [202]. The issues and limitations of WC have been noted several times throughout this thesis but there are also limitations to be

acknowledged in the other indices of abdominal obesity that were used. The authors suggest that neck circumference is a better indicator of visceral adiposity and metabolic disorder but further reading revealed that this was only the case in a group of individuals living with class III obesity (BMI > 40). The average BMI range of the participants in this study ranged from 27.9 at baseline to 28.1 at follow up. The authors acknowledge that echo-doppler data has greater variability than more invasive methods and that they could not conclude whether some of the weight changes that were observed between baseline and follow-up were a result of diet/exercise, muscle wasting, or other health issues. While upper body fat accumulation tends to be more common in post-menopausal women which has been touched on previously [130], there appear to be health risks women are exposed to as a result of their central adiposity regardless of menopausal status. One comparison of middle aged premenopausal women and early post-menopausal women found that postmenopausal women had up to 49% greater intra-abdominal or VF [203]. However, due to the aforementioned controversy surrounding the true magnitude of the role of VF in metabolic issues, we have controlled for VF in our comparative analysis of women with and without android obesity which is described in **chapter 4** of this thesis. This was done to better understand the true contribution of subcutaneous AF to metabolic disturbance and the risk of developing MetS. Other studies have also found that in some populations, AF may play a larger role in metabolic disturbances than VF [204]. Given the wealth of data available regarding the sexual dimorphism of BFD and the relationship between abdominal adiposity and metabolic disease which is elaborated upon in much greater detail in section **1.6**, the manuscript which makes up **chapter 4** aimed to evaluate

1) the true impact of female android obesity on markers of insulin resistance and lipid profiles and 2) the MetS risk in women with high levels of android adiposity independent of VF stores. While there are many association studies that have examined the correlation between central adiposity and various markers of metabolic health in women, there is little research that offers a direct comparison of women with similar BMIs and age with differing BFD patterns. Also, much of the existing literature draw conclusions on the impact of abdominal or truncal fat but fails to control or account for VF storage. We hypothesized that a higher AGR would be associated with a significantly higher risk of having MetS

The methods that were employed to achieve each of the objectives outlined above for each manuscript chapter are described below.

1.10 Methods/Protocols

Participants

All participants and participant data used in **chapters 2,3,** and **4** were recruited through the CODING study. All participants were recruited for this study through the use of advertisements, flyers, and word of mouth. The eligibility requirements for all CODING study participants are as follows:

1. 19 years of age or older
2. The participant must have been born in NL and the participant's family must have been in NL for at least 3 generations

3. Healthy with no serious metabolic, endocrine, or cardiovascular conditions.

4. Participants must not be pregnant at the time of the study.

Additional exclusion criteria were used for the research projects described in **chapter 2**. The additional exclusion criteria were that participants could have not been found to have "food addiction" in a previous study by Dr. Sun's research group and secondly, individuals who self-reported having diabetes or hypertension were also excluded from this analysis.

Anthropometric Measurements:

All measurements were taken with participants wearing only a standard hospital gown, socks, and underwear. Height was measured using a fixed stadiometer to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg using a platform manual scale balance (Health O Meter, Bridgeview, IL). Both hip circumference and WC were measured using a flexible non-elastic measuring tape. Hip circumference was measured at the level of the largest circumference between the waist and thighs to the nearest 0.1 cm. WC was measured using the same method at the level of the umbilicus, between the lowest rib and iliac crest.

Body Composition Measurements

Body composition measurements which included TF, AF, GF, and VF were assessed using DXA (Lunar Prodigy; General Electric Medical Systems, Madison, WI, USA). The principles of DXA and the exact definitions of each body fat region were previously

described in detail in sections **1.3** and **1.4**. Measurements were taken while the patient lied horizontally on the DXA scanner. Female participants were also asked to remove their bra if it contained any metal clips or metal wire since metal objects can interfere with the accuracy of the DXA scan.

Metabolic Marker Measurements

Serum concentrations of glucose, TC, HDL cholesterol, and TG were measured using the Lx20 analyzer (Beckman Coulter Inc., Fullerton, CA) with Synchron reagents. Serum insulin was measured using the Immulite Immunoassay analyzer. Insulin resistance and beta cell function were calculated using the HOMA equations.

Food Addiction Symptom Count Measurement:

Symptoms of food addiction were assessed using the YFAS. The full version of the YFAS questionnaire can be viewed in **appendix 1.** The YFAS has been described in much greater detail in previous sections but, to briefly re-iterate, it is a 25 item questionnaire that assesses the last 12 months of eating patterns. It is based on the criteria used for substance dependence in the DSM-IV TR. This criterion includes symptoms such as tolerance, withdrawals, anxiety in social situations, and difficulty lowering or quitting the use of the substance. YFAS. symptoms were counted using the Likert scoring method which ranges from 0 to 7. Each symptom on the YFAS represents a collection of questions from the questionnaire concerning that behaviour. If an individual answers affirmatively to certain questions, they are said to have the corresponding symptom.

Some of these questions are based on the frequency of the behaviour (ex. once a month, 2-4 times a month, etc.) and some are binary yes or no questions.

Calorie intake and Physical Activity Assessment:

Calorie intake was measured using the Willett Food Frequency Questionnaire (FFQ) which measures the last 12 months of dietary habits. The quantity of each food item was converted into a daily average intake value. This value was then entered into Nutribase Clinical Nutrition Manager (software version 9.0; Cybersoft inc. Arizona). To measure physical activity, we used the Baecke physical activity questionnaire. This questionnaire measures physical activity using three categories which are work, sport, and leisure. The full version of this questionnaire can be viewed in **appendix 2** and the limitations of these questionnaires are acknowledged and described in **chapter 5**.

Statistical Analysis:

All statistical analysis in **chapters 2, 3,** and **4** was completed using SPSS ver.23. The level of statistical significance was set at alpha=0.05. In **chapters 2** and **3** Pearson correlation analysis was used to evaluate potential relationships between YFAS symptom counts with measures of adiposity, insulins resistance, and lipid profiles. Partial correlation analysis was also performed which allowed us to control for age, total calorie intake, and physical activity levels. A one-way ANOVA was used to measure the difference in body fat levels between food addicted obese (FAO), non-food addicted obese (NFO), and normal weight controls. FAO and NFO were matched by age and BMI.

All correlations from the study described in **chapters 2, 3,** and **4** have been controlled for sex, age, physical activity, and caloric intake.

In **chapter 4** we divided all women into tertiles based on AGR and compared endocrine, anthropometrical, and vital measures between these groups using a one-way ANOVA. We then compared a group of women from the highest quartile of AGR to an age and BMI matched control group and noted the incidence of MetS in each group using the ATPIII criteria. We also controlled for calories, physical activity, and VF percentage to assess the true risk associated with excess subcutaneous abdominal obesity in women.

MetS is a collection of symptoms that increase the risk of CVD and diabetes. There are several criteria available for the diagnosis of MetS and for my manuscript we have chosen to use the ATPIII criteria. Diagnosis of MetS using this particular set of criteria requires that an individual have 3 out of 5 of the following symptoms [205].

i. Waist circumference >35 inches (88.9cm)
ii. Fasting glucose >100mg/dl
iii. TG >150mg/dl
iv. HDL <50mg/dl
v. Systolic blood pressure >130mmHg or diastolic blood pressure >85mmHg

This criterion was selected based on the physical and metabolic data made available by the CODING study up to the conception of this specific research project and not necessarily for its superiority to other MetS diagnostic criteria.

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2

Chapter 2. The Association Between an Addictive Tendency Toward Food and Metabolic Characteristics in the General Newfoundland Population

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2.1 Introduction

Obesity rates have been climbing for the last three decades and according to a report from Statistics Canada, in Newfoundland and Labrador (NL), 31% of adult women and 27.3% of men are obese [2, 206]. It follows that the population of NL also exhibits some of the highest rates of obesity-related health issues in Canada such as type II diabetes (TIID) and cardiovascular disease (CVD) which makes obesity research within this population so vital. Recent reports put the rate of TIID in this Province at 11.2% with CVD contributing to 20%-38% of total deaths in adults aged 35 years or older [207-209]. The development of obesity is highly complex and is comprised of a number of interacting genetic, environmental, and behavioural factors [210-213]. One issue that highlights this intricate balance of factors is that of an addictive tendency towards food. This is characterized by an obsessive consumption of foods known to be highly palatable with the corresponding activation of the bodies reward systems and significant difficulty controlling this behaviour [176]. Previous research on food addiction reported that there are tangible

neural correlates in the way of dopaminergic circuitry activity and it has drawn comparisons to nicotine addiction in regards to how the body's reward systems are effected [154, 214].

Symptoms of an addictive tendency towards food are quantified using the Yale Food Addiction Scale (YFAS) which has been adapted from the criteria for substance abuse from the DSM-IV TR [168]. Foods that display addictive qualities are those that are high in simple sugars, saturated fat, and are heavily processed. One study revealed that the processing of food was a strong predictor of it possessing addictive qualities [178]. There is substantial evidence that these very same types of foods can have a significant negative impact on health. Foods high in fructose can be highly lipogenic and could lead to an increased risk of developing non-alcoholic fatty liver disease and consequently, TIID [215]. A study concerning the consumption of sugar-sweetened beverages effects on health examined over 310 000 individuals and over 15 000 TIID patients and found that those in the highest quartile of sugar-sweetened beverage consumption had a 26% higher risk of developing TIID [216]. Excessive sucrose intake has also been found to be associated with a 37% increased risk of having a coronary event [217]. Furthermore, a 13 year follow up study performed on 4 999 individuals found that consumption of milk fats, various sweets, and cake was associated with increased CVD risk in women [218]. In addition to the behavioural and neurological evidence supporting the role of addictive food tendencies in health, we have recently found that there are different hormonal characteristics between food addicted (FA) and non-food addicted (NFA) individuals.

We have previously reported that those living with obesity who has been diagnosed with food addiction, had lower levels of thyroid-stimulating hormone (TSH), tumor necrotic factor-alpha (TNF-α), and amylin but higher levels of prolactin compared to non-food addicted obese individuals [190]. TSH levels have previously been implicated in the development of insulin resistance (IR) and diabetes while TNF-α has been shown to decrease appetite, therefore, lower levels of TNF-α may exasperate obesity-related comorbidities by lending to increased positive energy imbalance [219-221]. Amylin is known to be associated with the development of type 1 and TIID and increased prolactin levels have been shown to be a cardiovascular risk factor with correlations to diabetes as well [222-225]. However, our previous study was performed with only 58 individuals (29 FA obese, 29 NFA obese). Many studies in the field of "food addiction" focus on specific sub-populations such as the obese, bariatric surgery patients or those with an eating disorder [174, 175]. What remains to be seen is whether or not an addictive tendency towards food displays an association with metabolic markers and hormones in the general population, specifically IR and lipid profiles as these metabolic characteristics play a role in the development of TIID and CVD [226, 227].

The very same types of foods that possess addictive qualities are demonstrably dangerous to an individual's overall health when frequently consumed. It is therefore essential that the association between addictive tendencies towards food and metabolic markers of TIID and CVD be studied in the general population. Our investigation was performed in a sub-group of the CODING (Complex Diseases in a Newfoundland Population: Environment

and Genetics) study which consists of biochemical and body composition data from over 3200 men and women from the general NL population.

2.2 Materials and Methods

Ethics Statement

This study was approved by the Health Research Ethics Authority (HREA), Memorial University of Newfoundland, St. John's, Canada with project identification code 10.33. Written consent was provided by all who participated.

Participants

710 Adults (435 women, 275 men) from the Province of Newfoundland and Labrador were recruited for this study through the use of advertisements, flyers, and word of mouth. Eligibility requirements are as follows:

1. 19 years of age or older
2. The participant must have been born in NL and the participant's family must have been in NL for at least 3 generations
3. Healthy with no serious metabolic, endocrine, or cardiovascular conditions.
4. Participant must not be pregnant at time of study.
5. participants have not been found to have "food addiction" in our previous study
6. Individuals who self reported having diabetes or hypertension were also excluded from this analysis.

Individuals who had been previously diagnosed with food addiction were later included for additional comparative analysis.

Food Addiction Symptom Count Measurement

Symptoms of food addiction were assessed using the YFAS. This is a 25-item questionnaire that assesses the last 12 months of eating patterns. The YFAS is based on the criteria used for substance dependence in the Diagnostic and Statistical Manual IV-TR (DSM-IV TR). This criterion includes symptoms such as tolerance, withdrawals, anxiety in social situations, and difficulty lowering or quitting the use of the substance. Symptoms were counted using the Likert scoring method which ranges from 0 to 7 **[168]**. Each symptom on the YFAS represents a collection of questions concerning that particular behaviour. If a participant answers affirmatively to certain questions, they are said to have the corresponding symptom. Some of these questions are based on the frequency of the behaviour (ex. once a month, 2-4 times a month, etc.) and some are binary yes or no questions **[176]**. In our comparison of individuals with or without a diagnosis of FA, those classified as food addicts were required to have at least 3 symptoms and answer affirmatively to one of the two questions from the YFAS which indicates clinically significant dependence.

Caloric Intake and Physical Activity Assessment

Calorie intake was measured using the Willett Food Frequency Questionnaire (FFQ) which measures the last 12 months of dietary habits [228]. The quantity of each food item

was converted into a daily average intake value. This value was then entered into the Nutribase Clinical Nutrition Manager (software version 9.0; Cybersoft inc. Arizona). We employed the use of the Baecke physical activity questionnaire to assess physical activity levels. This questionnaire measures physical activity using three categories which are work, sport, and leisure.

Body Composition and Metabolic Marker Measurements

Body composition measurements, which in this study included total body fat, were assessed using dual-energy x-ray absorptiometry (DXA; Lunar Prodigy; GE Medical Systems, Madison, WI, USA). Measurements were taken while the patient lied horizontally on the DXA scanner following a 12 hour fast. Serum concentrations of glucose, TC, HDL cholesterol, and triacylglycerols were measured using the Lx20 analyzer (Beckman Coulter Inc., Fullerton, CA) with Synchron reagents. LDL cholesterol was calculated using the following formula: (total cholesterol) − (HDL cholesterol) − (triacylglycerols/2.2). Serum insulin was measured using the Immulite Immunoassay analyzer. Insulin resistance and beta cell function were calculated using the homeostasis model assessment (HOMA) [229].

Statistical Analysis

All statistical analysis was completed using SPSS ver.23. The level of statistical significance was set at P-Value <0.05. Statistical tests were run on men and women separately. Pearson correlation analysis was used to evaluate potential relationships between YFAS symptom counts and all metabolic markers. Partial correlation analysis

was also performed which allowed us to control for age, total calorie intake, physical activity levels, and total body fat % as necessary. An independent t-test was run between BMI matched food addicts and a control group to assess the difference of mean in the metabolic markers that were measured. Control variables were selected for each gender dependent on whether the potentially confounding variable in question shared a significant association with both dependent and independent variables. Following this method, we chose to control for age, physical activity, total body fat %, and calories. In order to better normalize the distribution of the data, HOMA-IR, and HOMA-β were square root transformed.

2.3 Results

Physical Characteristics and Adiposity Measures

The age, gender, BMI and anthropometric data of all men and women who participated in this study are presented in Table 2-1 as mean ± standard deviation. The average age of female participants was 45.4 years and the average age of male participants was 42.9 years. There was a significant difference observed between men and women for height, weight, BMI, total % body fat, waist, and hip measurements with men being higher for each measure. There was also a significant difference observed between pre and post-menopausal women for age, height, waist, and hip circumference as well as total body fat % which is highlighted in Table 2-2.

Metabolic Characteristics

Men had much higher levels of glucose and triglycerides compared to women. Women, however, had significantly higher levels of HDL cholesterol (Table 2-3). All other markers including insulin, HOMA-IR, HOMA-β, LDL, and total cholesterol were not significantly different between men and women. Metabolic characteristics were also compared between pre and post-menopausal women (Table 2-4). Post-menopausal women had notably higher levels of insulin, glucose, and triglycerides in addition to higher levels of both LDL and total cholesterol.

Correlations Between YFAS Symptoms and Metabolic Markers

The Pearson and partial correlation coefficients as well as p-values are presented in tables 2-5 to 2-8. Men exhibited significant positive correlations between YFAS symptoms and HOMA-β, TG as well as a significant negative correlation with HDL cholesterol (Table 2-5). In men, the correlation between YFAS symptoms and HOMA-IR just barely missed the cut-off of for statistical significance at $\alpha=0.05$ ($r=0.164$ $p=0.053$). These correlations remained significant after controlling for age, physical activity, total body fat %, and calories. YFAS symptoms counts in women exhibited no significant correlations (Table 2-6) however, when separated by menopausal status, post-menopausal (table 2-7) women showed a significant correlation with TG ($r=0.198$) after controlling for age, physical activity, total body fat %, and calories. Pre-menopausal women exhibited no significant correlations after controlling for all confounding variables (Table 2-8). The correlation between YFAS symptoms and HOMA-β was strongest for men and TG exhibited the only significant correlation strongest for post-menopausal women.

Comparison of Food Addicts and Non-Food Addicts

No significant difference was observed between BMI matched FA and NFA individuals from the general population for markers of IR or lipid profiles. These groups consisted of obese, overweight, and normal weight individuals. When separated by sex, there were still no statistically significant differences observed in men or women (table 2-9). FA men had significantly lower HDL levels than FA women.

Table 2-1 Physical Characteristics of Participants

	Female Mean ± SD n=479	**Male** Mean ± SD n=298
Age*	45.5 ± 13.1	43.0 ± 12.7
Height (cm)*	163.3 ± 6.0	177.6 ± 6.7
Weight (kg)*	70.8 ± 14.8	90.8 ± 17.3
BMI*	25.8 ± 5.0	29.9 ± 4.9
BF%*	37.0 ± 8.7	26.3 ± 8.4
Waist (cm)*	91.2 ± 13.8	101.2 ± 13.6
Hip (cm)*	99.8 ± 12.8	101.7 ± 10.8
Waist/Hip (cm)*	0.9 ± 0.05	1.0 ± 0.05

*-significant difference between men and women ($p<0.05$)
Mean ± Standard Deviation (SD), BF%- Total Body Fat Percent

Table 2-2 Physical Characteristics of Pre and Post-Menopausal Women

	Pre Mean ± SD n=282	**Post** Mean ± SD n=179
Age*	37.3 ± 9.4	57.8 ± 8.4
Height (cm)*	164.2 ± 6.07	161.8 ± 5.65
Weight (kg)	70.5 ± 15.7	71.9 ± 14.9
BMI	26.3 ± 5.79	27.4 ± 5.51
BF%*	35.6 ± 9.17	39.4 ± 7.45
Waist (cm)*	89.2 ± 14.5	94.6 ± 12.6
Hip (cm)*	98.1 ± 12.8	102.8 ± 10.8
Waist/Hip (cm)	0.91 ± 0.08	0.92 ± 0.06

*-significant difference between pre and post menopausal and women ($p<0.05$)
Mean ± Standard Deviation (SD), BF%- Total Body Fat Percent

Table 2-3 Metabolic Characteristics of Men and Women

	Female Mean ± SD n=435	**Male** Mean ± SD n=275
Insulin	77.8 ± 94.1	79.3 ± 53.7
HOMA-IR	2.90 ± 5.50	3.20 ± 3.30
HOMA-β	136.9 ± 123.8	122.8 ± 78.1
Glucose*	5.06 ± 0.60	5.55 ± 1.52
Triglycerides*	1.09 ± 0.69	1.35 ± 1.00
HDL*	1.51 ± 0.37	1.23 ± 0.29
LDL	2.98 ± 0.89	3.13 ± 1.00
Cholesterol	5.05 ± 0.96	5.06 ± 1.08

*-significant difference between men and women ($p<0.05$) Mean ± Standard Deviation (SD),

Table 2-4 Metabolic Characteristics of Pre and Post Menopausal Women

	Pre Mean ± SD n=277	**Post** Mean ± SD n=158
Insulin*	66.0 ± 50.6	92.4 ± 127.9
HOMA-IR	2.23 ± 1.62	3.68 ± 7.86
HOMA-β	139.4 ± 139.1	134.8 ± 104.2
Glucose*	4.93 ± 0.46	5.28 ± 0.74
Triglycerides*	0.98 ± 0.61	1.27 ± 0.77
HDL	1.52 ± 0.36	1.51 ± 0.38
LDL*	2.74 ± 0.78	3.38 ± 0.90
Cholesterol*	4.80 ± 0.83	5.51 ± 0.99

*-significant difference between pre and post menopausal and women ($p<0.05$)
Mean ± Standard Deviation (SD), BF%- Total Body Fat Percent

Table 2-5 Correlations between YFAS Symptom Counts and Metabolic Characteristics in Men

YFAS Symptom Counts	Men (n=275)				
	r1(P)	***r*2(P)**	***r*3(P)**	***r4(P)***	***r5(P)***
Insulin (pmol/L)	.248 (.001)*	.248 (.001)*	.231 (.002)*	.140 (.064)*	.135 (.080)
HOMA-IR	.262 (.001)*	.271 (.001)*	.255 (.002)*	.167 (.048)*	.164 (.053)
HOMA-β	.316 (.000)*	.302 (.000)*	.283 (.001)*	.201 (.016)*	.196 (.021)*
Glucose (mmol/L)	-.075 (.217)	-.040 (.511)	-.048 (.440)	-.075 (.224)	-.070 (.260)
TG (mmol/L)	.205 (.001)*	.222 (.000)*	.203 (.001)*	.137 (.026)*	.140 (.025)*
HDL (mmol/L)	-.232 (.000)*	-.222 (.000)*	-.201 (.001)*	-.137 (.025)*	-.133 (.033)*
LDL (mmol/L)	-.031 (.614)	.004 (.947)	-.005 (.935)	-.059 (.342)	-.055 (.378)
Cholesterol (mmol/L)	-.006 (.917)	.040 (.511)	.020 (.640)	-.025 (.683)	-.019 (.756)

*-p-value <0.05, r1-pearson correlation, r2-controlled for age
r3-controlled for age, physical activity, r4-controlled for age, physical activity, total % body fat, r5-controlled for age, physical activity, total % body fat, calories

Table 2-6 Correlations between YFAS Symptom Counts and Metabolic Characteristics in Women

YFAS Symptom Counts	Women (n=435)				
	r1(P)	***r*2(P)**	***r*3(P)**	***r4(P)***	***r5(P)***
Insulin (pmol/L)	.084 (.221)	.086(.209)	.069 (.319)	.011 (.880)	.021 (.766)
HOMA-IR	.066 (.355)	.064 (.370)	.054 (.458)	.049 (.496)	.036 (.624)
HOMA-β	.071 (.319)	.064 (.372)	.052 (.468)	.005 (.947)	.021 (.777)
Glucose (mmol/L)	-.039 (.423)	-.024 (.622)	-.042 (.388)	-.080 (.102)	-.085 (.081)
TG (mmol/L)	.122 (.011)*	.131 (.007)*	.110 (.023)*	.059 (.224)	.065 (.152)
HDL (mmol/L)	-.112 (.020)*	-.110 (.022)*	-.082 (.092)	-.010 (.841)	-.010 (.835)
LDL (mmol/L)	-.015 (.750)	.004 (.940)	-.001 (.980)	-.028 (.567)	-.030 (.537)
Cholesterol (mmol/L)	.011 (.824)	.035 (.465)	-.032 (.514)	.018 (.714)	.017 (.732)

*-p-value <0.05, r1-pearson correlation, r2-controlled for age
r3-controlled for age, physical activity, r4-controlled for age, physical activity, total % body fat, r5-controlled for age, physical activity, total % body fat, calories

Table 2-7 Correlations between YFAS Symptom Counts and Metabolic Characteristics in Post-Menopausal Women

YFAS Symptom Counts	Females (n=158)				
	r1(P)	r2(P)	r3(P)	r4(P)	r5(P)
Insulin (pmol/L)	.021 (.841)	.013 (.913)	.020 (.853)	-.027 (.803)	.009 (.936)
HOMA-IR	.015 (.889)	.014 (.899)	.018 (870)	-.024 (833)	.015 (.897)
HOMA-β	.032 (.763)	.016 (.880)	.033 (.763)	-.009 (.934)	.032 (.778)
Glucose (mmol/L)	-.047 (.557)	-.035 (.664)	-.058 (.477)	-.087 (.920)	-.089 (.223)
TG (mmol/L)	.227 (.004)*	.226 (.004)*	.216 (.007)*	.191 (.019)*	.198 (.016)*
HDL (mmol/L)	-.029 (.715)	-.010 (.902)	.008 (.922)	.064 (.438)	-.032 (.701)
LDL (mmol/L)	-.098 (.218)	-.086 (.285)	-.089 (.274)	-.084 (.303)	-.098 (.235)
Cholesterol (mmol/L)	.024 (.765)	.045 (.577)	.040 (.626)	.059 (.475)	.041 (.619)

*-p-value <0.05, r1-pearson correlation, r2-controlled for age
r3-controlled for age, physical activity, r4-controlled for age, physical activity, total % body fat, r5-controlled for age, physical activity, total % body fat, calories

Table 2-8 Correlations between YFAS Symptom Counts and Metabolic Characteristics in Pre-Menopausal Women

YFAS Symptom Counts	Females (n=277)				
	r1(P)	r2(P)	r3(P)	r4(P)	r5(P)
Insulin (pmol/L0	.141 (.120)	.142 (.119)	.113 (.227)	.052 (.571)	.053 (.572)
HOMA-IR	.087 (.366)	.087 (.369)	.071 (.468)	.073 (.455)	.059 (.546)
HOMA-β	.097 (.314)	.103 (.285)	.076 (.432)	.031 (.753)	.037 (.709)
Glucose (mmol/L)	-.012 (.843)	-.017 (.784)	-.032 (.602)	-.073 (.234)	-.079 (.201)
TG (mmol/L)	.078 (.200)	.077 (.204)	.049 (.418)	-.016 (.790)	-.012 (.842)
HDL (mmol/L)	-.162 (.007)*	-.163 (.007)*	-.128 (.035)*	-.054 (.377)	-.047 (.441)
LDL (mmol/L)	.066 (.277)	.064 (.288)	.066 (.282)	.017 (.778)	.017 (.788)
Cholesterol (mmol/L)	.038 (.528)	.036 (.556)	.036 (.559)	-.001 (.985)	.001 (.990)

*-p-value <0.05, r1-pearson correlation, r2-controlled for age
r3-controlled for age, physical activity, r4-controlled for age, physical activity, total % body fatr5-controlled for age, physical activity, total % body fat, calories

Table 2-9 Metabolic Marker Measures in BMI Matched Food and Non-Food Addicted Individuals

	Total Population		Men		Women	
	FA Mean ± n=38	NFA Mean ± n=38	FA Mean ± n=9	NFA Mean ± n=9	FA Mean ± n=29	NFA Mean ± n=29
Insulin	122.1±13	87.9±41.8	231.3±84.	96.4±33.9	81.9±35.4	84.4±45.0
HOMA-	0.75±1.40	0.45±0.20	1.99±2.85	0.50±0.15	0.40±0.22	0.43±0.22
HOMA-β	2.14±0.24	2.13±0.17	2.20±0.40	2.15±0.18	2.12±0.18	2.12±0.18
Glucose	5.44±1.20	5.14±0.41	6.37±2.09	5.29±0.36	5.14±0.50	5.09±0.42
TG	1.32±0.70	1.29±0.75	1.50±0.69	1.50±0.95	1.26±0.71	1.23±0.68
HDL	1.36±0.35	1.37±0.31	1.06±0.17	1.12±0.26	1.46±0.34	1.44±0.29
LDL	3.18±1.07	3.00±0.77	3.06±1.48	3.09±0.45	3.22±0.93	2.97±0.85
Cholester	5.19±1.23	5.00±0.91	4.80±1.52	4.88±0.74	5.32±1.14	5.04±0.97

*significant difference between FA men and women at $p<0.05$ Mean±standard deviation(SD) FA-Food Addict, NFA-Non-Food Addict, HOMA-IR-Homeostatic Model of Assessment-Insulin Resistance HOMA-β-Homeostatic Model of Assessment-Beta Cell, TG-Triglyceride, HDL-High Density Lipoprotein LDL-Low density Lipoprotein

2.4 Discussion

In 2018 the prevalence of obesity among Canadian adults ages 18-34 was 18.7%, it was 30.3% among those aged 35-49, 31.3% among those aged 50-64, and 28.1% for individuals age 65 and over [13]**.** The global rate of obesity reported by WHO is 13% [2]. Not surprisingly, the rapid rise in obesity over the same period is paralleled by a substantial rise in diabetes both in Canada and globally [14, 15]. There is evidence supporting the role of processed and fast foods as one contributor to the obesity epidemic and it is worth noting that these same types of foods may override the body's normal satiety signals leading to overconsumption [29, 230-233]. The very same foods which possess addictive qualities can lead to a cascade of metabolic disturbances if frequently consumed [216, 217, 234, 235] which contribute to the development of diabetes and CVD [236-238]. This marks the need for more exploration of the relationship between an addictive tendency towards food and health. No study, to our knowledge, has explored the association between an addictive tendency toward food and metabolic characteristics in the general population. A better understanding of how symptoms of food addiction are associated with insulin resistance and lipid profiles would help us better comprehend the impact of specific eating behaviours on health.

The main finding produced from our study was that in adult males, despite not meeting the criteria for a "food addiction" diagnosis, YFAS symptom counts were still significantly, associated with HOMA-β and TG levels as well as inversely associated with HDL levels. Both HOMA-IR and HOMA-β have been implicated in diabetes risk in the

past [239]. HOMA-β, a measure of insulin secretion, has also been found to initially parallel rising TG levels in newly diagnosed type 2 diabetics only to decrease as TG levels continued to rise higher [240]. Interestingly, HOMA-β levels tend to be lower in individuals with a family history of diabetes due to lower levels of insulin secretion as a result of an impaired β-cell function [241]. The aforementioned studies demonstrate the complexity of the relationship between insulin secretion and metabolic health. In the current study, there was a significant positive correlation between HOMA-β and YFAS symptom counts which may suggest that food addicted behaviours result in higher insulin secretion as a compensatory mechanism. This could potentially be problematic as consistently high insulin levels can often precede diabetes which can eventually damage the β-cell to the point where the cell can no longer produce sufficient levels of insulin to combat hyperglycemia. This is evidenced by the enlargement of β-cells observed in obese individuals and those in the pre-diabetic phase [242-244]. HOMA-β measurements, therefore, must be interpreted cautiously as high insulin secretion can suggest an individual is at risk of developing diabetes and low insulin secretion may suggest that the damage has already been done to the β-cell. A study by the Canadian Heart Health Surveys Research Group found that in a sample of over 29 000 Canadians, high TG and low HDL levels were common among diabetics and those with hypertension [245]. Elevated TG levels have also been associated with atherosclerotic CVD and all cause mortality in a study comprised of over 15 000 patients [246, 247]. It stands that behaviours that may influence TG and HDL levels may also increase the risk of CVD. There is currently limited research on the relationship between food addiction, its

symptoms, and their relationship with these metabolic characteristics, however, one study did find that food addiction was significantly more prevalent in newly diagnosed type 2 diabetics when compared to a control group. This same study also compared the metabolic characteristics of FA and NFA diabetics and found that those who were food addicted had a substantially higher HOMA-IR value [193]. However, our results indicated that there was no significant difference in HOMA-IR or other metabolic characteristics between FA and NFA individuals when matched for BMI. Food addiction has also been found to account for a large portion of BMI variance among T2D patients [192]. This may suggest that an addictive tendency towards food is not only a risk factor for T2D but could in fact exasperate the condition since patients will have greater difficulties adhering to dietary recommendations that may improve their health and help manage their condition. As previously noted, some of the hormones associated with addictive behaviours also share associations with a number of health risks which may further compound the effects of an addictive tendency towards food.

In females, Pearson correlation analysis revealed no significant correlations between YFAS symptoms and any of the metabolic markers measured. However, after women were separated according to menopausal status to further elucidate the potential effects of sex hormones on these outcomes, post-menopausal women exhibited a significant correlation between YFAS symptoms and TG after correcting for age, physical activity, total body fat percent, and calories. While there are currently no past studies investigating the association between YFAS symptoms and metabolic abnormalities in women, other

studies on disordered eating patterns such as binge eating have been found to have signification associations with T2D [248]. The role of addictive food tendencies in T2D has also been found to be harmful. Varying levels of food addiction based on YFAS symptom counts were associated with a significant increase in BMI among T2D patients in a sample that was 67.4% women, however, there was no adjustment for menopausal status [249]. The limited associations seen in our female population may be due to the protective effects of lower body fat common among women which may help keep blood glucose and lipid profiles within a normal range despite problematic eating behaviours [250-252]. However, this effect could be somewhat diminished in post-menopausal women as decreasing estrogen levels have been shown to influence central fat accumulation and TG levels [128, 253]

The greatest strength of our study is the large number of individuals successfully recruited from the general population in conjunction with good screening efforts to control for potential confounders such as health disorders that could influence an individual's dietary habits or result in them presenting with addictive behaviours beyond that which is seen a general population. We have also benefitted from the ability to collect blood samples from every participant for reliable measurement of hormones and lipid profiles. Our extensive list of questionnaires to collect details on physical activity and dietary history adds strength to the validity of our results as they allowed us to effectively control for these confounders. The use of DXA scanning to measure total body fat % ensured this particular confounding variable was measured using one of the most accurate

methods available [86]. One possible limitation present in our study could be that caloric intake and physical activity levels were self reported, both of which were controlled for in this study. self-reporting bias is another factor that researchers must be cognizant of when dealing with self-administered questionnaires. The number of food addicts used in the comparative analysis. Although this was a large sample size, food addiction was present in only about 5% of participants [183]. It should also be noted that the exclusion of previously diagnosed food addicted individuals contributed to the modest correlation coefficients produced from the partial correlation analysis. However, exclusion of these outliers allowed us to better capture the true contribution of addictive eating tendencies to metabolic disturbance in a general population. Replications of this study would greatly benefit from a larger number of individuals diagnosed with food addiction. It is also possible that with a larger overall sample size, the correlation between YFAS symptoms and HOMA-IR in men may reach the required cut-off for statistical significance as it was narrowly missed in this analysis (Table 2-5). Future studies could also benefit from measuring a larger number of metabolic markers or health outcomes and their association with an addictive tendency toward food. Finally, an intervention study measuring metabolic characteristics in individuals living with food addiction before and after treatment to address addictive eating behaviours would better highlight the impact these behaviours have on health and whether meaningful improvements in IR and lipid profiles can be achieved through this. In conclusion, we have demonstrated that an addictive tendency towards food is associated with several metabolic characteristics that may contribute to insulin resistance and CVD in men of the general NL population and to a

lesser extent, post-menopausal women. Our findings help elucidate the role of addictive food tendencies in metabolic disturbance in a general population and how this may impact men and women differently. A proper, standardized assessment of FA is an important first step to address these behaviours. These symptoms must be managed and treated appropriately, ideally, through education and guidance by nutritionist and therapist as it may require both dietary intervention and knowledge of effective coping strategies to combat urges and recognize detrimental behaviours. Furthermore, efforts to control addictive eating behaviours could potentially become a factor in preventative efforts concerning diabetes and CVD in the future.

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3

Chapter 3. The Association between Food Addiction and Body Fat Distribution in Men and Women of the General Newfoundland and Labrador Population

Author Contributions: Matthew Nelder assisted in recruiting and collecting data from research participants, analyzed data, and wrote the manuscript; Farrell Cahill is credited with previous work in data collection and participant recruitment; Michael Wahl provided equipment essential to the completion of this work. Wayne Gulliver, Guangju Zhai, Weiping Teng, and Zhongyan Shou provided important input for the revision of the manuscript. Hongwei Zhang conducted data collection and entry; Guang Sun designed the research and was responsible for the final content of the manuscript as Principal Investigator.

3.1 Introduction

Obesity is one of the most ubiquitous public health problems in Canada as well as most developed and even developing countries [1]. The Province of Newfoundland and Labrador (NL), Canada, has the highest prevalence of obesity at 35.2% [2]. Residents of this province also exhibit high rates of obesity related health disorders such as type II diabetes which affects 11.2% of the provincial population [3] and cardiovascular diseases which results in nearly 202.3 deaths per 100,000 individuals yearly which ranks the worst among all provinces in Canada [4]. It is clear that the issue of obesity must be addressed in this population. The etiology of obesity is highly complex with the interaction of many environmental, genetic, and psychological factors involved [5, 6]. The overconsumption of calorie dense foods is one of these factors and it has been found that high calorie, highly palatable foods may have addictive qualities that promote frequent consumption in some individuals [7-9]. This type of behaviour towards eating can be described as

addictive and it has recently been shown that an addictive tendency toward food is, in fact, an important factor contributing to the development of obesity [10].

Food addiction, not to be confused with the occasional overindulgence, is defined as an obsessive consumption of highly palatable foods that trigger the body's reward systems, despite adverse health effects. This phenomenon is supported by a collection of physiological evidence in the way of dopaminergic circuitry activation correlating with food addictive behaviours in both human and animal studies [11-13]. Similarities have been drawn between food addiction and nicotine addiction regarding the way each influences the body's reward systems [14]. Chronic intake of certain foods has even been compared to cocaine and opioid use [15, 16]. Despite this evidence, food addiction is not yet recognized by clinicians but the quantification of food addictive behaviours is made possible through the Yale Food Addiction Scale (YFAS) which was developed in 2009 [17]. The YFAS has been used and studies among bariatric surgery patients, adults seeking weight loss treatment, and eating disorder patients [18-20]. As one might imagine, the types of food that are normally found to have addictive qualities are those which are high in sugar, fat and are heavily processed. A study by Schulte and colleagues revealed that whether or not a food was processed, was a strong predictor of its possessing addictive- like qualities [21]. Although the prevalence of obesity in Canada has tripled in the past 30 years, fast foods make up only 6.3% of total calorie intake in the Canadian diet [22] so it may be possible that food choices at home may be a larger factor. While excessive levels of body fat increase the risk of developing a number of

comorbidities, there are many individuals who, in spite of maintaining high levels of body fat, barely exhibit any signs of metabolic disturbance [23, 24]. This might be partly due to the heterogeneity of how different individuals can accumulate body fat and how it is distributed within the body [25] which brings us to a more specific concern, the issue of fat distribution.

One way of framing the issue of body fat distribution is the classic apple vs. pear shape example. The “apple” shape, otherwise known as central obesity, is often used to refer to excessive fat in the android and trunk region of the body with a high waist to hip ratio and is far more common in males. The “pear” shape, is characterized by more body fat in the hips, thighs, and buttocks, known as the gynoid region, with a lower waist to hip ratio and is more often observed in women [26-28]. The way in which an individual accumulates body fat in terms of both mass and distribution can result in very different cardiometabolic outcomes [29]. Evidence indicates that the often male associated central and android obesity defined as excess adipose tissue in the abdominal region and intra-abdominal or visceral cavity is more important in the association with the prevalence of diabetes and cardiovascular diseases than overall subcutaneous fat [30]. Visceral adiposity has also been found to increase arterial inflammation and serve as a predictor of future cardiovascular events [31]. Conversely, the relationship between gynoid or gluteo-femoral fat with favorable metabolic profiles has been a consistent finding in many studies [32-34]. Body fat distribution appears to play an important role in overall health. However, meaningful evidence regarding the relationship between an addictive tendency

toward food and its relationship to specific body fat distribution patterns remains to be seen.

We have previously demonstrated that the severity of food addiction is strongly correlated to the degree of adiposity in the NL population [10]. However, it is unclear if an addictive tendency towards food is associated with an increase in specific fat distribution patterns such as an excess of fat in the android region, gynoid region, or visceral cavity. VF is of unique concern as it has been shown to increase circulating free fatty acids and inflammatory adipocytokines which may contribute to insulin resistance [35, 36]. A recent study has suggested that YFAS symptom counts may in fact be associated with visceral adiposity in young females [37]. This study, however, was performed with only female participants of a relatively small range of ages, which makes it difficult to apply to a general population. Furthermore, bioelectrical impedance (BIA) was the method by which adiposity measures were taken [38] which may lack accuracy regarding the measurement of visceral adiposity. The study did, however, take into consideration other potential confounding factors that may influence body fat measures such as physical activity and total caloric intake. These factors are highly variable between individuals and can easily mask the true contribution of food addiction symptoms to body fat distribution if not properly controlled for in the statistical analysis. Physical activity levels exhibit significant influence on adiposity and it has been consistently shown that individuals who regularly engage in some form of exercise have lower body fat than those who do not [39-41]. Total caloric intake has also demonstrated a positive association with adiposity [42].

Due to the dangers surrounding certain patterns of body fat distribution, for example, the "apple" shape or central obesity as mentioned above, more specific investigations concerning factors that contribute to this issue are warranted. We have performed an in-depth analysis of YFAS symptom count correlations with several measures of body fat distribution in men and women of a general NL population using DXA and controlled for major confounding factors such as age, physical activity, and caloric intake. To the best of our knowledge, no study to date has assessed this relationship in such detail or in such a large sample size.

3.2 Materials and Methods

Ethics Statement

This study was approved by the Health Research Ethics Authority (HREA), Memorial University of Newfoundland, St. John's, Canada with project identification code 10.33. Written consent was provided by all who participated.

Study Sample:

777 adult volunteers (479 women, 298 men) from the Province of NL were recruited for this study through the use of advertisements, flyers, and word of mouth. Eligibility for the study required that all participants be

1. 19 years of age or older

2. The participant must have been born in NL and the participant's family must have been in NL for at least 3 generations

3. Healthy with no serious metabolic, endocrine, or cardiovascular conditions.

4. Participant must not be pregnant at time of study.

Anthropometric Measurements:

Height, weight, waist, and hip circumference were measured following a fasting period of 12 hours. All measurements were taken with participants wearing a standard hospital gown. Weight was measured to the nearest 0.1 kg using a platform manual scale balance (Health O Meter, Bridgeview, IL). Height was measured using a fixed stadiometer to the nearest 0.1 cm. Hip circumference was measured using a flexible measuring tape at the level of the largest circumference between the waist and thighs to the nearest 0.1 cm. Waist circumference was measured using the same method at the level of the umbilicus, between the lowest rib and iliac crest.

Body Composition Measurements and Definitions:

Body composition measurements which included trunk fat, android fat, and VF were assessed using dual-energy x-ray absorptiometry (DXA; Lunar Prodigy; GE Medical Systems, Madison, WI, USA). Measurements were taken while the patient lied horizontally on the DXA scanner following a 12 hour fast. The trunk region is defined as the area from the lowest boundary of the pelvis cut to the highest boundary of the neck. The android region as defined by the DXA software runs from above the pelvis cut by

20% of the distance between the pelvis and neck cuts. The gynoid region, also within DXA software definitions, is defined as the lower boundary of the umbilicus to a line equal to twice the height of the android fat distribution [43, 44].

Food Addiction Symptom Count Measurement:

Symptoms of food addiction were assessed using the Yale Food Addiction Scale. This is a 25 item questionnaire that assesses the last 12 months of eating patterns. The YFAS is based on the criteria used for substance dependence in the Diagnostic and Statistical Manual IV-TR (DSM-IV TR). This criterion includes symptoms such as tolerance, withdrawals, anxiety in social situations, and difficulty lowering or quitting the use of the substance. Using the YFAS. symptoms were counted using the Likert scoring method which ranges from 0 to 7 [17]. Each symptom on the YFAS represents a collection of questions from the questionnaire concerning that particular behaviour. If an individual answers affirmatively to certain questions, they are said to have the corresponding symptom. Some of these questions are based on the frequency of the behaviour (ex. once a month, 2-4 times a month, etc.) and some are binary yes or no questions [45].

Calorie intake and Physical Activity Assessment:

Calorie intake was measured using the Willett Food Frequency Questionnaire (FFQ) which measures the last 12 months of dietary habits [46]. The quantity of each food item was converted into a daily average intake value. This value was then entered into Nutribase Clinical Nutrition Manager (software version 9.0; Cybersoft inc. Arizona). We employed the use of the Baecke physical activity questionnaire to assess physical activity

levels. This questionnaire measures physical activity using three categories which are work, sport, and leisure [47].

Statistical Analysis:

All statistical analysis was completed using SPSS ver.23. The level of statistical significance was set at alpha=0.05. All statistical tests were run on the entire cohort as well as men and women separately. Pearson correlation analysis was used to evaluate potential relationships between YFAS symptom counts and measures of adiposity. Partial correlation analysis was also performed which allowed us to control for age, total calorie intake, and physical activity levels. A linear regression analysis was also performed to assess the variance of each fat distribution measure attributed to YFAS symptom counts. A one-way ANOVA was used to measure the difference in body fat levels between food addicted obese (FAO), non-food addicted obese (NFO), and normal weight controls. FAO and NFO were matched by age and BMI.

3.3 Results

Physical Characteristics and Adiposity Measures

The age, gender, BMI, and anthropometric data of the entire cohort, as well as men and women separately are presented in Table 3-1 as mean ± standard deviation. Table 3-1 also contains all adiposity measures expressed as mean ± standard deviation. The average age of women was 45.3 years and the average age of men was 42.8 years. There was a

significant difference between men and women for all anthropometric and adiposity measures.

The Correlation Between YFAS Symptom Counts and Measures of Fat Distribution

Both men and women showed highly significant correlations between YFAS symptom counts and all measures of fat distribution (table 3-2) including total body fat (men: r=0.30, women: r=0.33), trunk fat (men: r=0.30, women: r=0.31) android fat (men: r=0.34, women: r=0.33), gynoid fat (men: r=0.23, women: r=0.30) and VF (men: r=0.32, women: r=0.31). These measures are expressed in percentages as well. Women showed slightly higher correlations than men in all measures except for VF and android fat, for which men showed slightly higher correlations. Women exhibited a much higher correlation between gynoid fat and YFAS symptom counts. All partial correlation analysis has been controlled for age, physical activity, and total calorie intake

Comparison of Body Fat Distribution Measures for FAO, NFO and Control Groups

An ANOVA was performed between FAO, NFO, and normal weight controls with FAO and NFO groups matched by sex and BMI. The control group was also matched by sex. There were 21 individuals in each group. ANOVA revealed that all measures of body fat distribution differed significantly between the obese groups and the controlled groups as expected, however, a significant difference was not observed for FAO and NFO individuals. The F value, which is a measure of the variation between samples divided the variation within samples, was highest for trunk percent fat and android percent fat. The results of the ANOVA can be found in Table 3-3.

Table 3-1 Characteristics of Participants

	Female Mean ± SD n=479	Male Mean ± SD n=298	P-value
Age*	**45.3 ± 13.1**	**42.8 ± 12.7**	**0.011**
Height (cm)*	**163.3 ± 6.0**	**177.6 ± 6.7**	**<0.001**
Weight (kg)*	**70.8 ± 14.8**	**90.8 ± 17.3**	**<0.001**
BMI (kg/m^2)*	**25.8 ± 5.0**	**29.9 ± 4.9**	**<0.001**
BF%*	**37.0 ± 8.7**	**26.3 ± 8.4**	**<0.001**
TF%*	**38.4 ± 10.0**	**31.9-10.1**	**<0.001**
GF%*	**44.0 ± 7.3**	**28.9 ±7. 8**	**<0.001**
AF%*	**42.6 ± 11.7**	**36.9 ± 11.5**	**<0.001**
VF%*	**2.0 ± 1.5**	**4.8 ± 2.5**	**<0.001**
Waist (cm)*	**91.2 ± 13.8**	**101.2 ± 13.6**	**<0.001**
Hip (cm)*	**99.8 ± 12.8**	**101.7 ± 10.8**	**0.019**
Waist/Hip*	**0.9 ± 0.05**	**1.0 ± 0.05**	**<0.001**

*significant difference of means between men and women Mean ± standard deviation (SD), BMI–Body mass index, BF% Percent body fat, TF%–Percent trunk fat, AF%-Percent android fat, VF%-Percent VF

Table 3-2 Partial Correlations of YFAS Symptom Counts with Measures of Body Fat Distribution Controlled for Age, Physical Activity and Caloric Intake

	Entire Cohort	Women	Men
Total Body Fat (g)*	**r=0.32 (p<0.001)**	**r=0.33 (p<0.001)**	**r=0.30 (p<0.001)**
Total Body Fat %*	**r=0.29 (p<0.001)**	**r=0.30 (p<0.001)**	**r=0.24 (p<0.001)**
Trunk Fat (g)	**r=0.298 (p<0.001)**	**r=0.31 (p<0.001)**	**r=0.30 (p<0.001)**
Trunk Fat %	**r=0.299 (p<0.001)**	**r=0.31 (p<0.001)**	**r=0.30 (p<0.001)**
Gynoid Fat	**r=0.29 (p<0.001)**	**r=0.30 (p<0.001)**	**r=0.23 (p<0.001)**
Gynoid Fat %*	**r=0.21 (p<0.001)**	**r=0.24 (p<0.001)**	**r=0.15 (p<0.001)**
Android Fat(g)*	**r=0.31 (p<0.001)**	**r=0.33 (p<0.001)**	**r=0.34 (p=0.002)**
Android Fat %*	**r=0.30 (p<0.001)**	**r=0.31 (p<0.001)**	**r=0.25 (p<0.001)**
And./Gyn. Ratio (%)*	**r=0.09 (p=0.011)**	**r=0.22 (p<0.001)**	**r=0.17 (p=0.003)**
VF (g)*	**r=0.21 (p<0.001)**	**r=0.31 (p<0.001)**	**r=0.32 (p<0.001)**
VF %*	**r=0.08 (p=0.039)**	**r=0.23 (p<0.001)**	**r=0.19 (p=0.001)**
BMI*	**r=0.34 (p<0.001)**	**r=0.36 (p<0.001)**	**r=0.34 (p<0.001)**

***p<0.05, And%/Gyn%- ratio of percent android fat to percent gynoid fat, BMI- Body Mass Index**

Table 3-3 ANOVA for Body Fat Differences Between Sex and BMI matched Food Addicted Obese, Non-Food Addicted Obese and Control groups

n=21 in each group	F	P
BF (g)	14.8	<0.001*
BF%	25	<0.001*
TF (g)	11.5	<0.001*
TF%	44.5	<0.001*
AF (g)	15.6	<0.001*
AF%	44.4	<0.001*
GF (g)	10	<0.001*
GF%	7.8	0.001*
VF (g)	15.3	<0.001*
VF%	4.38	0.017*

*p<0.05, BF-Total Body Fat, TF-Trunk Fat, AF-Android Fat, GF-Gynoid Fat, VF-VF

3.4 Discussion

Obesity has become one of the widest spread and burdensome health issues facing us today. Some studies suggest it may be equally, if not more destructive than cigarette smoking [48]. Chronic positive energy balance, whether it's due to excessive caloric intake or lack of physical activity, continues to be the driving force of the obesity epidemic [49-51]. It follows that the consumption of highly palatable, calorie dense foods only exasperate this problem. Our previous studies have indicated that food addiction or an addictive tendency towards food is an independent contributing factor to the development of obesity [10, 52]. However, the relationship between symptoms of "food addiction" and body fat distribution remains unclear. We have shown that YFAS symptom counts exhibit a highly significant correlation with not only total body fat percent, which has been highlighted in previous studies of ours [10], but with several measures of fat distribution which are far more sensitive indicators of future obesity related health issues [53-56]. A better understanding of how an addictive tendency towards food contributes to specific body fat distribution patterns could aid in understanding how compulsive eating patterns contribute to overall health. To date, no other study has performed such a detailed investigation of the relationship between YFAS symptoms and body fat distribution, in a large general population.

We measured body fat distribution in 777 men and women in the general NL population using DXA, which allowed us to safely and accurately measure both subcutaneous and VF stores with great accuracy comparable to that of computed tomography scans [57, 58].

DXA also provides a much more complete assessment of body composition than BMI [59]. The first and most significant finding of the present study is the correlation that was observed between VF mass and YFAS symptom counts in both men and women. VF percentage was also found to be significantly associated with YFAS symptoms in men and women. This is the first time this relationship has been reported in men and women of a general population. The present study is an important addition to the current body of knowledge on the relationship between YFAS symptoms and BFD and how it applies to a general population. Our findings are particularly important as they suggest that food addiction plays a significant role in, not only the accumulation of peripheral adipose tissue but could have serious metabolic implications as well since VF is a risk factor of a number of health issues. These issues include but are not limited to diabetes and high blood pressure, additionally, an addictive tendency toward food has recently been found to be much more prevalent in a cohort of recently diagnosed type II diabetics [60-63]. Excess adipose tissue in the visceral cavity has also been found to exhibit an association with arterial stiffness among other cardiometabolic risk factors and all-cause mortality [50, 64, 65]. This finding is also reinforced by a study that found many of the same foods that have been shown to influence addictive like behavior are also associated with visceral adiposity [21, 66]. The correlation of YFAS symptoms with VF percentage was higher in women (table 3-2). This particular finding is concurrent with other measures of adiposity in women, as they generally have higher body fat percentages [67]. This finding highlights the potentially detrimental effects an addictive tendency towards food can have on fat distribution and by extension, overall health. This might suggest the need for

dietitians to take a more complete assessment of individual eating habits to address health issues that can be exasperated by or are associated with excessive VF.

A significant correlation between YFAS symptom counts with both total mass and percentage of the trunk and android fat was also observed in both men and women. A correlation between trunk fat and YFAS symptoms counts had been previously reported by our lab but subjects were grouped as either food addicted, or non-food addicted and not by gender thereby masking gender specific effects. The number of subjects in the previous study was also much smaller [52]. Therefore, this is the first time that the sex specific relationship between YFAS symptoms, trunk fat, and android fat has been reported in the general population. While men normally tend to carry more weight in this region of the body, the association between trunk fat and dietary patterns in women has been observed in a recent study [68], so it may stand that addictive eating behaviours in women are likely to lend themselves to the development of truncal obesity. A large population study also reported that foods with addictive qualities may contribute to excessive truncal fat [69] Trunk and android fat, much like VF, has been shown time and time again to exhibit strong associations with insulin resistance, diabetes, high cholesterol, and metabolic syndrome [43, 70-75]. Our finding, in conjunction with the growing body evidence that truncal obesity can be dangerous for the long-term health of an individual, indicates a need for a greater understanding of the factors that contribute to this particular body fat distribution pattern [70, 76-79]. A significant correlation between symptoms of food addiction and gynoid fat was also observed in men and women

although this association was much more pronounced in women (table 3-2). It has long been observed that women tend to exhibit gynoid obesity far more than men and our results are in agreement with this trend [80, 81]. Gynoid fat is thought to be protective against metabolic illnesses such as diabetes and CVD [82-86]. While gynoid fat does exhibit a positive correlation with YFAS symptoms, additional endocrinological studies are required to uncover the metabolic implications of this relationship and whether the same protective factors are present in food addicted obese women. Lastly, we compared FAO, NFO, and control groups (table 3-3) which revealed that all measures of body fat distribution were significantly different between these groups. The body fat regions that exhibited the greatest variation between groups was VF mass, trunk fat mass, android fat %, and trunk fat %. While differences in body fat measures between healthy controls and obese individuals differed greatly, as can be reasonably expected, the post-hoc analysis revealed the differences in body fat measures between FAO and NFO groups were not statistically significant. However, the prevalence of food addiction among obese individuals remains to be much higher than in non-obese individuals as indicated by recent studies. Food addiction has also been investigated and validated as a phenotype of obesity [10, 87, 88]. This serves to highlight the complexity of obesity and provide evidence of the heterogeneity of this disease.

This study revealed many unique findings; however, potential limitations would be that the YFAS questionnaire may be susceptible to self-reporting bias and there is always the possibility of undiagnosed illness in a population this large that was not accounted for at

the time of data collection. This study also could have benefitted from the inclusion of hormonal characteristics to further highlight the effects that food addiction can have on components of metabolic syndrome such as triglycerides, blood pressure, or fasting glucose. In the future, it would be a worthwhile endeavor to examine the correlation between specific symptoms of food addiction and measures of adiposity, as well as hormonal characteristics. A longitudinal study would also be helpful in documenting the relationship between food addiction and body composition at different stages in life, although it should be noted that cross-sectional studies such as this cannot determine causality or directionality of the correlation that is observed.

This association study has successfully demonstrated that YFAS symptom counts are significantly correlated with multiple measures of fat distribution in both men and women of a large, general, NL population even after controlling for several confounding factors. It is the first to demonstrate the gender specific association of YFAS symptom counts with visceral, trunk, and total fat in such a large cohort. It is also the first to demonstrate the correlation between YFAS symptom counts with android and gynoid fat. This is the most comprehensive study to date, that highlights the relationship between symptoms of food addiction and body fat distribution patterns that are consistently shown to be sensitive indicators of diabetes and CVD risk. Additional research is required to reveal direct cause and effect relationships between these variables. Our analysis indicated that YFAS symptom scores are associated with several measures of adiposity in both men and women, independent of physical activity or caloric intake. YFAS symptom scores were

significantly associated with measures such as total BF% (men=0.24 women=0.30), AF% (men=0.25 women=0.31) and VF% (men=0.19 women=0.23). The variance in regional fat percentage attributable to symptoms of FA ranges from 3.6% to 9.6%, suggesting that FA is a factor to consider in obesity treatment and prevention. Perhaps individuals seeking weight-loss treatment should also be evaluated for symptoms of FA and/or the severity of FA based on YFAS symptom scores so that dietitians are able to better understand the challenges individuals face when attempting to lose weight. This can assist dietitians in making more informed recommendations as to what types of food their clients are struggling with and the behaviors that make weight-loss a more challenging endeavor for some people.

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4

Chapter 4. The Comparison of Metabolic Characteristics Between Women With and Without Android Obesity from a General Newfoundland and Labrador Population

Author Contributions: Matthew Nelder assisted in recruiting and collecting data from research participants, analyzed data, and wrote the manuscript; Hongwei Zhang conducted data collection and entry; Guang Sun designed the research and was responsible for the final content of the manuscript as Principal Investigator.

4.1 Introduction

Obesity is among the most challenging public health issues facing the world today, particularly in the Canadian Province of Newfoundland and Labrador where 35% of residents are obese [1, 2]. There is a large body of evidence that suggests that comorbidities often associated with obesity such as diabetes and cardiovascular disease (CVD) exhibit higher correlations with specific body fat distribution (BFD) patterns, as opposed to overall body fat percentage [3-8]. BFD can vary greatly between different individuals and certain sites of body fat storage are more metabolically active as they are more sensitive to lipase activity, the enzyme responsible for the hydrolysis of triglycerides, which can lead to an increased risk of metabolic dysfunction [9-14]. The way in which individuals store body fat is also modified by sex hormones such as estrogen [15-17]. This accounts for some of the variations in BFD between men and women, as men tend to store fat in the android or central region and women more commonly store fat in the gynoid or gluteal-femoral region [18, 19]. This is why men and women often present with what is commonly known as the “apple” and “pear” shape, respectively, which can have serious implications in an individual's health [20, 21]. The “pear” shape which results from a predisposition to store fat in the lower body is often

thought to be protective and the “apple” shape may increase an individual's risk to a number of health issues [22-24]. Women can also exhibit the android obesity more commonly seen in men, however, there is limited data directly comparing the metabolic characteristics of women with android obesity to those without in a large general population. The role of lower body fat in metabolic health is also in need of further clarification because, despite numerous studies that suggest it is protective, a loss in leg fat has been found to be equally important to the improvement of insulin sensitivity when compared to a loss in trunk fat [25].

Many of the existing studies on this topic have limited sample sizes, examine only certain subsets of the population (ex. diabetics, elderly), or fail to control for sex specific effects [26-32]. Those that do include the general population test only a small number of metabolic markers or use less accurate means of measuring BFD compared to imaging technologies such as magnetic resonance imagery and dual energy x-ray absorptiometry (DXA), that is capable of providing highly accurate BFD data [33-37]. Therefore, we have designed a study that compares a large panel of metabolic characteristics in 2323 women with and without android obesity as measured by DXA scans from the general NL population. DXA scanning technology offers a significant advantage as it is a safe, efficient, and highly accurate method of assessing body fat distribution and is often described as the “gold standard” of performing such measurements. It also allows a detailed look at the actual body shape of research participants [38-42]. Furthermore, DXA is unique in that it allows us to control for VF which may mask the true contribution of

subcutaneous android fat as visceral adipose tissue is independently associated with a number of metabolic issues and is located within the android region [43-47]. The inability to control for VF is another limitation that is common among many studies on this topic.

This paper describes the comparison of a wide range of metabolic and anthropomorphic measurements between women with different BFD patterns recruited through the CODING (Complex Disease in the Newfoundland Population: Environment and Genetics) study which has generated several papers in the field of obesity research [38, 48-50]. We have also included an analysis of a sub-group of 470 BMI matched women of similar age with and without upper body obesity which has been adjusted to control for VF. Using the same BMI matched sub-group, we have additionally calculated the risk of metabolic syndrome (MetS) for women with upper body obesity in the NL population as defined by the Adult Treatment Panel III (ATP III) which was designed by the National Cholesterol Education Program (NCEP) [51]. MetS is a collection of symptoms that often occur together in clusters that significantly increase an individual's risk of developing CVD or other serious illnesses [52]. A better understanding of the relationship between female android obesity and MetS could prove extremely helpful to clinicians and public health efforts to mitigate the risk of CVD.

4.2 Materials and Methods

Ethics Statement

This study was approved by the Health Research Ethics Authority (HREA), Memorial University of Newfoundland, St. John's, Canada with project identification code 10.33. Written consent was provided by all who participated.

Study Sample

2323 adult women from the Canadian Province of Newfoundland and Labrador were recruited for this study through the use of advertisements, flyers, and word of mouth. Eligibility requirements are as follows:

1. 19 years of age or older

2. The participant must have been born in NL and the participant's family must have been in NL for at least 3 generations

3. Healthy with no serious metabolic, endocrine, or cardiovascular conditions.

4. Participant must not be pregnant at time of study.

Metabolic Marker Measures

Serum concentrations of glucose, total cholesterol, HDL cholesterol and triacylglycerols were measured using the Lx20 analyzer (Beckman Coulter Inc., Fullerton, CA) with Synchron reagents. LDL cholesterol was calculated using the following formula: (total cholesterol) − (HDL cholesterol) − (triacylglycerols/2.2). Serum insulin was measured using the Immulite Immunoassay analyzer. Insulin resistance and beta cell function were calculated using the homeostasis model assessment (HOMA) [53]

Anthropometric Measurements

Height, weight, waist, and hip circumference were measured following a fasting period of 12 hours. All measurements were taken with participants wearing a standard hospital gown. Weight was measured to the nearest 0.1 kg using a platform manual scale balance (Health O Meter, Bridgeview, IL). Height was measured using a fixed stadiometer to the nearest 0.1 cm. Waist circumference was measured using the same method at the level of the umbilicus, between the lowest rib and iliac crest.

Body Composition Measurements and Definitions

Body composition measurements which included android fat, gynoid fat, and VF were assessed using dual-energy x-ray absorptiometry (DXA; Lunar Prodigy; GE Medical Systems, Madison, WI, USA). Measurements were taken while the patient lied horizontally on the DXA scanner following a 12 hour fast. The android region as defined by the DXA software runs from above the pelvis cut by 20% of the distance between the pelvis and neck cuts. The gynoid region, also within DXA software definitions, is defined as the lower boundary of the umbilicus to a line equal to twice the height of the android fat distribution [43, 54-57].

Metabolic Syndrome Diagnosis

MetS was diagnosed according to the NCEP ATP III criteria. Diagnosis in females requires that individuals have at least 3 out of 5 of the following symptoms [51]

i. WC >35 inches

ii. Fasting glucose >100mg/dl

iii. TG >150mg/dl

iv. HDL <50mg/dl

v. SBP >130mmHg or DBP >85mmHg

Statistical Analysis

All statistical analysis was completed using SPSS ver.23. The level of statistical significance was set at alpha equal to or less than 0.05. Women were separated into tertiles and quartiles based upon android: gynoid (AGR) ratio. Metabolic and anthropometric characteristics between tertiles were compared using one-way ANOVA. Women in the top quartile were compared to a control group of BMI matched women of similar ages using multivariate testing controlled for VF percentage. Odds ratio (OR) was calculated to determine the risk of metabolic syndrome among women in the top quartile of AGR.

4.3 Results

Comparison of AGR Tertiles

Females in the lowest, middle and highest tertile of AGR all differed significantly from one another in mean insulin, glucose (figure 4-1), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC) (figure 4-2), systolic blood pressure (SBP), diastolic blood pressure (DBP), and waist circumference (WC) (figure 4-3). The lowest and middle tertile did not exhibit a significant difference

between each other for HOMA-IR or HOMA-β, although HOMA-IR did not come quite close to reaching the appropriate p-value for statistical significance (p= 0.055). The highest tertile was significantly higher than both the lowest and middle tertile for HOMA-IR and HOMA-β.

Comparison of Top AGR Quartile with BMI Matched Women

After controlling for VF percent, women in the top AGR quartile, when compared to a BMI matched group of women who populated the lower quartiles of AGR, there was no significant difference observed for any of the markers that were studied (Table 4-3). However, women in the top quartile were found to be 2.4x more like to have metabolic syndrome compared to their BMI matched counterparts of a similar age which may be mostly attributed to VF depots.

Table 4-1 Physical Characteristics of Participants

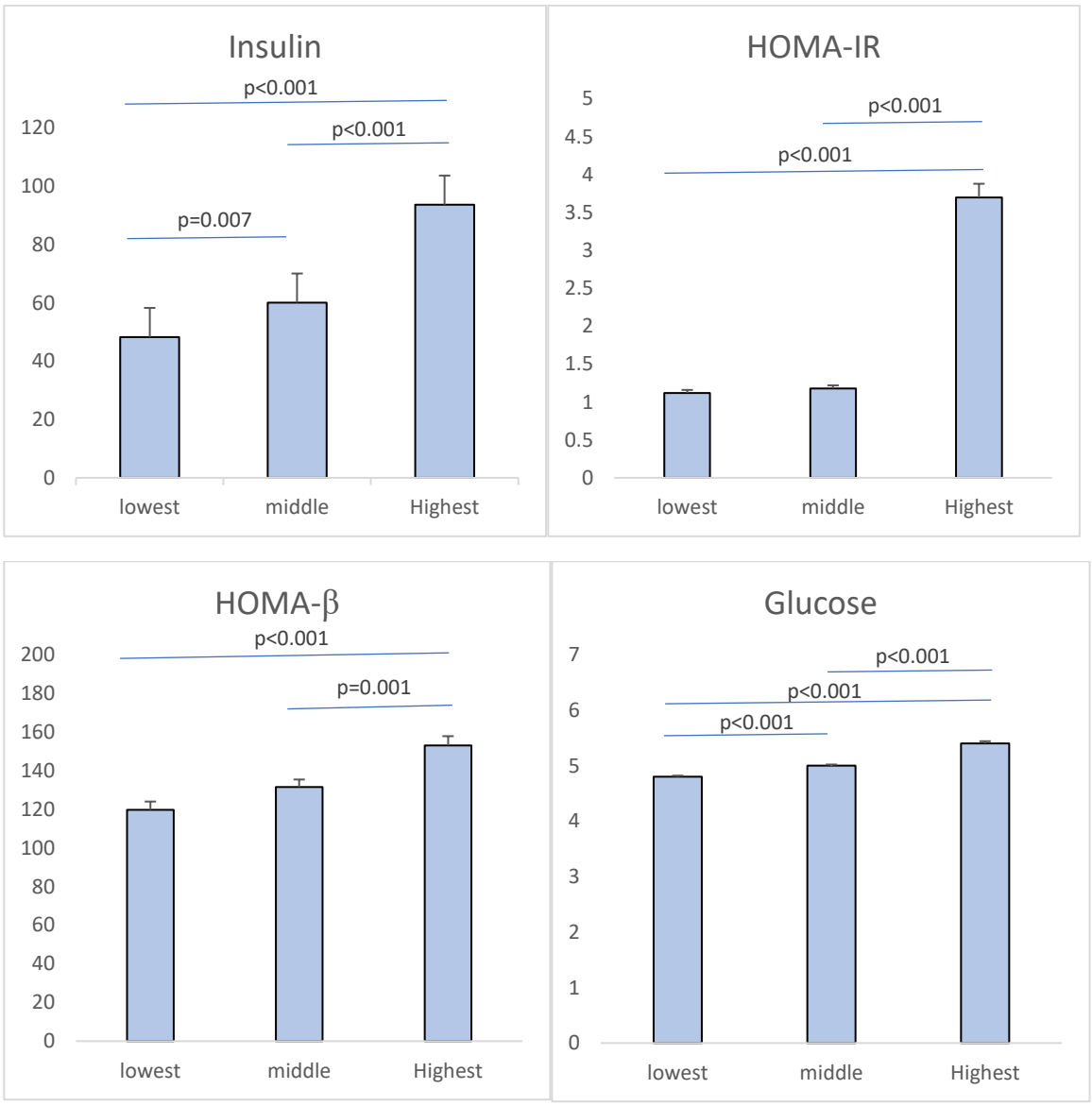
	Mean ± SD n=2323
Age	44 ± 12.7
Min-max	19-90
Height *cm)	163 ± 6.0
Min-max	158-196
Weight (kg)	70 ± 14.4
Min-max	47-157
BMI (kg/m^2)	30.8 ± 5.4
Min-max	16-48
BF%	37 ± 7.9
Min-max	5-59
GF%	44 ± 6.8
Min-Max	7-63
AF%	43 ± 10.9
Min-max	4-66
A:G Ratio	0.45 ± 0.16
Min-max	<0.001-1.29
VF%	2 ± 1.5
Min-max	<0.001-14.7

Mean ± standard deviation (SD), (Maximum – Minimum), BMI–Body mass index, BF% Total Percent body fat, GF%- Percent Gynoid Fat, AF%-Percent android fat, A:G Ratio-Android:Gynoid Fat Ratio VF%-Percent VF

Table 4-2 Characteristics of BMI Matched Participants

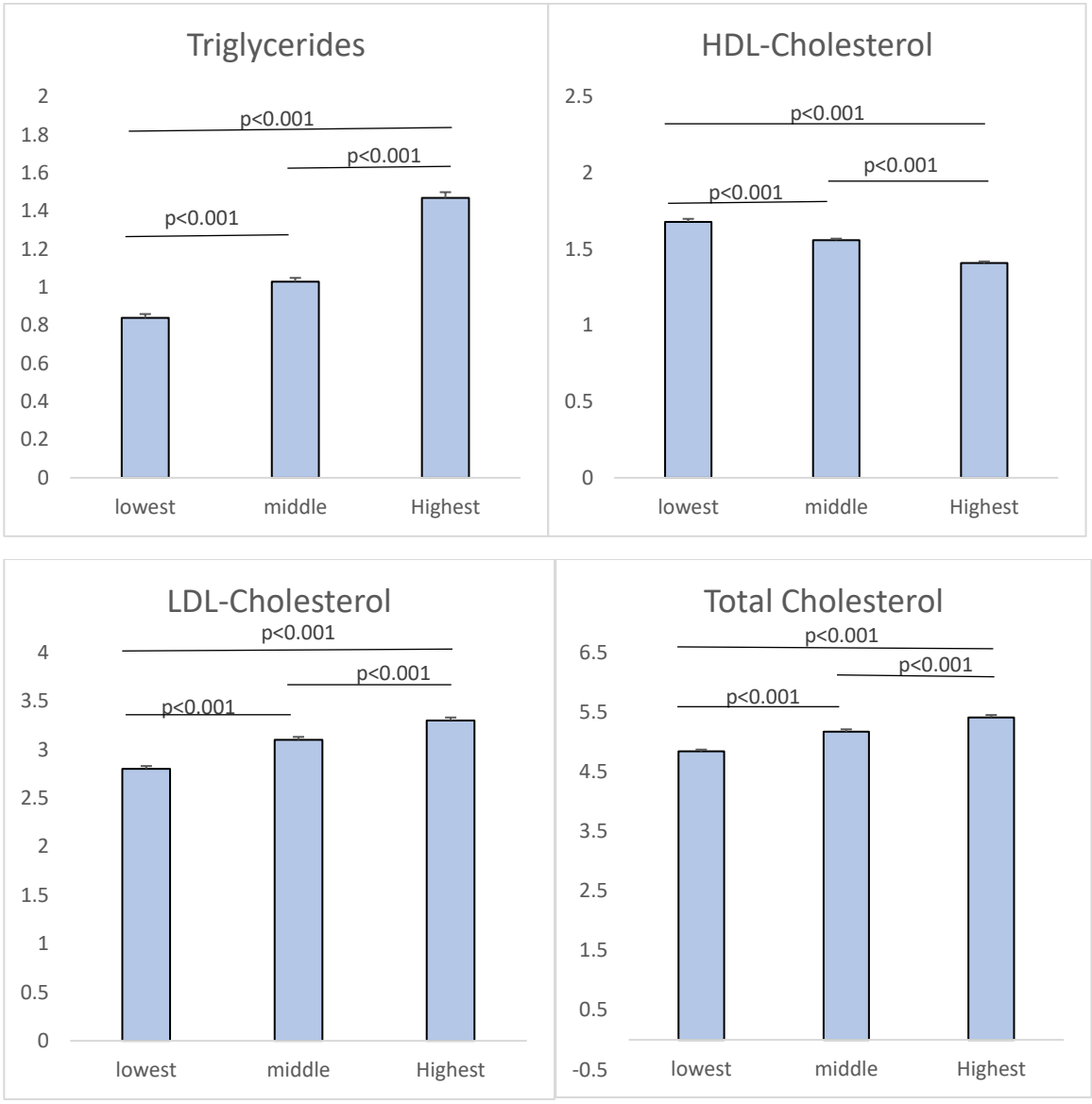
	A:G Ratio Top Quartile Mean ± SD n=235	Control Mean ± SD n=235
Age	50.8 ± 9.2	49.3 ± 9.0
Min-max	24-76	20-70
Height (cm)	161.2 ± 5.5	162.0 ± 6.3
Min-max	135-179	140-187
Weight (kg)	80.1 ± 14.9	80.9 ± 16.1
Min-max	53-132	52-130
BMI (kg/m^2)	30.8 ± 5.4	30.8 ± 5.4
Min-max	19-48	19-48
BF%*	42.0 ± 5.7	43.4 ± 6.0
Min-max	25-59	22-58
GF%*	44.0 ± 6.8	49.6 ± 5.7
Min-Max	22-62	28-63
AF%*	52.9 ± 5.9	50.6 ± 6.9
Min-max	32-66	28-64
A:G Ratio*	0.71 ± 0.09	0.49 ± 0.08
Min-max	0.61-1.02	0.23-0.60
VF%*	24.15± 1.3	2.76 ± 1.3
Min-max	0.15-8.11	0.04-14.7

*Mean ± standard deviation (SD), (Maximum – Minimum), BMI–Body mass index, BF% Total Percent body fat, GF%- Percent Gynoid Fat, AF%-Percent android fat, A:G Ratio-Android:Gynoid Fat Ratio VF%-Percent VF,



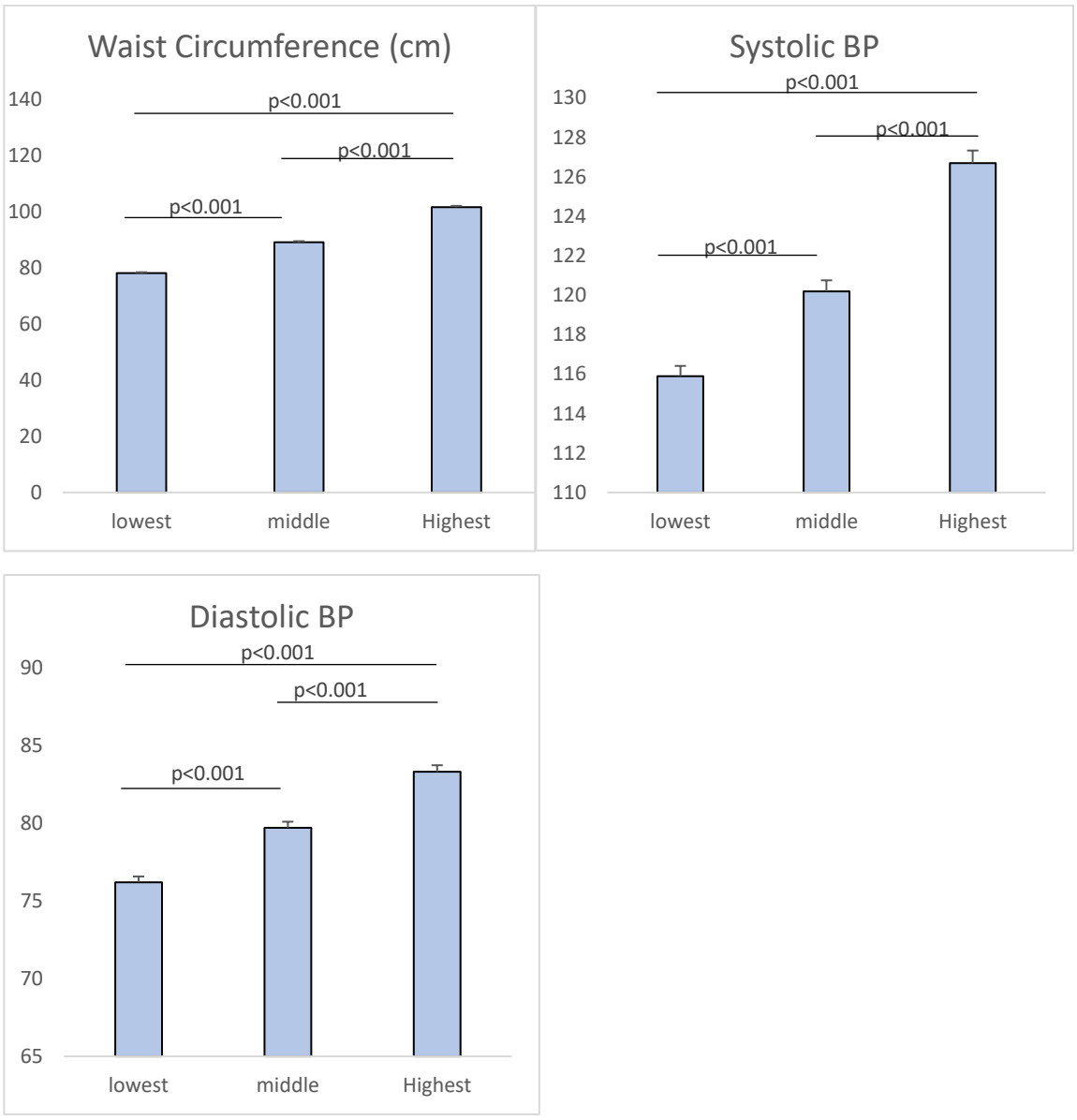
*p < or = 0.05 indicates statistical significance, Homeostatic Model of Assessment-Insulin Resistance – HOMA-IR, Homeostatic Model of Assessment-Beta Cell – HOMA-β

Figure 4-1 Comparison of Insulin Resistance Between AGR Tertiles



*p < or = 0.05 indicates statistical significance, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein

Figure 4-2 Comparison of Lipid Profiles Between AGR Tertiles



*p < or = 0.05 indicates statistical significance, BP – Blood Pressure

Figure 4-3 Comparison of Waist Circumference and Blood Pressure Between AGR Tertiles

Table 4-3 Comparison of Metabolic Markers Between AGR Top Quartile and BMI, Age Matched Control Group

	AGR ratio Top Q	Control
	n=235	n=235
Insulin*	98.5	75.7
HOMA-IR*	3.61	2.61
HOMA-β	153.9	137.3
Glucose*	5.56	5.25
TG*	1.67	1.25
HDL*	1.34	1.45
LDL	3.42	3.29
TC *	5.56	5.34
SBP*	130	125.5
DBP	84.4	83.6

*p<0.05, TG=triglycerides, HDL-High density lipoprotein
LDL -Low density lipoprotein, TC-Total cholesterol
SBP-Systolic blood pressure, DBP-Diastolic blood pressure

4.4 Discussion

Obesity is defined as a chronic condition characterized by excessive body fat which can lead to poor health outcomes and the specific way in which excess fat is distributed throughout an individual's body is more telling of current and future health risks [58-60]. Gynoid or "pear shaped" obesity which is often observed in women is frequently associated with a decreased risk of CVD and other co-morbidities, however, some women also develop android or "apple shaped" obesity which is more prevalent among men [61-64]. While many studies have made efforts to better understand the effects of android obesity in women, there are still gaps in our knowledge that have not been properly addressed. An investigation of a comprehensive panel of metabolic characteristics in a large general population, including all those necessary for the diagnosis of MetS, would significantly advance the understanding of the consequences that upper body obesity plays in the health and well-being of women. Furthermore, performing a study of this nature with the use of advanced imaging technology which we have done using DXA scanning, would add another layer of accuracy to such findings.

We analyzed a wide range of metabolic and physical characteristics of over 2000 women from the general NL population and obtained detailed x-ray images of each participant to assess body fat distribution, VF included. Our primary finding from this investigation was that MetS risk was 2.4x higher in a group of 235 women exhibiting android obesity when compared to 235 BMI matched women of similar age ($p<0.001$, 95% CI 1.64-3.46) However, after controlling for VF percent, the differences between these groups for all other metabolic markers was no longer significant. This is contrary to other findings that

suggest subcutaneous fat stores have more of an impact on metabolic health than VF stores [65]. While there are numerous studies in other populations, including a small sample of normal weight women (n=22) and the elderly, that have found android fat to be independently associated with both insulin resistance and MetS [7, 24], these studies were not able to control for VF mass or percentage. A significantly larger study of a healthy cohort (n=3399) has also noted the relationship between abdominal obesity and insulin resistance in women, however, this was an association study and no direct comparisons were made between women exhibiting android obesity or gynoid obesity [66]. Another past study found that the difference between metabolically healthy and unhealthy obese women was largely due to VF mass with abdominal subcutaneous fat playing no significant role [67]. While it is possible that subcutaneous fat stores may contribute to metabolic disturbance, many studies simply do not have the means of accurately measuring VF and therefore unable to control for it. Trunk and android fat regions exhibit very strong correlations with VF which may, at least partially explain why they are often observed to have such strong independent associations with various metabolic markers. Our findings suggest that, while acknowledging the role of subcutaneous fat in metabolism, VF appears to account for much of the variance observed in insulin resistance and lipid profiles between individuals with different patterns of body fat distribution. This is in agreement with a recently published longitudinal study on 1964 subjects from a healthy Asian population which included a 5 year follow up, that found that VF was significantly associated with the incidence of MetS but subcutaneous fat was not [68]. Other investigations have suggested that MetS risk, was modified by both

subcutaneous abdominal fat and VF stores according to the ATP III criteria, however, this was in a sample of elderly men and women aged 70-79 [69]. The lack of significant difference we observed in some markers such as LDL and TC lines up with past research as a study on aerobic fitness and metabolic characteristics in women found that these two same measures exhibited no relationship with aerobic health [70]. It is possible that changes in LDL and TC are simply less sensitive to differences in subcutaneous BFD and environmental factors and perhaps are more attributable to genetic variation or VF mass. To the best of our knowledge, this marks the first time such a complete panel of metabolic and anthropometric characteristics have been compared between women from a general population measured using DXA scanning. Our results support the recommendation of an increased focus on an individual's VF stores when assessing health risks and further emphasis on actions to decrease VF in women as it can have serious long-term impacts on their well-being.

There were several additional findings also yielded by this study. A comparison of women grouped by tertiles for AGR revealed that, while all groups were significantly different from one another for most markers, only the top tertile was significantly higher than the two bottom tertiles for measures of insulin resistance, HOMA-IR, and HOMA-β. HOMA measures were not significantly different between the bottom and middle tertiles. Lipid profiles worsened as android fat increased which was to be expected, however, the fact that HOMA measures did not differ significantly between the lowest and middle tertile may suggest that only in the most abdominally obese women do the effects of

obesity on insulin sensitivity considerably worsen. These findings concur with past studies on the relationship between abdominal fat with insulin resistance and lipid profiles [70, 71]. Interestingly, measures of insulin resistance did not significantly worsen between the lowest and middle tertile while LDL and TC levels did. One study found that increased LDL levels interact with abdominal obesity to exasperate insulin resistance and diabetes risk [72]. Many clinicians still opt to use BMI to assess an individual's risk of CVD but based on these findings, it may be in a patient's best interest to have a more in-depth analysis of overall body shape, how they can carry excess weight, and as previously noted, VF percentage.

Overall, we have accomplished our goal of improving our understanding of the effects of android obesity and BFD on the health of women from a general population, but our study was still subject to some limitations. Our BMI matched sub-group was only 470 women since some of the most severely centrally obese women had to be excluded as there BMI reached into the '40s and no control match was available in our population. While AGR exhibits strong correlations with MetS and many of the markers we studied, the android region does not include the entirety of upper body fat such as the arms and upper portion of the torso which may also be responsible for free fatty acid contribution in circulation and subsequent metabolic disturbance. While the goal of our study was to investigate the body type specific to excess android fat accumulation, future studies may benefit from using total upper body fat to total lower body fat ratio. It may also be of interest to examine a wider range of biomarkers using a similar study design, including

inflammatory cytokines and appetite hormones. A study measuring metabolic characteristics between women with android or gynoid obesity before and after an exercise intervention could also further elucidate the connection between metabolic characteristics in relation to BFD.

This comparative study of specific BFD patterns in women has succeeded in highlighting some of the important metabolic implications and health risks in women with excessive android fat or “apple shaped” obesity in participants from a general population, although our findings suggest that this may be more so attributed to the strong correlation between “apple shaped” BFD and VF. It is the first to study a full-scale panel of metabolic and anthropometric characteristics in a general population, including all those necessary for the diagnosis of MetS with the added accuracy of DXA scanning. This study strengthens the proposal that the use of BFD measures and tools such as DXA or MRI capable of generating highly accurate data regarding fat stores would be more beneficial to individuals than simply relying on BMI. As noted in this study, women with similar BMIs can have vastly different health outcomes, especially as it pertains to MetS and therefore, CVD and diabetes risk. The information produced by this research is especially beneficial to the women of Newfoundland and Labrador, who, as previously noted exhibit a high rate of obesity and obesity comorbidities [2, 73, 74]. This research reaffirms the urgent need for more detailed assessments of obesity, BFD, and VF measurements in women so that clinicians and public health workers can better prioritize resources to those most at risk and hopefully decrease the prevalence of the metabolic disease in this Province.

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5

Chapter 5. Conclusions, Limitations and Future Directions

5.1 Discussion

The rate of obesity has rapidly soared over the last 30 years and it is predicted that it will continue to increase for the foreseeable future. Given the impact the obesity epidemic is having on the health and quality of life of so many people, combined with the immense economic burden due to healthcare expenditure and lost working hours, it is vital that we increase our understanding of obesity etiology. There is growing evidence concerning the role of addictive eating tendencies as a contributing factor to obesity and obesity-related comorbidities such as T2D. The goal of this thesis was, primarily, to investigate the association of FA and its symptoms with various forms of obesity defined by certain BFD patterns as well as the metabolic consequences of FA. The secondary objective was to better quantify the impact of BFD, specifically android fat, on metabolism and MetS risk in adult women. This would provide an improved understanding of how addictive eating behaviours contribute to android adiposity and the health outcomes of this particular BFD pattern.

My thesis consists of three manuscripts that explore the role of FA in BFD and metabolic health. The role of BFD in metabolic health is expanded upon in a subsequent manuscript on android obesity in women. To the best of my knowledge, all studies are the first of their kind and all findings are unique.

In the first manuscript titled “The Association Between an Addictive Tendency Towards Food and Metabolic Characteristics in the General NL Population” we found that, in adult men, YFAS symptom counts were significantly associated with HOMA-β, TG and

inversely associated with HDL. Amongst women, those who were pre-menopausal exhibited no significant correlation between YFAS symptoms and metabolic characteristics while post-menopausal women displayed a significant association between YFAS symptoms and TG. Additionally, a comparison of age and BMI matched individuals with food addiction revealed that males with food addiction had significantly lower HDL levels than females with food addiction. This would suggest that men may be subject to a greater risk of metabolic disturbance as a result of addictive eating behaviours. The reason for this is yet to be discovered but it may be at least partly attributable to common BFD differences between men and women. Men's propensity to accumulate VF and women's tendency to accumulate gynoid fat, which may exert protective effects, might account for some of the sex-related differences observed in this study. BFD distribution may also partially explain differences observed between pre and post-menopausal women, as post-menopausal women tend to have lower levels of estrogen which can lead to greater fat accumulation in the android region and VF stores. There is very little comparable research in this regard. One of the few other studies to even investigate the correlation between YFAS symptoms and metabolic markers compared a group of individuals with T2D to a healthy control group. They reported that those who met the criteria for FA had less favourable metabolic characteristics such as higher glucose levels, higher TG, and lower HDL. We observed that YFAS symptoms were correlated with similar variables in our general population so the report that FA is more common among those with T2D is consistent with our findings. This group did not examine the correlation for all of these variables with YFAS symptom scores. This group

also analyzed all men and women together, so they were unable to observe any differences due to the sex of their participants and they did not adjust for body fat percentage as we did [193].

Our findings would suggest that a holistic approach to treating obesity or diabetes should account for individuals eating behaviours as addictive eating behaviours may make it more difficult to follow dietary guidelines that might improve health, thereby worsening the condition.

Based on the findings from the study mentioned above and the suggestion that the sex and menopausal related differences that were observed may be partially mediated by BFD, my next paper investigated the association between YFAS symptom counts and various measures of BFD in men and women of a general NL population. We reported that both men and women shared highly significant correlations between YFAS scores with a number of BFD measures including trunk fat, android fat, gynoid fat, and VF stores. Correlation coefficients did not differ much across the board with the exception of gynoid fat mass (women: r=0.30, men: r=0.23) and gynoid fat percent (women: r=0.24, men: r=0.15). We also performed a comparative analysis of FAO, NFO, and a control group, matched for sex. This revealed no significant difference in the BFD measures between the FAO and NFO group. FA remains far more prevalent among obese individuals and our analysis revealed that, even after controlling for sex, age, physical activity, and calories, symptoms of FA still account for a notable share of variance attributed to various body fat regions. For example, YFAS symptom counts accounted for 11.6% of the variance in

android fat in men and 10.9% of the variance in android fat in women. While there are several studies that report on the relationship between obesity status, BMI, and FA, very little research concerning the relationship between FA and regional BFD, particularly VF, is limited. One study, though limited in comparison to our cohort, investigated the relationship between VF and YFAS scores in a small group of young women [184]. While this study also demonstrated a significant correlation between YFAS scores and BAI measured VF, it was only performed in a group of 93 women with an average age of 24. Much more research is needed in this regard in far more populations consisting of different ethnicities and nationalities to confirm whether the relationship between FA and VF holds true for cohorts that may have vastly different diets.

These findings support the previously stated premise, that the protective effects of gynoid fat in women, may also somewhat mitigate the metabolic effects of addictive eating tendencies. Also, screening for FA or YFAS symptoms in individuals seeking obesity treatment and dealing with these addictive symptoms appropriately rather than the consequences of them could prove beneficial to the patient.

The final manuscript of my thesis explores the relationship between android adiposity in women, performing a direct comparison between adult women with varying degrees of android fat percent. This study was comprised of 2323 women who were first divided into tertiles based on AGR. This revealed that women in the lowest, middle, and top tertile of AGR differed significantly in levels of insulin, glucose, TG, HDL, LDL, TC, systolic BP, diastolic BP, and of course WC. There was also a significant difference between the

highest tertile and the bottom two tertiles for HOMA-IR and HOMA-β. An additional comparison of women from the top DGR quartile with a BMI and age-matched control group revealed that women of similar age and BMI were 2.4x more likely to have MetS if they carried higher levels of android fat, independent of VF. The relationship between AGR ratio and metabolic markers has been investigated by other groups as well. A study that consisted of 685 women with an average age of 35 reported that in women, AGR was significantly correlated with fasting glucose, TG, and negatively correlated with HDL [94]. While this study also employed the use of DXA, VF was not accounted for. Another study which consisted of 10,770 women and 8324 men investigated the relationship between MetS and BFD. This study used BAI as a means of measuring body composition and WHR as an index of AGR. While WHR was associated with an increased risk of MetS at a level body of body fat between 20% and 40% in each sex, the impact of WHR on the relationship between body fat and MetS was much more pronounced in women [254]. Again, this study was unable to measure and control for VF and WHR has many limitations which have been discussed so while it does highlight the importance of BFD as a factor of MetS, particularly among women, conclusions should be made cautiously.

Our findings suggest that android adiposity alone can be indicative of serious metabolic disorders in women and reinforce the need for thorough assessments of women's BFD, as opposed to relying solely on BMI, to evaluate their risk of developing metabolic issues such as CVD and T2D. The accurate measurement of VF is not obtainable for many researchers and among those with DXA scanners, the ability of DXA to produce accurate

measurements of VF is still somewhat new. Hopefully, in the coming years, those with the requisite technology will produce more research on the importance of BFD and health outcomes while being able to discern whether visceral or subcutaneous fat stores are the risk factor.

In conclusion, this thesis provides new insights into the role of FA and FA symptoms as a contributing factor to obesity, especially central obesity and metabolic disturbance in an otherwise healthy general population. It also serves to better quantify the importance of BFD in metabolic health in adult women. The major strengths of this thesis include the large sample of individuals from a general population used for each manuscript, the use of advanced imaging technology (i.e. DXA), and the large amount of behavioural, endocrine, and dietary data collected on each participant which allowed us to not only answer our initial research questions but control for important confounding factors as well.

5.2 Limitations

Despite the unique and interesting findings presented in this thesis, like all research efforts, certain limitations must be accounted for. While many of these limitations are discussed in each manuscript's discussion section, there are a few additional limitations that warrant mentioning or additional elaboration. First and foremost, this was a cross-sectional study, meaning all data collected and presented was based on each research volunteer's health or behaviours at their time of participation. This can make it difficult at times to establish a reliable cause and effect relation or the directionality of a relationship.

Another possible limitation was the substantially smaller sample size of men compared to women. We have observed that there are male-specific associations between FA, BFD, and metabolic characteristics but a larger group of men would certainly help in assessing the true magnitude of these sex-specific effects.

Finally, it is worth reiterating that data on food intake, physical activity, and eating behaviours are self-reported which is, of course, always somewhat vulnerable to self-reporting or possible re-call bias among our participants. Measuring physical activity by way of questionnaire may be the most practical means of measurement in large cohorts but it is not without its inadequacies. Physical activity levels can vary greatly based on the season or even the day of the week. These variations are not accounted for in the Baecke questionnaire and although this questionnaire can be useful for categorizing individuals and as active or inactive, it does not measure energy expenditure. While occupational activity may remain relatively constant for many people, leisure time and sports-related activity can vary greatly based on the time of year. For example, someone may spend more leisure time walking during the summer and far less during the winter or someone who participates in seasonal sports may be very active during that season only for physical activity to reduce significantly once the season is over. It is for these reasons that we must also be wary of recency bias when individuals are self-reporting physical activity levels (ex. physical activity levels may be underestimated if the questionnaire is completed during a particular sports offseason or vice versa). It has been reported that the Baecke questionnaire tends to exhibit more reliable for measuring actual energy

expenditure in men than women and is more likely to misclassify women's level of physical activity, particularly among older women as household chore related activity is not accounted for. It also appears to better assess high intensity and low intensity activity than moderate levels [255, 256]. Regarding the FFQ, it is worth mentioning that it deals with the frequency of consumption and not portion size. This can lead to a great deal of variability as an individual's portion sizes for some foods, whether it be pasta, rice, or snacks such as potato chips can be quite different. It can also lack accuracy among people or populations that regularly consume mixed dishes composed of many different types of ingredients.

5.3 Future Directions

The results generated from this research have opened the door to a number of future projects. Eventually converting the CODING study into a longitudinal, as opposed to a cross-sectional study, could help us better understand cause and effect relationships between the variables observed and observe how aging modifies some of these measures.

In the future, it would also be helpful to measure energy and appetite-regulating hormones in a greater number of individuals to evaluate their role in FA and metabolic health. If this data was available for all 3000+ CODING study participants we could conduct valuable research on the relationship of these hormones with sex, age, medication usage, obesity status, and many other variables. Additional data on other disordered eating behaviours as well as participant data on past or current substance abuse issues

could also go a long way in understanding FA and its place in the spectrum of substance abuse disorders and how well it fits the addiction model.

Appendix 1 Yale Food Addiction Scale

Yale Food Addiction Scale

Gearhardt, Corbin, Brownell, 2009
Contact: agearhar@umich.edu for scoring instructions

This survey asks about your eating habits in the past year. People sometimes have difficulty controlling their intake of certain foods such as:

- **Sweets like ice cream, chocolate, doughnuts, cookies, cake, candy, ice cream**
- **Starches like white bread, rolls, pasta, and rice**
- **Salty snacks like chips, pretzels, and crackers**
- **Fatty foods like steak, bacon, hamburgers, cheeseburgers, pizza, and French fries**
- **Sugary drinks like soda pop**

When the following questions ask about "CERTAIN FOODS" please think of ANY food similar to those listed in the food group or ANY OTHER foods you have had a problem with in the past year

IN THE PAST 12 MONTHS:	Never	Once a month	2-4 times a month	2-3 times a week	4 or more times or daily
1. I find that when I start eating certain foods, I end up eating much more than planned	0	1	2	3	4
2. I find myself continuing to consume certain foods even though I am no longer hungry	0	1	2	3	4
3. I eat to the point where I feel physically ill	0	1	2	3	4
4. Not eating certain types of food or cutting down on certain types of food is something I worry about	0	1	2	3	4
5. I spend a lot of time feeling sluggish or fatigued from overeating	0	1	2	3	4
6. I find myself constantly eating certain foods throughout the day	0	1	2	3	4
7. I find that when certain foods are not available, I will go out of my way to obtain them. For example, I will drive to the store to purchase certain foods even though I have other options available to me at home.	0	1	2	3	4
8. There have been times when I consumed certain foods so often or in such large quantities that I started to eat food instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.	0	1	2	3	4
9. There have been times when I consumed certain foods so often or in such large quantities that I spent time dealing with negative feelings from overeating instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.	0	1	2	3	4
10. There have been times when I avoided professional or social situations where certain foods were available, because I was afraid I would overeat.	0	1	2	3	4
11. There have been times when I avoided professional or social situations because I was not able to consume certain foods there.	0	1	2	3	4
12. I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I cut down or stopped eating certain foods. (Please do NOT include withdrawal symptoms caused by cutting down on caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)	0	1	2	3	4
13. I have consumed certain foods to prevent feelings of anxiety, agitation, or other physical symptoms that were developing. (Please do NOT include consumption of caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)	0	1	2	3	4
14. I have found that I have elevated desire for or urges to consume certain foods when I cut down or stop eating them.	0	1	2	3	4
15. My behavior with respect to food and eating causes significant distress.	0	1	2	3	4
16. I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of food and eating.	0	1	2	3	4

IN THE PAST 12 MONTHS:	NO	YES
17. My food consumption has caused significant psychological problems such as depression, anxiety, self-loathing, or guilt.	0	1
18. My food consumption has caused significant physical problems or made a physical problem worse.	0	1
19. I kept consuming the same types of food or the same amount of food even though I was having emotional and/or physical problems.	0	1
20. Over time, I have found that I need to eat more and more to get the feeling I want, such as reduced negative emotions or increased pleasure.	0	1
21. I have found that eating the same amount of food does not reduce my negative emotions or increase pleasurable feelings the way it used to.	0	1
22. I want to cut down or stop eating certain kinds of food.	0	1
23. I have tried to cut down or stop eating certain kinds of food.	0	1
24. I have been successful at cutting down or not eating these kinds of food	0	1

25. How many times in the past year did you try to cut down or stop eating certain foods altogether?	1 time	2 times	3 times	4 times	5 or more times

26. Please circle ALL of the following foods you have problems with:

Ice cream	Chocolate	Apples	Doughnuts	Broccoli	Cookies	Cake	Candy
White Bread	Rolls	Lettuce	Pasta	Strawberries	Rice	Crackers	Chips
Pretzels	French Fries	Carrots	Steak	Bananas	Bacon	Hamburgers	Cheese burgers
Pizza	Soda Pop	None of the above					

27. Please list any other foods that you have problems with that were not previously listed:

Appendix 2 Baecke Physical Activity Questionnaire

Physical Activity Form

Date: (/ /2005) (day/month/year)

Identification # = |__|__|__|__|__|__|

Name: Family Middle First

Data Entry 1 Initial ☐ Data Entry 2 Initial ☐

To be completed by the participant.

Note This assessment instrument has been modified from the Physical Activity questionnaire used in the NIH supported Atherosclerosis Risk in Community study (ARIC).

Note **Blanks allowed on QS # 18, 22 only if No is checked for Qs # 17, 21.**

1. What is your main occupation?
2. At work I sit:

   never / seldom / sometimes / often / always
3. At work I stand:

   never / seldom / sometimes / often / always
4. At work I walk:

   never / seldom / sometimes / often / always
5. At work I lift heavy loads:

   never / seldom / sometimes / often / always
6. At work I am tired:

never / seldom / sometimes / often / always

7. At work I sweat:

never / seldom / sometimes / often / always

8. I n comparison with others of my own age I think my work is physically:

much heavier / heavier / as heavy / lighter / much lighter

9. Which sport or exercise do you do most recently?

10. How many hours a week do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 2
3 ☐ At least 2 but not quite 3
4 ☐ At least 3 but not quite 4
5 ☐ At least 4 but not quite 5

11. How many months a year do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 4
3 ☐ At least 4 but not quite 7
4 ☐ At least 7 up to and including 9
5 ☐ More than 9

12. Do you do other exercise or play other sports?

1 ☐ Yes 2 ☐ No

If NO, DO NOT COMPLETE QUESTIONS 13-23. CONTINUE WITH QUESTION 24.

13.What is your second most frequent exercise or sport?

14. How many hours a week do you do this activity or sport?

1 ☐ less than 1
2 ☐ At least 1 but not quite 2
3 ☐ At least 2 but not quite 3
4 ☐ At least 3 but not quite 4
5 ☐ At least 3 but not quite 4

15. How many months a year do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 4
3 ☐ At least 4 but not quite 7
4 ☐ At least 7 up to and including 9
5 ☐ More than 9

16. Do you do other exercise or play other sports?

1 ☐ Yes 2 ☐ No

IF NO, DO NOT COMPLETE QUESTIONS 17-23. CONTINUE WITH QUESTION 24.

17. What is third most frequent exercise or sport?

18. How many hours a week do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 2
3 ☐ At least 2 but not quite 3
4 ☐ At least 3 but not quite 4
5 ☐ At least 3 but not quite 4

19. How many months a year do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 4
3 ☐ At least 4 but not quite 7
4 ☐ At least 7 up to and including 9
5 ☐ More than 9

20. Do you do other exercise or play other sports?

1 ☐ Yes 2 ☐ No

IF NO, DO NOT COMPLETE QUESTIONS 21-23. CONTINUE WITH QUESTION 24.

21. What is your fourth most frequent exercise or sport?

22. How many hours a week do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 2
3 ☐ At least 2 but not quite 3
4 ☐ At least 3 but not quite 4
5 ☐ At least 3 but not quite 4

23. How many months a year do you do this activity?

1 ☐ less than 1
2 ☐ At least 1 but not quite 4
3 ☐ At least 4 but not quite
4 ☐ At least 7 up to and including 9
5 ☐ More than 9

24. In comparison with others of my own age, I think my physical activity during leisure time is:

1 ☐ Much less
2 ☐ Less
3 ☐ The same
4 ☐ More
5 ☐ Much more

25. During leisure time, I sweat:

1 ☐ Never
2 ☐ Seldom
3 ☐ Sometimes
4 ☐ Often
5 ☐ Very often

26. During leisure time, I play sports or exercise:

1 ☐ Never
2 ☐ Seldom
3 ☐ Sometimes
4 ☐ Often
5 ☐ Very often

27. During leisure time, I watch television:

1 ☐ Never
2 ☐ Seldom
3 ☐ Sometimes
4 ☐ Often
5 ☐ Very often

28. During leisure time, I walk:

1 ☐ Never
2 ☐ Seldom
3 ☐ Sometimes
4 ☐ Often
5 ☐ Very often

29. During leisure time, I bike:

1 ☐ Never
2 ☐ Seldom
3 ☐ Sometimes
4 ☐ Often
5 ☐ Very often

30. How many minutes do you walk and/or bike to and from work?

1 ☐ less than 5
2 ☐ At least 5 but not quite 15
3 ☐ At least 15 but not quite 30
4 ☐ At least 30 up to and including 45
5 ☐ 45 or more

Appendix 3 Manuscripts Published and Prepared During Masters

1. **Matthew Nelder**, Farrell Cahill, Hongwei Zhang, Guangju Zhai, Wayne Gulliver, Weiping Teng, Zhongyan Shan, Guang Sun
The Association Between an Addictive Tendency Towards Food and Metabolic Characteristics in the General Newfoundland Population
Published in *Frontiers in Endocrinology* Nov.9, 2018
https://doi.org/10.3389/fendo.2018.00661

2. **Matthew Nelder**, Farrell Cahill, Hongwei Zhang, Guangju Zhai, Wayne Gulliver, Michael Wahl, Weiping Teng, Zhongyan Shan, Guang Sun
The Association between an Addictive Tendency Toward Food and Fat Distribution in Men and Women of the General Newfoundland & Labrador Population
In Submission

3. **Matthew Nelder**, Hongwei Zhang, Guang Sun
The Comparison of Metabolic Characteristics Between Women With and Without Android Obesity from a General Newfoundland Population
In Progress

4. Sherif Youssef, **Matthew Nelder**, Guang Sun
Association of Upper Body Obesity with Insulin Resistance in the Newfoundland Population
In Submission

Appendix 4 Published Conference Abstracts and Presentations During Masters

Oral Presentations

1. **Matthew Nelder**, Hongwei Zhang, Guang Sun

The Comparison of Metabolic Characteristics Between Women With and Without Android Obesity from a General Newfoundland Population

6th Canadians Obesity Student Meeting, June 20-22, 2018 London, On. Canada

Poster Presentations

1. **Matthew Nelder**, Farrell Cahill, Hongwei Zhang1, Guangju Zhai, Wayne Gulliver, Weiping Teng, Zhongyan Shan, Guang Sun

The Association between Food Addiction and Body Fat Distribution in Men and Women of the General Newfoundland Population

The 34th Annual Scientific Meeting of The Obesity Society & the 4th Annual ObesityWeek Event. October 31-November 4, 2016, New Orleans, LA, USA

2. Farrell Cahill, Tara Reilly, Mike Wahl, Fabien A. Basset, Jason Blair, Joseph Whitten, **Matthew Nelder**, Adebayo Adeboye, Michael Browne, Guang Sun, and Edward Randell

Physical Employment Standard (PES) Development Study: Measurement of the Physical Demand for Self-Evacuation Aboard an Offshore Oil and Gas Installation

International Conference of Physical Employment Standards, July 17-19, Portsmouth UK

3. **Matthew Nelder**, Farrell Cahill, Hongwei Zhang1, Guangju Zhai, Wayne Gulliver, Weiping Teng, Zhongyan Shan, Guang Sun

The Association Between an Addictive Tendency Towards Food and Metabolic Characteristics in the General Newfoundland Population

The 36th Annual Scientific Meeting of The Obesity Society & the 6th Annual ObesityWeek Event. November 11-15, 2018, Nashville, TN, USA

4. Sherif Youssef, **Matthew Nelder**, Guang Sun

Association of Upper Body Obesity with Insulin Resistance in the Newfoundland Population

The 36th Annual Scientific Meeting of The Obesity Society & the 6th Annual ObesityWeek Event. November 11-15, 2018, Nashville, TN, USA

Appendix 5 Awards During Masters

1. Top Oral Presentation for Masters Student
The Comparison of Metabolic Characteristics Between Women With and Without Android Obesity from a General Newfoundland Population
6th Canadian Obesity Student Meeting, June 20-22, 2018 London, On. Canada

2. Obesity Week Obesity Canada Student Travel Award
The Association Between an Addictive Tendency Towards Food and Metabolic Characteristics in the General Newfoundland Population
The 36th Annual Scientific Meeting of The Obesity Society & the 6th Annual ObesityWeek Event. November 11-15, 2018, Nashville, TN, USA