A longitudinal study of fat mass accrual from adolescence through to emerging adulthood and its impact on cardiometabolic risk later in life

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Abstract

Overweight and obesity (OWO), specifically abdominal obesity, are linked with cardiovascular and metabolic disease risk (CMR) at every stage of life. The prevalence of OWO nearly doubles in Canadians between childhood/adolescence and adulthood, suggesting that normal weight (NW) status is not stable through the life course and that there is a period in adulthood when fat mass (FM) increases. Emerging adulthood (EA; 18-25 years) has been identified as a potential critical period when FM accrues, the degree to which is potentially influenced by childhood and adolescence FM accrual. EA is also a period which favors trunk fat depots and when CMR likely commences or increases from child and adolescent levels. However, there is a paucity of longitudinal data describing the patterns and predictors of FM accrual during EA. Furthermore, there is also a lack of information showing how EA fat mass trajectories relate to adult cardiometabolic health. Thus, the primary purpose of this thesis is to describe patterns and predictors of total body fat (TBF) and trunk fat (TrF) mass accrual and OWO status in EA. The second purpose is to identify if trajectories of FM accrual in EA influence later adult CMR. The thesis will also explore sex differences.

In study 1, 126 participants (59 male) were drawn from the Pediatric Bone Mineral Accrual Study (PBMAS) (1991-2011). Participants of the PBMAS were aged 8 to 15 years at the initial measurement. Serial measures of participants included chronological age (CA), biological age (BA - years from peak height velocity (PHV)), body mass index (BMI), and percent total body fat (%TBF). Study 1 is divided into two papers - 1a and 1b. The results from paper 1a based on this study indicated that fat mass increased from PHV into EA. At PHV, 9% of males and 14% of females were OWO by BMI, rising to 65% and 32%, respectively, 15 years after PHV (approximately 27 years in females, and 29 years in males). The prevalence of OWO by

%TBF, increased from 29% to 45% in males, and from 33% to 59% in females over the same period. Differences in values of %TBF and BMI at PHV between those identified as NW had disappeared by 19-22 years ($p>0.05$) (i.e. fat mass between NW and OWO youth became more similar with age). OWO status at PHV did not predict OWO status during EA ($p<0.05$). These results indicate that EA appears to be a major period of transition from NW to OWO status. In addition, sex and FM metrics showed differences in ages when NW individuals became OWO.

Study 1 also attempted to address the potential discrepancy in OWO identification and age at onset of OWO by different metrics in paper 1b, using the same PBMAS cohort. Longitudinal measures, including anthropometrics and dual x-ray absorptiometry from 1991-2017 were used to create hierarchical random effects models. Coefficients from the models were then used to develop growth curves, and these were compared to known cut-points. The age at onset of OWO was considered that age at which the predicted line crossed metric specific cut-offs. Age at onset of OWO in males was identified as 23.5 years by BMI and 21.5 years for % fat mass (%FM). Waist circumference (WC) cut-offs for OWO classification were not reached by 39 years. In females, onset was at 22.5 years by BMI, 15 years by %FM and 33.5 years by WC. Cut-points for BMI failed to identify 21.4% of OWO males and 56% of OWO females identified by %FM. The discrepancy in age at OWO between measures suggests that the most conservative indicator of age at onset is sex specific. BMI identifies OWO in males sooner than %FM. The opposite is true in females; however, BMI likely misses "over fatness" - more in females. WC may not be as appropriate for indicating risk in young adults and youth as in older adults.

Using the same participants identified in study 1, study 2 created longitudinal models of fat accrual during EA and beyond (18 to 30 years of age) and identified concurrent and childhood/adolescent predictors of FM accrual, including measures of physical activity (PA) and

energy intake (EI). It was found that childhood and adolescent TBF and TrF (0.30 ± 0.05, $p<0.05$) predicted EA accrual in both sexes and that concurrent PA (-0.06 ± 0.02, $p<0.05$) was significant in males only. These results underscored the importance of maintaining lower amounts of TBF and TrF mass during childhood and adolescence, and maintaining high level of PA in EA in order to mitigate TBF and TrF mass accrual and reduce the risk of transitioning from NW to OWO during EA.

In study 3 (1991-2017) participants of the PBMAS, now aged 32 to 40 years of age, were invited back for reassessment. Blood analysis was used to create a Continuous Cardiometabolic Risk (conCMR) score for each participant. Multi-level models of TrF and TBF accrual were created looking at the same predictors as study 2, with the addition of cardiometabolic risk (CMR) group. Childhood TBF and TrF z-scores were again found to be the most significant predictor of TBF and TrF accrual, this time from 18-39 years. PA was also significant. CMR group did not influence the trajectory of TBF or TrF accrual, potentially due to the homogeneity of the group and the small sample size.

In conclusion it was found that FM continues to increase steadily from late adolescence through EA leading to a marked increase in the prevalence of OWO in young adulthood. Greater trajectories during EA are related to higher levels of FM accrual in childhood and adolescence, and higher scores on individual CMR factors in later adulthood. The results suggest that maintaining high levels of PA throughout the life span is beneficial to adult health directly and through its mitigating effect on FM accrual in EA, and indirectly by limiting FM accumulation in childhood and adolescence.

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LIST OF ABBREVIATIONS

BMI - Body Mass Index (kg/m2)

BW - Birth Weight

CDC - Center for Disease Control

CMR - Cardiometabolic Risk

Con CMR - Continuous Cardiometabolic Risk

CVD - Cardiovascular Disease

DXA - Dual X-ray Absorptiometry

EA - Emerging Adulthood

EI - Energy Intake

FFM - Fat Free Mass

FM - Fat Mass

IOTF - International Obesity Task Force

LM - Lean Mass

MetS - Metabolic Syndrome

NW - Normal Weight

OB - Obesity

OW - Overweight

OWO - Overweight/Obese

PA - Physical Activity

PHV - Peak Height Velocity

SES - Socioeconomic status

%TBF - Percent Total Body Fat

TBF - Total Body Fat

TrF - Trunk Fat

WC - Waist Circumference

WHO - World Health Organization

Acknowledgments

Four years ago I began the academic endeavor of completing my PhD. I was unsure of the processes, of my study topic and even of my own capabilities. I would likely have given up, or at the very least struggled substantially to complete this journey without the support of my supervisor, Dr. Adam Baxter-Jones. Adam, you did not hold my hand through every step or coddle me, but rather encouraged me to take initiative, to find my own way, and to explore my own passion for research. You believed in me and helped me believe in myself by giving me the reins to my project and trusting me to do a good job. You were never overly verbose but always provided me with enough feedback and encouragement to push me forward and to find my academic independence. It was exactly what I needed. Thank you also for your super power of cutting word counts and taking my excessive loquaciousness (is that word pedantic enough for you ;) and making it succinct. I feel privileged to have had you as my supervisor. Thank you also to my committee members Drs. Marta Erlandson, Heather Foulds, and Nazeem Muhajarine for your advice and valuable feedback throughout this process. I would also like to express an extra bit of gratitude to Dr. Marta Erlandson. I have appreciated your warmth and willingness to chat with me about direction, goals, and advice pertaining to my larger academic journey.

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Dedication

This PhD dissertation, and all the time, effort, stress, and tears that have gone into it are dedicated to my family.

To my mom and dad in-law, thank you for understanding and for supporting my desire to return to school. You were always available to watch the boys and, more than that, I did not have to worry or feel guilt when I was away from them. I knew they were so deeply loved and cared for while I was away from them. This was the greatest support you could have offered me. Thank you.

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Finally and most importantly, thank you to my husband Brad and my boys Jack, Sawyer and Knox. Boys, you did not sign up for a mom that was stressed out over exams and assignments, deadlines and defenses but you have put up with it like champs. I do all that I do for you - well, almost. I hope that I have role-modeled the importance of pursuing your dreams, and the irreplaceable value of family who will be your greatest allies. You are my heart forever. Brad, what can I say to fully express how grateful I am to you and how incredibly privileged and lucky I feel to have you by my side as my partner for life. This entire endeavor would have failed miserably without your unyielding love, encouragement, support and affirmation. You changed your idea of what our life was going to look like and took on so many different roles than you had originally planned to enable me to get to this place. Thank you. This past decade has been quite the ride and I hope for much, much more of the same.

CHAPTER 1

INTRODUCTION AND RESEARCH AIMS

1.1 *INTRODUCTION*

Canadian rates of obesity have more than doubled over the past 40 years. Almost 1 in 4 Canadian adults have obesity, 1 in 7 youth (5-17 years) have obesity and 1 in 3 youth have overweight or obesity (OWO) (1–3). OWO in adults, adolescents and children correlates with several chronic diseases including coronary heart disease and type II diabetes, as well as to risk factors for these diseases such as hypertension, dyslipidemia, and insulin resistance (4–7) . While some data suggests a plateau of combined OWO rates in the last decade, obesity remains a major Canadian public health concern. Still more concerning are the rates of abdominal obesity which demonstrate a stronger relationship with health consequences than total body obesity in diverse age groups (8–10). Between 1981 and 2007/09, the prevalence of abdominal obesity in Canada rose from approximately 11% to 37% in adults and from 2% to 13% in adolescents (12-19 years) (3,11). Youth rates (children and adolescents) of OWO warrant extra attention as fat mass (FM) accumulated by adolescence is often retained into adulthood, and the cardiovascular disease (CVD) risk associated with OWO is cumulative (8,12,13).

Alterations to the normal growth and development processes during critical periods can result in permanent change to systems and organs, or entrain future form, function or dysfunction (14). Critical periods associated with FM accrual include: intrauterine growth, indexed by birth

weight (BW); post-natal growth; the period of adiposity rebound in early childhood; and the peri-pubertal period or adolescence (14–16). There has been a large amount of attention placed on preventing OWO during these critical periods, as having OWO at one period increases the risk of having OWO in subsequent periods or of transitioning upward from overweight to obese, or to a greater degree of obesity (17–21). Although the prevalence of overweight youth has dropped slightly over the past decade, the prevalence of obesity has remained high, despite a variety of available interventions and preventative programs (1–3,22–24). The most recent estimates of OWO from Statistics Canada (2015) suggest that 23% of 12 to 17-year-old Canadians have OWO. This number almost doubles to 42% in young adults (20-34 years) (25,26). Longitudinal data on Canadians from 1981 to 2002/04 show the same trend of increasing prevalence of OWO with age, as 85% of overweight adults were NW youth (27). Combining these two pieces of evidence, the suggestion is that a large number of NW Canadian youth are at risk of accruing OWO adults and that onset occurs at some point between late adolescence and young adulthood. Thus the period of emerging adulthood (EA; 18 to 25 years) (28) appears to be another potential critical period for fat mass gain, onset of OWO and, by association, an increased CVD risk (28,29).

During EA, fat mass continues to accrue, the incidence of OWO increases and the likelihood of shifting from OWO to NW status is low (30,31). Although EA has not previously been considered a “critical” period for FM accrual, it may have a stronger and more permanent influence on later adult OWO status than the adolescent critical period, as the establishment of long-term health behaviors characterizes this period (28,32,33). Furthermore the stability of OWO increases with age; for example, body mass index (BMI) at 35 is strongly predicted by BMI at 18 years, but only moderately predicted by BMI at 13 years and younger (34). Increasing

BMI should be particularly concerning because of its strong correlation with %TBF (35,36); and its significant tracking coefficient (>0.7) over the period of EA (37); yet, there is little information on the factors that contribute to FM gains in EA (29,38).

The life course perspective suggests that an individual's health trajectory can be set by earlier exposure to beneficial or adverse circumstance (39). According to this approach to chronic disease, exposure to biological and socio-environmental factors at any stage of life can have long-term effects on health (40). It has been repeatedly demonstrated that rapid, early or excessive FM gains during critical periods entrains excess FM and obesity in later life (41–43); but the life course perspective also acknowledges that social environments and human agency can alter trajectories of FM and disease, and provide compensatory mechanisms for altered form or function (40,44). For example, poor intrauterine development may alter endocrine properties and increase the risk of future metabolic illness; but a social environment consisting of a healthy diet and regular activity can modify this disease trajectory and assist in the maintenance of health (33,45). Roughly two-thirds of Canadians become OWO by adulthood, having been NW youth (27), but the extent to which OWO in adulthood is predetermined by earlier life antecedents (such as low PA, high energy intake and high FM accrual) or personal health behaviors in EA is not clear. Furthermore, the implication of FM accrual and health behaviors during EA on future cardiometabolic health is unknown.

Cardiometabolic risk (CMR) is a term that refers to a comprehensive list of factors that contribute to the development and onset of cardiovascular disease and type II diabetes (46). These factors include elevated blood pressure, abdominal fat (above healthy waist circumference cut-offs), elevated triglycerides (TG), total cholesterol, insulin resistance (IR) and lowered high density lipoproteins (HDL). The presence of these risk factors often accompanies excess

adiposity which leads to inflammation of adipocytes (fat cells). Adiposopathy is the term given to inflamed "sick" fat cells (47). Metabolic syndrome (MetS) is the clustering of three or more CMR factors, the presence of which increase the overall lifetime risk of CVD (48). Adiposopathy is more likely to occur in association with elevated visceral and abdominal (trunk) body fat than with elevated subcutaneous or peripheral fat, respectively (47). In adults, lower PA, higher caloric intake and higher measures of adiposity demonstrate significant relationships with CMR levels (4,49–51). Although the occurrence of CVD and MetS are still rare in children and adolescents, CMR factors have been found, and these risk factors, similar to adults, correlate with higher total and central adiposity and lower PA (5,52). As such, the elevated CMR found in OWO adults may have origins associated with a lack of child/adolescent PA, poor child/adolescent diet and elevated child/adolescent FM (indexed by BMI); or low adult PA, adult diet and high adult FM.

The relationship between OWO and health status within each critical period of growth (and later periods) is complex. Predictors of adult weight and health status have been previously identified; some, such as predisposing genetics, are fixed, while other factors, such as lifestyle behaviors and the factors influencing those behaviors (i.e. social and environmental factors), are modifiable (53,54). Early lifestyle factors (diet and PA), rapid or early FM gains and pubertal timing are associated with child and adolescent obesity and CMR (8,22,55–57). These same childhood and adolescent factors are associated with adult obesity and cardiometabolic health, in addition to adult FM and adult lifestyle (58–61). In contrast, some data suggests that the link between child and adult obesity is reliant on tracking of weight status. Figure 1.1 illustrates the possible mechanisms linking factors across adolescence and adulthood. The complex relationship between factors is often bi-directional.

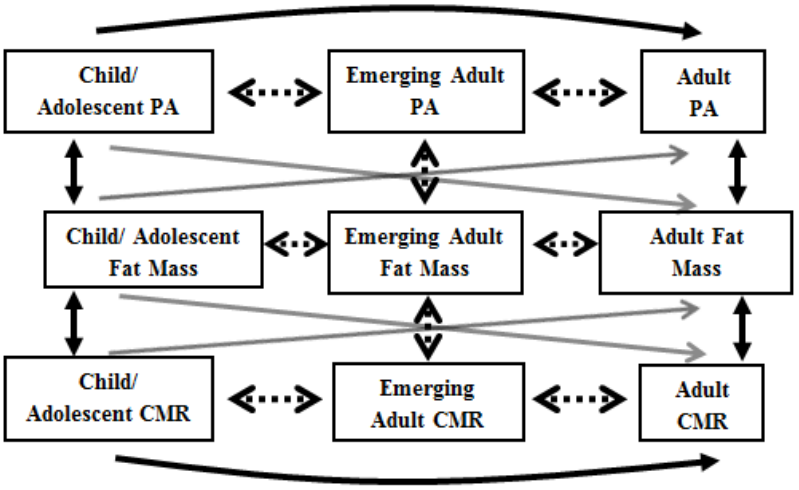

Figure 1.1 Schematic of possible relationships between PA, CMR and FM at each period. Solid black and grey lines represent associations with strong evidence. Dotted lines are less-studied associations that may represent intermediate steps in emerging adulthood

There is a lack of information about EA and how it may play a mediating role between adolescence and young adulthood. Insufficient data may be due to a lack of longitudinal data spanning the period from childhood to adulthood. Discrepant findings may be due to the method of defining OWO, as not all measures and cut-offs provide the same estimates, nor are all metrics equally accurate at representing FM (62–65) .

In adulthood, BMI is the most commonly used measure of OWO because it is non-invasive in nature, inexpensive, and accurate at high levels of FM; however, it has demonstrated lower specificity and sensitivity in identifying high levels of FM in youth with BMI in the normal ranges (65). This is because there can be great variation in the adiposity of adolescents despite similar values of BMI. As such, using BMI as a surrogate of adiposity and as an indicator of health risk is likely to overlook normal BMI-high adiposity, especially in youth with mid-range BMI values (65). Similarly, BMI cannot identify trunk fat mass (TrF), which has an even

stronger relationship with CMR than general adiposity (66,67); or lean mass (LM), which has a reciprocal relationship with metabolic health (insulin sensitivity, metabolic flexibility) (68). Healthy adolescents demonstrate significant gains in FM (females more so than males) and LM (more so in males than in females), and the beginning of a re-distribution of fat from the periphery to the trunk which corresponds with the onset of puberty (69–71). Lean and fat mass gains contributing to weight gain continue into and through EA, meaning that not all BMI gains during these periods represent the same health risk (72). Recent literature suggests that measures other than, or in addition to, BMI that can partition FM from LM should be used for clarifying the relationship between growth, body composition and health (65). Therefore, the overall purpose of this dissertation is to explore fat mass accrual during the period of EA - contributing factors, associated outcomes, and the potential for EA to be an additional critical period for weight status and health.

1.2 *RESEARCH AIMS AND HYPOTHESES*

Study 1, Paper a: Longitudinal patterns in BMI and percent total body fat development from peak height velocity through emerging adulthood into young adulthood

> **Aim:** To identify if EA is a critical period for fat accumulation by examining the prevalence of OWO status from PHV to +15 years after PHV (CA approximately 12-27 years in females, 14-29 years in males).
>
> **Hypothesis:** The prevalence of normal weight will decrease with age with a significant change occurring during the period of EA.

Study 1, Paper b: At what age do normal weight Canadian children become overweight adults? Differences according to sex and metric.

Aim: To examine the age of onset of overweight by sex and three metrics: body mass index, fat mass and waist circumference.

Hypothesis: The period of EA will be highlighted as a time of onset of OWO by all metrics, but that there may be age-of-onset differences by sex and by metric.

Study 2: The influence of childhood and adolescent fat development on fat mass accrual during emerging adulthood: a 20-year longitudinal study.

Aim: To identify predictors of fat mass gains in EA including factors during childhood and adolescence.

Hypothesis: Having a greater fat mass during childhood and adolescence will predict greater TBF and TrF accrual during EA.

Study 3: Fat accrual during early adulthood and continuous cardiometabolic risk score in the fourth decade: a longitudinal analysis.

Aims: To identify the effects of EA fat accrual trajectories on subsequent cardiometabolic risk scores in early adulthood (25-39 years).

Hypothesis: Those with higher TBF, and even more so TrF, trajectories during EA into early adulthood will have higher cardiometabolic risk scores in early adulthood.

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CHAPTER 2

LITERATURE REVIEW

The following chapter provides an overview of the literature relevant to this research topic, including: an overview of the underlying paradigm of life course health guiding the research; a discussion on growth and maturation; a report on the prevalence of OWO and metrics used to measure OWO; a summary of the mechanisms and etiology linking OWO with cardiovascular and metabolic disease; and an overview of the relationship between physical activity (PA) and adiposity. The final section of this chapter elaborates on the known critical periods of growth and clarifies the current understanding of the interlinkages between PA, diet, FM accrual, and cardiometabolic health.

2.1 *LIFE COURSE HEALTH*

The Adverse Childhood Exposures (ACE) study in the early 1990's revealed the link between negative childhood experiences and adult disease and called into question the traditional view of proximate causes of adult disease (73). Since then it has been identified that the stress of physical, psychological and sexual abuse, parental neglect, divorce and even family relocation can manifest in adulthood as cardiovascular disease, metabolic abnormalities and premature death (74–76). Many of these relationships originate from the chronic overload of the acute

stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, and the resulting up regulation of catecholamines, and cortisol release in response to minor stressors (15,42,77). Downstream in this pathway is the elevated release of inflammatory agents which alter body systems, contributing to the onset of overweight and obesity (OWO) and related disease. The ACE findings build upon and affirm the health paradigm known as the life course framework. The life course framework suggests that the prenatal stage is a period of significant risk exposure and posits that health is a dynamic and cumulative condition rather than a static and temporary state (40,77,78).

The life course framework underlies much of the obesity literature as it acknowledges that a comprehensive understanding of chronic diseases, such as obesity, is reliant upon the identification of multiple determinants, including prenatal and childhood/adolescent experiences, genetics/heritability and environmental exposures (40). A life course model operates on one of two hypotheses. The first is the biological programming (or embedding) hypothesis: stating that adult disease risks are the outcomes of programming *in utero* and in early infancy. The classic example of programming in regards to OWO and CVD risk is intrauterine development and the thrifty genotype hypothesis (79). This hypothesis states that poor maternal nutrition or, alternatively, high maternal body mass index (BMI) or fat mass (FM), gestational diabetes mellitus (GDM) and insulin resistance (IR), have long lasting implications for the health of the offspring, such as increased risk of adult OWO, high blood pressure and diabetes (14,80). In this case, the metabolic processes relating to insulin-glucose imbalance, insulin sensitivity and hyper/hypoglycemia of the mother affects and permanently alters the metabolic and endocrine function of the fetus (14,79–82). This hypothesis is revisited in section 2.7.1. The second hypothesis is the cumulative exposure hypothesis, stating that repeated exposure to adverse

physical and social environments over the life course will cluster, perpetuate, and link one period to another in a pathological process in which risk is additive (Figure 2.1) (40,83) .

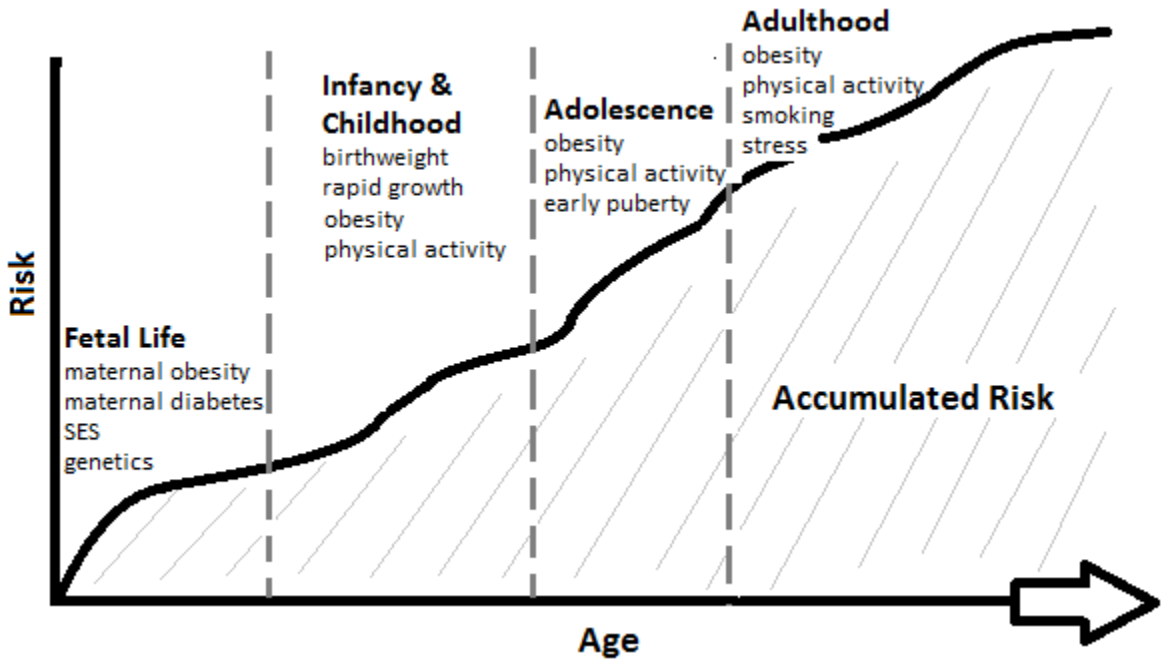

Figure 2.1 Cumulative exposure contribution to accumulated risk. (Figure adapted and redrawn from Darnton-Hill, I., Nishida, C., & James, W. (2004). A life course approach to diet, nutrition and the prevention of chronic diseases. Public Health Nutrition, 7(1a), 10

Infancy, childhood, and adolescences are critical periods which are markedly associated with adult health (14) . The alteration in normal development during a critical period can change the structure or function of the body, organ, system or tissue; for example, rapid "catch-up growth" following low birth weight is linked with early signs of adverse cardiovascular health, adiposity and abdominal adiposity by early childhood (84).

Obesity research has demonstrated that there is a cumulative effect of FM from one stage to the next, as high and low birthweight (BW), early onset of OWO, rapid gains in FM and elevated FM during critical periods can independently relate to adult OWO, lipid profiles, insulin

sensitivity and CVD risk (85–87). These early life risk factors have also demonstrated a summative risk: the more exposures, the greater the risk. The likelihood of childhood OWO, adult OWO and adult cardiometabolic diseases are elevated in those exposed to early life stressors such as domestic violence, food insecurity, parental depression, housing transitions and insecurity, potentially due in part to their combined effect on the HPA axis (85,88,89). Studies have also found that children with OWO who become adults with NW are at no greater risk of hypertension than adults who have NW who never acquired OWO. This suggests that for some parameters, adult OWO has a greater implication on adult health than does childhood OWO (90). Negative exposures such as childhood/adolescent OWO combined with positive future exposures such as PA and dietary interventions, may result in weight loss and improved health status in adulthood (91,92). Studies also demonstrate that OWO in adults who also had OWO as children have the highest risk (90) . This demonstrates the cumulative critical periods hypothesis, suggesting that the negative exposure (childhood OWO) manifest as an amplified negative outcome (adult health) when paired with successive negative exposures (adult OWO or low PA).

A life course framework underpins the research questions of this thesis. The dynamic character of health is acknowledged in the analyses of longitudinal data which encompasses critical periods of growth. The assessment of growth can provide valuable information about health. Alternatively, when growth is not accounted for it can confound the interpretation of health-related measures. Thus, it is essential to consider the implications of the processes of growth and maturation. Exploring or controlling for age and time-dependent factors such as height or FM necessitates a foundational understanding of the age and maturation-related anthropometric and morphological changes in order to infer deviation from a healthy trajectory

and to parse the effects of normal biological processes of growth from external influences such as diet and PA (69).

A more thorough discussion of how growth, maturation and the environment interact during critical periods to promote or mitigate FM gain and CMR is provided in Section 2.7.

2.2 *GROWTH AND MATURATION*

The period of life spanning conception to young adulthood demonstrates rapid changes in body composition. The timing and tempo of growth have major implications for adolescent health status as well as long-term health (83). As such, the processes and alterations of growth are highly monitored (69). Height (cm), weight (kg) and BMI (kg/m^2)-for-age and sex are often used to measure growth status and identify altered growth to ensure that optimum growth is occurring (93–95). An individual's status, according to each of these metrics, is used to identify nutritional deficits or disease leading to deviations from optimum growth (95). The emergence of the OWO epidemic created an urgent need to identify excess growth in FM and standards by which to classify OWO status. BMI became this criterion (96). Adult height is static and adult weight gain is often a result of increased FM; as such, BMI and corresponding cut-offs of OWO are accepted as indicators of excess fatness and linked to poor health (96,97). Attempting to identify OWO in children is more complicated as one must consider the effects of normal growth and maturation. Children and adolescents (up to young adulthood) experience non-linear height-to-weight and sex specific changes in body composition (98). This can result in erroneous BMI classifications of OWO which may not correlate with adiposity or the underlying health consequences, particularly because FM accounts for only 50% of BMI changes between 5-18

years (99). BMI correlates well with %TBF in 20-39 year olds (r=0.790 and 0.84 in males and females, respectively) (35), and in 5-19 year olds (r2 =0.63 and 0.69 for males and females, respectively); however, large confidence limits on the BMI-%TBF relationship suggest large individual variation in fat mass at a given BMI (36). Pediatric sex-specific BMI-for-age, and percentage (%) total body fat (TBF)-for-age references and OWO cut-offs have been developed to better reflect the normal and abnormal changes in BMI and body fat occurring in childhood (95,100,101). The effect of growth and maturation can also mask the influence of other external factors such as PA or diet on FM accrual. As such, any conclusions drawn about body composition, overweight status, or relationships between change in body composition and external factors must consider growth and maturation, especially during and surrounding the period of rapid growth in adolescence.

2.2.1 Development

Development refers to the biological differentiation of cells, and the acquisition and refinement of behavioral (social, cognitive) competency (69). Behavioral development includes: understanding aspects of socially acceptable behaviors; cultural symbolism and significance; intellect and sense of humor; aspects fully established by adulthood. Full biological development or differentiation is attained when a tissue or system is fully capable of carrying out its function. Like maturation and growth, there can be great inter-individual variability in the rate of development.

2.2.2 Growth

Growth refers to a change in size of a part, or the entire body (69). Children grow bigger and taller with chronological age (CA), due to one or more cellular processes. Processes include: hypertrophy - increase in cell size; hyperplasia - increase in cell number; or accretion - increase

in intracellular-substance. Although all three cellular processes govern growth, one may predominate over the other two at different stages of growth. For example, fat cells will increase primarily through hypertrophy for the first year of life, while hyperplasia of fat cells will dominate through childhood and adolescence (69). The timing of growth is not the same in all tissues or in all individuals; however, the patterns of growth of systems and tissues generally follow one of four curves: the neural curve (e.g. brain, spinal cord and head), the lymphoid curve (e.g. lymph nodes, glands, tonsils), general curve (e.g. height, weight or body mass, FM, etc.), and genital curve (e.g. reproductive organs). The respective patterns are shown in Figure 2.2 in which the y-axis represents the percentage of adult size attained and the x-axis represents the time from birth to 20 years of age. The general curve is followed by most of the body systems, particularly those relevant to this review, the musculoskeletal system or somatic growth.

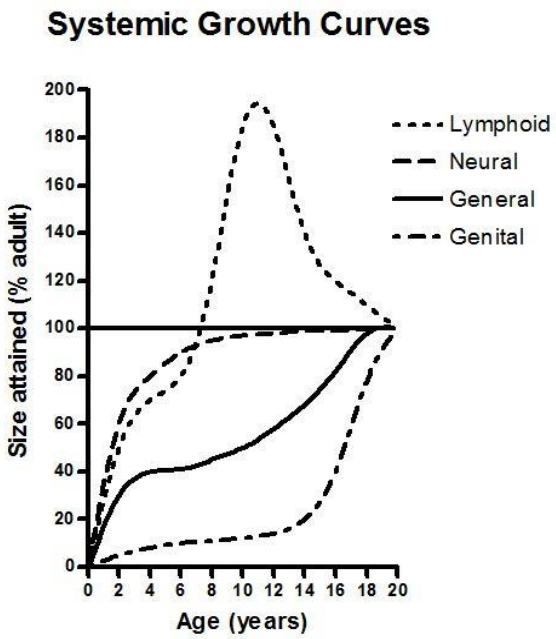

Figure 2.2 Scammon's curves of systemic growth. (Figure adapted and redrawn from Scammon R.E., 1930, The measurement of the body in childhood. In *The measurement of man*. Minneapolis, MN: University of Minnesota Press, p 193).

The most frequently measured components of growth are height (standing surface to top of the head), sitting height (sitting surface to top of head; trunk length) and weight (body mass including lean, fat, and bone mineral mass). Somatic growth follows a sigmoidal pattern with rapid growth in the first year of life followed by deceleration to a relatively stable velocity during childhood (4 to 8 years of age). The rate of growth accelerates again (although not to the same velocity as year one) with the commencement of puberty during the adolescent period of growth. The assessment of healthy growth can be carried out by plotting serial measures of height and weight on to reference curves. Although simplistic in their execution, measurements of growth are susceptible to error. Error can occur because of changes in the technique of those taking measurements, activities and time of day (individuals will be shorter after activity and in the evening due to compression of intervertebral discs), or hydration and diurnal variation in weight (93) .

2.2.3 Maturation

Maturation is defined as a process, or one's point of progress, towards the adult (mature) state of the body's systems, tissues, organs etc. (69). This process includes the maturation of the nervous system, such as decreasing plasticity and development of prefrontal cortex; maturation of the musculoskeletal system, such as ossification of bones; maturation of the endocrine system, such as the transition from preferential use of fat to use of carbohydrate during aerobic exercise; and sexual maturation, such as changes in the pattern of hormonal release and the development of secondary sex characteristics (98).

Rates of maturation differ between individuals, between systems and between tissues. Individual differences are often referred to as an individual's timing and tempo of progress (69). Timing refers to the discrete age at which maturational milestones are met, such as the age of

menarche. Tempo refers to the rate at which an individual moves from one event, or milestone, to the next. The attainment of one milestone may not have the same timing as subsequent milestones; for example, an individual may have a slow tempo in the rate of breast development but reach a subsequent milestone such as menarche at an early age.

There are a variety of methods used to estimate maturity. The most common are skeletal age (SA), secondary sex characteristics, age at peak height velocity (PHV) and age at menarche (93). SA uses radiographs of the wrist and hand which are analyzed by comparing a subject's scans to age-specific reference scans. Ossification of the bones occurs in a predictable, universal and irreversible process towards the adult state. As such, an individual's radiograph can be matched to a reference scan and a SA can be determined. The assigned SA will be the same as the CA on a matched reference scan. An estimate of maturation is then the difference, or ratio, of the assigned SA to the individual's actual CA. For instance, if a 12-year-old girl has a radiograph that matches the reference radiograph of a 14-year-old, her SA is 14 and her maturation estimate, or Biological Age (BA), is +2 years. In this case she is likely maturing earlier than her peers (93).

The estimation of maturity status from the evaluation of secondary sex characteristics relies on visually identifying the individuals' stage of secondary sex characteristic development. Individuals are placed in one of five progressive stages of pubertal development based on observed characteristics (self-observations, parental observation or observation by a medical professional). Characteristics include: the assessment of pubic hair, genitalia (males), axillary hair, testicular volume (males), voice change (males), facial hair (males), and breast development (females). Stage 1 of each characteristic is considered pre-pubertal with no observable changes present from the pre-pubertal state. Stage 5 is the mature state. A weakness of this method for

maturity assessment (other than being highly invasive) is the inability to compare between the sexes as stages are not equivalent in timing between sexes (i.e. pubertal hair stage 2 in females does not equate to pubertal hair stage 2 in males) (93). Furthermore, stages within an individual are not necessarily the same; pubic hair 3 does not necessarily mean that breast stage 3 has been attained. Finally, stages of secondary sex characteristics are discreet and as such using this method as a maturational estimate does not recognize the tempo of the continuous process of maturation. Estimation of maturation from secondary sex characteristics does not allow for an estimation of the length of time an individual has been in each stage and, as such, an individual who has just entered a stage will be classified the same as an individual almost leaving the stage, even though they may be quite different in terms of maturation (93).

Age of PHV is the point at which stature is changing the most rapidly during adolescence. Like other maturational milestones, this will occur in all individuals and within a predictable pattern (69).

When longitudinal measures are taken close together across the adolescent growth spurt, the age when PHV is occurring can be measured. Individuals can be classified as before or after PHV; or be assigned a BA (number of years before or after the attainment of PHV). This allows for individuals to be aligned by a common maturational milestone (at PHV BA=0) rather than by chronological age (CA). On average, males reach PHV around 14 years of age and females at

around 12 years of age (Figure 2.3).

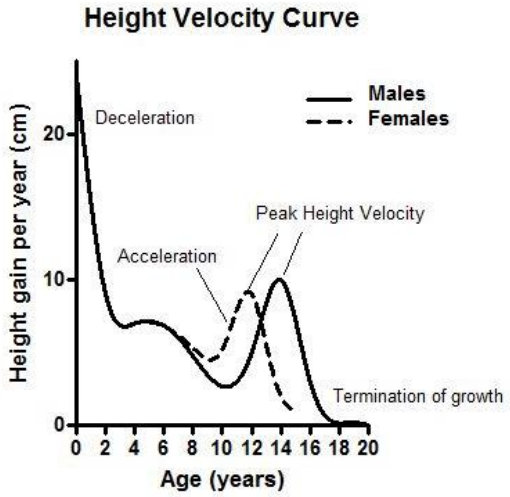

Figure 2.3 Typical velocity curve for height (or length) in males and females. (Figure adapted and redrawn from Tanner, Whitehouse and Takaishi, 1966, "Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1961-I*", Archives of Disease in Childhood* 41:454-471).

If serial measures are not available, there are also several commonly used predictive equations that estimate when PHV will occur or has occurred. These are based on sex and age specific anthropometric ratios of height to sitting height (102,103). In this case, the timing in years from PHV is used as a BA. The accuracy of this prediction equation, however, depends on the time from the actual event when measurements occur. The prediction works best within a narrow age range surrounding PHV (from -2 to +2 years from PHV) in individuals with a normal maturational tempo (102).

Age at menarche can be used to classify females as pre/post menarche or years before or after menarche like attainment of PHV. Menarche occurs around 13 years of age, after attainment of PHV, and is a relatively late occurring maturational milestone.

2.2.4 Somatic Growth

There has long been a keen interest in the study of human growth and its variations as an indicator of health (95). This interest led to the creation of growth curve references (representation of the spread of data in a population) and growth curve standards (indicator of healthy optimal growth) (e.g. Figure 2.4) (69,95). On a growth reference chart, the middle line, the 50^{th} centile, indicates that 50% of children at a specific age will fall at values above the line and 50% at values below the line. Comparing an individual's growth to the growth reference and identifying their status and/or progress can provide an indication of their health. Status considers the placement of an individual within the spread of population data and infers inter-individual (between individuals) variation. Progress can then be considered in terms of intra-individual (within individual) change from one measurement occasion to the next, or inter-individual progress - the point of progress towards maturation compared to reference data (98). These terms are more thoroughly discussed in sections 2.2.4.1 and 2.2.4.2.

2.2.4.1 Status

Growth status is a single, time-dependent achievement of size, maturation or development and requires comparison to a standard, or comparison of one individual to other individuals. Reference charts plot the distribution of sex- and age -specific growth data so that an individual's status can be expressed relative to a representative population. These charts are commonly used during infancy and childhood to assess status or growth, measured by length-for age percentile charts (up to 36 months). From 2 to 20 years, stature-for-age, weight-for-age and BMI-for-age (Figure 2.4) are used to plot an individual's status and/or their progress.

a) b)

Figure 2.4 CDC Body mass index-for-age percentile charts for a) females and b) males. (Reprinted with permission as part of the public domain. See Appendix M for copy of authorization).

For example, using the WHO BMI charts (Figure 2.4), a 12-year-old female with a BMI of 23 kg/m^2 would be at the 90th percentile indicating that 10% of the population has a higher BMI and 90% have a lower BMI. Stability or divergence from one's centile is considered a characteristic of progress.

2.2.4.2 Progress

Progress considers the change between two or more consecutive measurement occasions in the same individual. Size in the first year of life is poorly correlated with adult size as fetal development is highly dependent on maternal characteristics; however, by the age of two the correlation (under optimal environmental conditions) increases to approximately 0.80 and is reflective of genetics and other environmental influences (104). A small-for-gestational-age infant under the 5th percentile at birth can experience catch-up growth in the first year of life thus achieving the 50th centile status by one year of age. A child's growth centile will normally

stabilize after the first 1-2 years of life, often remaining within a small range around a constant centile for the remainder of their life (98). This process of centile stabilization is known as canalization (104).

Significant departure from one's centile during childhood is likely due to nutritional and other environmental influences causing growth restriction; whereas departure from one's centile during adolescence does not have the same implication. "Centile Crossing" is common during adolescences as it is related to the timing of maturation and inter-individual variation. This is because the 50th centile lines represent the average size and timing of maturation. As such, those who mature earlier than average are more likely to cross growth centiles as they approach their adolescent growth spurt, indexed by PHV. Alternatively, a decrease in centile is seen in late matures because same aged peers have already begun their growth spurt (104). A return to one's pre-adolescent centile is common towards the end of adolescence.

Estimating the progress of an individual over time can be addressed using anthropometric measures. Serial measures of height can identify PHV, and thus be used to assign a maturational age or BA (as described previously). For example, a growth rate of 5cm/year from 9-10 years, 12 cm/year from 10-11 years and 7cm/year from 11-12 years identifies acceleration from up to the 10th year and deceleration following the 11th years. This identifies the 10th-11th year as the year that encompassed PHV. The equation for proportional allotment can be used to estimate the exact age at which PHV is occurring.

$$\textit{Age of peak velocity (APV)} = A + \left[\frac{VApeak - VAbefore}{(VApeak - VAbefore) + (VApeak - VAafter)}\right] - 0.5$$

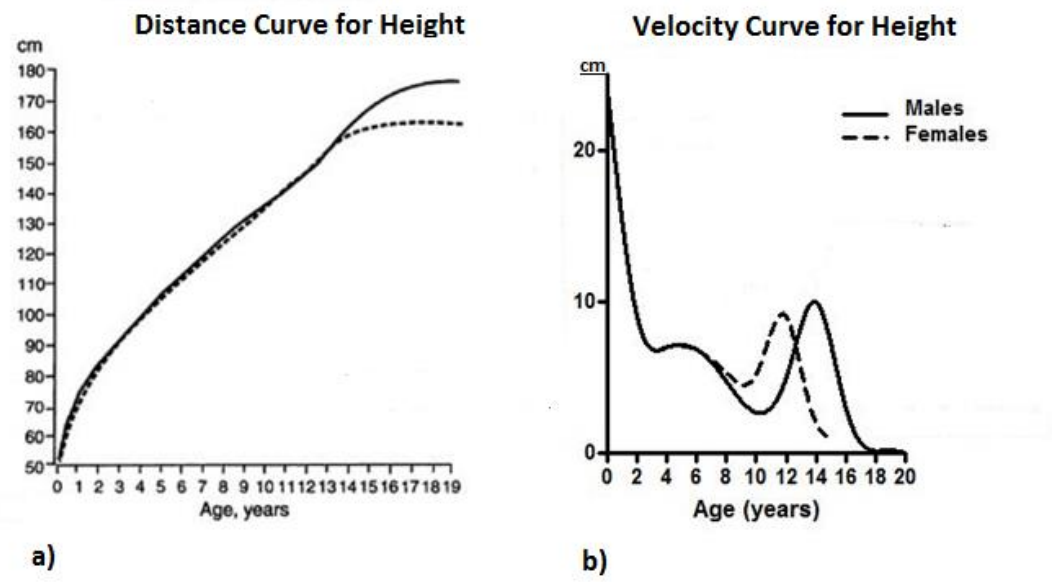

Figure 2.5 Developmental curves of a) height distance, and b) height velocity for males and females. Distance curve used with permission from Malina, Bouchardand Bar-Or, 2004. Growth, Maturation and Physical Activity, Figure 3.6, p49. See Appendix N for copy of authorization to use. Velocity curve adapted and redrawn from Tanner, Whitehouse and Takaishi, 1966, "Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1961-I*", Archives of Disease in Childhood* 41:454-471.

Velocity curves are better representations of statural, body mass and fat mass growth than the curve of distance because growth is not linear.

2.2.4.3 Statural Growth

Velocity growth curves demonstrate three distinct peaks or growth spurts: periods of increased growth rates, specifically seen in height and weight. The first spurt occurs prenatally during weeks 20-30 and reaches approximately 120 cm/year (104). At birth, an infant is approximately 30% of their final adult stature. In the first year of life, statural growth continues to be rapid, at a rate of approximately 25 cm/year, followed by 11-12 cm/year in the child's second year. By the age of 18 months in females, and 24 months in males, an individual will have attained approximately 50% of their adult stature. The rate of growth decelerates from birth

to adolescence with an overall velocity close to 5 cm/year (98). There is a second small growth spurt occurring at 6-8 years known as the juvenile or mid-growth spurt. The final spurt is the adolescent spurt (or PHV) occurring between 11.3 and 12.2 years (take-off at 8.2 to 10.3 years) in females and between 13.3 and 14.4 years (take-off at 10.0 to 12.1 years) in males (Figure 2.5) (69).

Males begin their adolescent spurt on average 2 years later than females, and thus experience an additional 2 years of preadolescent growth at a velocity of roughly 5 cm/year (69). The adolescent spurt has a velocity of approximately 8 cm/year in females and 10 cm/year in males. Females stop growing approximately 2 years earlier than males (16 years versus 18-19 years, respectively), in addition to having a lower peak rate of growth (2 cm/year greater in males). The difference in adult stature (~13cm) between males and females is largely explained by these sex differences occurring during adolescent growth. There are also sex differences in other body components that similarly become more prominent in adolescence.

2.2.4.4 Body Mass

The development of body mass (weight) is similar in pattern to that of stature. Rapid gains in infancy and early childhood, a two-fold increase by one year and a four-fold increase by year two, followed by stable rates of gain during mid to later childhood. The growth of body mass is often tracked using BMI growth charts which consider mass relative to height (Figure 2.4). Acceleration of body mass gains occurs with the onset of adolescence as both FM and fat free mass (FFM) accrual increase rapidly during this period. Peak body mass velocity occurs roughly 0.2-0.4 years after PHV in females and 0.3-0.9 years after PHV in males. The increase of body mass is comprised of gains in lean, bone and fat mass in both sexes, but the relative contributions of each component differs between the sexes. Females gain more FM while males

gain more LM and bone mass (i.e. greater statural growth). Peak bone mass precedes peak body mass. Peak LM occurs approximately 0.3 years after PHV in both sexes followed by peak body mass. While gains in FFM often levels out, FM gains may continue into adulthood and, as such, so too does body mass.

2.2.4.5 Fat mass

Subcutaneous fat is the first fat depot to be accrued, beginning *in utero*. Subcutaneous fat represents 15% of body mass at birth, increasing to 30% by one year. Skinfolds are a measure of subcutaneous fat, and these measures decrease from approximately 6-9 months to a nadir around 6-8 years. The point when fat mass accrual returns to a positive velocity immediately following the nadir is known as the adiposity rebound (AR). The AR corresponds with a reversal and rise in the BMI curve. The terms BMI rebound and AR are sometimes used interchangeably; however, it has been demonstrated that it is most often FM that is altering BMI during this time rather than LM (105). It has also been demonstrated that an earlier AR is associated with greater FM at the time of rebound, more rapid gains following the AR and greater FM in adulthood (106). This is why the AR has been indicated as a critical period for fat mass accrual (see section 2.7.3).

The patterns of FM accrual are similar to BMI curves from childhood to young adulthood. From the AR through adolescence, FM continues to rise. Once adolescence is complete some individuals' FM will plateau while the majority of individuals will continue to have incremental gains of FM into early adulthood and beyond (107). There are significant sex differences and individual differences in the magnitude of FM gains throughout the life span due to genetic, hormonal, and external influences such as stress, diet and PA (108) (see Section 2.2.5).

2.2.5 Periods of growth and sex differences

Growth is often divided into periods, or phases, with distinct characteristics, albeit within somewhat arbitrary CA boundaries. These periods overlap with the critical periods described in Section 2.1. There cannot be firm chronological boundaries, especially during the years of adolescence, because of the great inter-individual variability in timing of onset and completion of each phase (109). The first period, the prenatal period, is the exception as it has consistent boundaries. During this period, the process of development predominates. The embryonic tissues differentiate from stem cells to their tissue specific cellular form and function. This period is especially important to a life course perspective of health because this perspective emphasizes that exposure to certain stimuli during intrauterine development has long-standing implications for later life health (i.e. biological programming). The thrifty genotype hypothesis, or fetal origins hypothesis, developed by Hales and Barker, illustrates the importance of this period in regard to future health (see Section 2.9.4.1.) (79).

The second and third periods are infancy and childhood, respectively. Infancy, or post-natal growth, is a period of extremely rapid increases in many body systems, particularly the neuromuscular system. As already indicated, somatic changes of increased stature, muscle, bone and fat mass are also occurring at a rapid rate in infancy which slows to a steady pace in early childhood.

Sex differences in stature are very small during this period with a difference of only 1 cm by the age 5 favoring males. FM will be consistently higher in females than in males during early childhood with males having approximately 15% TBF and females approximately 17% TBF by the age of 5. From 6 years of age onwards, females have higher rates of FM gain leading to a sex difference in FM of approximately 6% by 10 years of age (Figure 2.7) (104).

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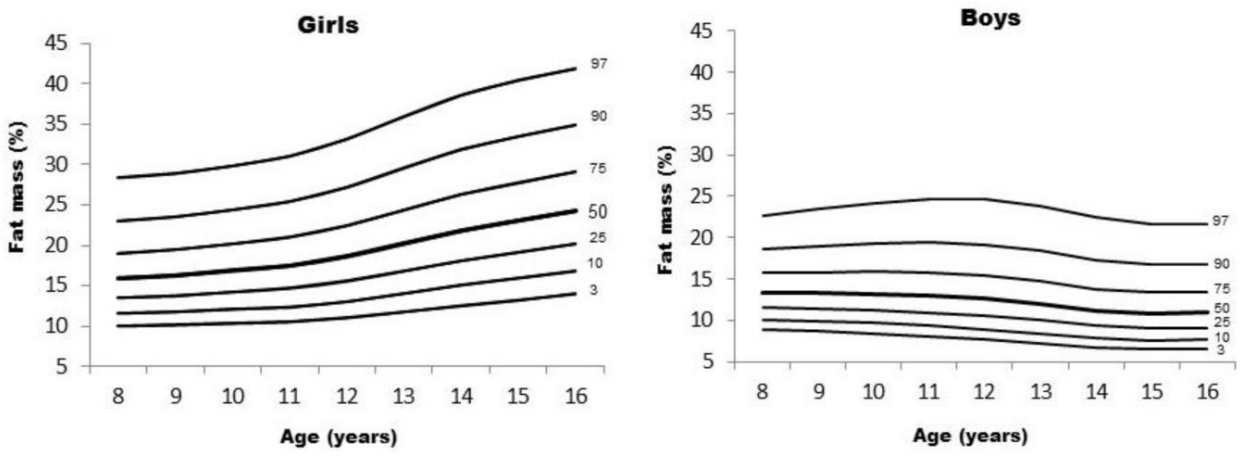

Figure 2.6 Development of %TBF in a) female and b) male adolescents. (Reprinted with authorization. Silva, Baxter-Jones, & Maia, 2016. Fat Mass Centile Charts for Brazilian Children and Adolescents and the Identification of the Roles of Socioeconomic Status and Physical Fitness on Fat Mass Development. *International Journal of environmental Research and Public Health*, 13[2]. This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. [CC BY 4.0]).

During early childhood, sex differences in FFM and %FFM are small; however, by adulthood females have, on average, about 70% of FFM, 50% of LM and 150% of TBF of adult males (69). Many of the sex differences in fat, bone and lean mass become evident just prior to the final growth period of adolescence and the beginning of emerging adulthood (EA).

The adolescent period follows late childhood with the onset of the somatic growth spurt. Although puberty refers more specifically to the development of reproductive capacity and secondary sex characteristics, there is significant synchronization between puberty and musculoskeletal maturation. Just prior to puberty, males can be slightly heavier than females. But due to an earlier onset of puberty seen in females (by approximately 2 years), males are often shorter and lighter than females at ages 11, 12 and 13. Aside from an earlier onset of the pubertal growth spurt in females and the slightly higher maximum rate reached in males, the pattern of

statural growth is very similar between sexes. The pattern of FM accrual, however, diverges during adolescence and the previously small sex disparity in FM enlarges. Beginning as early as 8 years (Figure 2.7), females will see increases in FM and in %TBF while males will see increases in FM but often decreases in %TBF from about 12-17 years (Figure 2.6) (109).

The sex difference in pattern of %TBF is because FFM, and specifically LM, increases at a much greater rate in males during adolescence than in females. Males also continue to accrue LM for almost 2 years longer than females (similar to patterns of height). Throughout adolescence, males will also have greater bone mineralization (contributing to total mass) even when controlling for LM and age (110). The continuous gains in FFM found in males compared to plateauing gains of FFM in females, combined with greater FM gains in females throughout adolescence, leads to a greater fat-to-lean mass ratio in females than in males (Figure 2.7).

During the periods of infancy and childhood, both sexes have more fat deposited in the subcutaneous fat depots than visceral (deep) depots, and in the extremities than in the trunk. Adolescence is a time when the distribution of fat (where the fat is laid down) begins to change and noticeably differ between sexes. The accrual of TrF and visceral fat are characteristic of the adolescent period. Adolescent females will accrue more absolute TrF (g) than males but also a greater amount of extremity fat; and, although males will also accrue TrF they will simultaneously begin to lose extremity fat. This results in males carrying a greater percentage of TBF on their trunks in comparison to females. Furthermore, males' skinfolds decrease over adolescence while females' skinfolds continue to increase, so while females may have a greater amount of TBF, subcutaneous fat makes up a larger percentage of TBF in females than in males. These sex differences continue and broaden during subsequent periods of emerging, early and mid-adulthood (69,111,112).

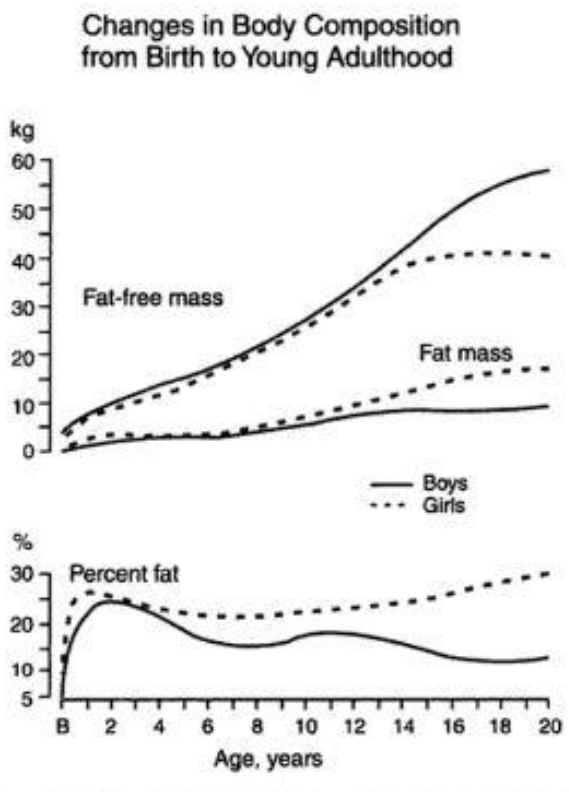

Figure 2.7 Changes in fat, fat-free mass and percent body fat in males and females from birth to young adulthood. (Reprinted with permission from Malina, Bouchard and Bar-Or, 2004. Growth, Maturation, and Physical Activity, ch.5, p113. See appendix for copy of authorization).

Emerging adulthood (EA) is a socially constructed stage of life in which the majority of physiological changes to the body associated with adolescent or pubertal growth have ceased and yet weight and fat gains begun in adolescence may continue (28). This period has been referred to as the volitional period in which there is broad individual variance, more so than at any other time in the life course, as individuals experiment with different adult habits, choices, and lifestyles. This is especially true in industrialized countries where this period of prolonged adolescence is socially sanctioned (32). As such, there is a lack of predictability in growth due to individuals experimenting with lifestyle choices including those related to health behaviors such as dietary intake, alcohol consumption, sleep/awake schedules and PA behavior. Increasing rates

of obesity, and an almost negligible numbers of individuals moving from obese to non-obese, are observed over this transitional period from high school to young adulthood (27,31,107). There are suggested links between childhood and adolescent factors such as PA, FM and health and the growth and health status of emerging and early adulthood (31,113–118). The role of EA on FM and lifestyle in predicting adult health cannot be fully elucidated without consideration of childhood and adolescent lifestyle and body composition. In turn, both body composition and lifestyle (i.e. PA) are heavily influenced by the auxological (growth) processes and adult health is influenced by genetics, hormones and environmental factors interacting throughout the life course.

2.3 *OVERWEIGHT AND OBESITY*

2.3.1 Regulation of fat mass accrual and Onset of Overweight and Obesity

The most simplistic reason for overweight (OW) and obesity (OB) is the "calories in-calories out" theory; the idea that if you eat too much or burn too little you will gain excess fat. This theory is supported by studies of caloric restriction and increased PA leading to weight loss, and correlations between moderate-to-vigorous PA and lower adiposity (91,119–121). The onset of OWO in early adulthood also supports this theory as a large number of individuals acquire OWO in late adolescences and emerging adulthood when the caloric demand for growth processes decreases but the caloric intake remains unaltered (107). Habitual food intake that was once required to meet the body's energy demands for growth becomes excessive after growth is complete. As a result, excess calories are stored as FM, bringing about the onset of OWO.

Some argue that this theory of OWO is an oversimplification. Studies in support of a more complex cause cite no association or an inverse relationship between OWO and caloric

intake, suggesting that there are likely metabolic, genetic, epigenetic, and endocrine contributors to this disease (15,122,123).

Single-nucleotide polymorphisms (SNPs) are genetic variations of single nucleotide building blocks; for example, the presence of cytosine instead of thymine in a string of DNA(124). Recent technological advancements have allowed for Genome-Wide Association Studies (GWAS) identifying over 300 SNP's related to BMI, waist-to-hip ratio and other measures of adiposity; however, these SNPs cannot account for the entire phenotypic expression (124). For example, it has been suggested that only around 30% of the variance in BMI can be explained by related SNP's, yet other estimates suggest a genetic basis for obesity between 40 and 70% (124). Single gene deficiencies causing obesity are rare and as such it is must be considered a polygenic disease in which individuals' predispositions to FM gains interact with environemental and lifestyle factors (69,125,126) (see Section 2.9).

There is a significant heritability component to an individual's body mass and/or FM . At birth, the correlation between parental and child body mass is low, and the correlation increases to about 0.3-0.4 (low to moderate) following the adolescent growth spurt. This is because the first year of growth reflects the intra-uterine environement rather than genetics or extra-uterine environment. Early twin studies demonstrate concordance rates of BMI and body mass between monozygotic (identical) twins that are twice that of dizygotic (fraternal) twins, suggesting a strong genetic influence on adiposity (127). The correlation of weight between monozygotic twins increases from birth to early adulthood to values at 19 years of 0.92. Although not as strong as the link between parental and child height (60%), the age and sex adjusted phenotypic variance in FM accounted for by heritability is 25-40% (69,128).

There are also familial similarities in the characteristics and behavior of adipocytes in terms of proliferation, hypertrophy (cell number and capacity), level of lipolytic activity and fat depots. *In vitro* studies of twins demonstrate greater variablility in fat mobilization (release of fat for oxidation) cascades between dizygotic than between monozygotic twins. Heritability coefficients for subcutaneous fat distribution (upper, lower or abdominal body fat) as well as visceral abdominal fat are approximated at 50%, even after adjutsing for TBF (69). Waist to hip ratio has demonstrated similar heritability, with estimates ranging from 22% to 61% (129). Furthermore, findings from the Quebec Family Study found that heritability was even higher for visceral fat (56%) than for subcutaneous fat (42%) (130) which is concerning as visceral fat has significant implications for cardiovascular health. Genetic underpinnings suggest that visceral fat may be a less modifiable characteristic (see Section 2.4.3).

2.3.2 Age at onset of OWO

The age at onset of OWO may reflect different underlying causes. From a very early age, those individuals who will become obese have a different trajectory of growth, even before they are overweight (107), and those with metabolically normal obesity tend to have an earlier onset (131). In one study looking at never, early and late onset OWO groups, those with an earlier onset of OWO (before 25 years) compared to a later age of onset (after 25 years) had higher levels of adult BMI in addition to higher BMI from the age of 2 in females, and 8 years in males (107). An earlier study examining subcutaneous adipose tissue of adults and children demonstrated those with weight-for-height above the 97th centile by 1 year, and those adults who identified as having been obese children, had higher levels of %TBF, a greater number of adipocytes, but smaller size of adipocytes compared to late childhood or adult onset obesity (132). It is known that smaller and more numerous adipocytes have a lower correlation with IR

and type II diabetes, are less likely to become inflamed, and thus less likely to lead to cardiovascular and metabolic disease in comparison to large adipocytes (47,133). As such these differences in the timing of OWO onset suggest that while those with earlier onset OWO may become larger, the fat accumulated may be healthier. This adipocyte dimorphism is delineated by Salans et al. (1973) as hyperplastic obesity - early onset with small adipocytes - versus hypertrophic obesity - late onset with larger adipocytes (134). The relationship of adiposopathy (sick fat cells) leading to CMR with late childhood or adult onset of OWO may be stronger than with early childhood onset (i.e. by 1 year), and yet OWO and CMR also demonstrates antecedents in early fetal development.

Altered fetal development leading to dysfunction of the endocrine and fetal hypothalamic-pituitary-adrenal axis can occur due to various forms of early stress or through trans-generational mechanisms from conditions such as maternal obesity and gestational diabetes. These maternal conditions expose fetuses to endogenous glucocorticoids such as cortisol, elevated insulin and glucose levels, and exposure to inflammatory agents (135–137). This results in an elevated risk to the fetus such as IR, future OWO and adult vascular disease (138,139) (see Section 2.7.1). Alternatively, an early onset of OWO in childhood from an overconsumption of calories and a sedentary lifestyle may be benign in terms of health. This theory is supported by findings that childhood BMI may have a protective effect at a given level of adult BMI and that the link between childhood BMI and adult disease is dependent on tracking of BMI (140). With that said, OWO also has a cumulative effect on morbidity and as such children with OWO that have stable OWO have had a more chronic and long term assault on the cardiovascular and metabolic systems and are likely to present with higher CVD risk profiles (17,20,140).

2.3.3 Measuring body composition and adiposity

Body composition is measured using a variety of methods. Each measure is used to estimate the volume or percentage of fat mass comprising total body mass. Body composition can be expressed by a two, three or four-compartment model in addition to singular units or compartments such as weight/body mass (kg) measures or BMI. Two compartment models parse the body into FM and FFM components. The three compartment models partition fat from fat-free and total body water (or fat, lean and bone). The four compartment models partition fat from fat-free (non-bone) and bone mineral and residual mass (69). Some of the most common used body composition methods include dual x-ray absorptiometry (DXA), bio-electrical impedance (BIA), computed axial tomography (CT), hydrostatic underwater weighing or air displacement plethysmography, magnetic resonance imaging (MRI) and skinfolds.

Underwater or air displacement weighing estimates the volume of the body and, using assumed density characteristics of body tissues, estimates FM and %TBF. The underwater weighing technique (hydrostatic weighing) was once considered the gold standard of body composition and has been used to develop regression equations for estimates of body fat based on skinfolds, and as a validation method for other methods of measuring body composition (141). However, hydrostatic weighing has since been replaced by MRI as the gold standard of body composition assessment. The issue with hydrostatic weighing is that the density of FFM is assumed to be consistent but can change with time or show discrepancies between sexes, fitness levels, hydration and (most relevant for this dissertation) by age and degree of maturation of an individual. The variation in body density can result in variance of calculated %TBF by approximately 3.9% (141) .

Bioelectric impedance analysis (BIA) operates on the electrophysiological theory. This theory posits that water containing tissues such as blood and muscle conduct electricity better than fat mass. The volume of FFM is estimated by analyzing the magnitude of electrical conductivity and the combined resistance of water and electrolyte containing tissues (141). As with other methods that rely on underlying assumptions (e.g. electrical resistance of body water), there is the possibility of error, particularly in children and adolescents in whom some of these assumptions are yet to be verified (69).

DXA estimates bone mineral content (BMC), lean mass (LM), and fat mass (FM) for both total body (TB) and regional (e.g. hip and spine) body components (141). Estimates of FM and LM content are made from known constants at which each body tissue absorbs or attenuates x-ray photon beams. A 2-dimensional posteroanterior image is provided representing body structures, which can then be divided into different compartments. Theoretically, the hydration of the individual can again compromise the accuracy of estimates by DXA; however, in a study conducted by Going et al. (1993), when subjects were intentionally dehydrated there were only small losses in accuracy for up to 3 kg water loss. Furthermore, the loss of weight with dehydration was mostly attributed to losses in LM by DXA, not FM (141).

MRI estimates FM and FFM using an external magnetic field applied to the body. The nuclei of the cells of the body absorb MRI energy like magnets. When the electromagnetic wave is turned off, the body tissues releases the absorbed energy as a signal which is then used to develop an image of the chemical composition of the body which is then translated into body composition estimates (141). This method is now considered the gold standard.

Computed Tomography (CT) also estimates fat, bone and lean mass. Like DXA, the CT scan uses known properties of different tissues and the attenuation of x-rays passing through the

body to indicate the volume of different components. CT and MRI scans provide a cross-sectional anatomical image and as such can be used to identify the location of fat (subcutaneous versus visceral) (69).

The concerns with radiographic methods such as MRI, CT and DXA include the cost of the method, accessibility to the machines, and exposure to radiation (CT and DXA only). CT exposes individuals to ionizing radiation and as such, repeated measures or measures on children and pregnant individuals are not advised. MRI does not use ionizing radiation and DXA uses far less radiation than the CT (141).

One of the least expensive and most accessible methods for estimating body composition is skinfold assessment. Using skinfolds, equations based on regression equations calculated from hydrostatic weighing are then used to estimate FM. Correlations with %TBF are high (r=0.7 to 0.9) while correlations with FFM are low (0.2). Multi-site skinfold equations provide the most accurate predictions and demonstrate higher correlations with TBF as measured by radiographic methods. Skinfolds measure subcutaneous fat rather than visceral fat. There can be a high degree of error associated with this measure depending on the reliability of the measurer and the measurement tool (caliper). With that said, skinfolds are useful for monitoring change over time when the measurer is kept constant (69).

Weight status can also be indicated using anthropometric measures. Body composition measures indirectly estimate FM whereas anthropometry such as weight-for-age, or weight-for-height (Body Mass Index, BMI; kg/m2) use ratios of indices known to correlate with FM (69). Individuals' ratios are considered in relation to reference data to draw conclusions about health. Values may be assigned a centile (i.e. 85th centile for OW by BMI) or compared to a cut-off

value (>25kg/m^2 for OW by BMI) that corresponds to OWO cut-offs. Cut-offs are (ideally) developed with strong associations to FM as well as to health-related consequences of FM.

2.3.4 Definition of Overweight and Obesity

According to the National Institute of Health (NIH), overweight in adults is defined by a BMI of 25 kg/m^2 to 29.9 kg/m^2, whereas obesity is defined as having a BMI of 30 kg/m^2 or over (21). As such an OB individual is also OW. OB is then delineated according to increasing severity: Obese I, II and III. These are the same definitions used by the WHO and the International Obesity Task Force (IOTF) (142). Health Canada adopted these same weight classification guidelines in 2003 to correspond with the WHO criteria. Healthy weights guidelines were altered from those of 1988, which indicated that a BMI < 20 kg/m^2 "may be associated with health problems for some people"; a BMI 20-25 kg/m^2 was "a good weight for most people"; a BMI 25-27 kg/m^2 "may lead to health problems in some people"; and a BMI > 27 kg/m^2 was associated with "increasing risk of developing health problems" (143).

BMI was first developed as an indicator of body fatness under the assumption that expressing weight in proportion to height should indicate something about body build, body fatness, and obesity (144). This ratio is useful because it is independent of height and because adults' BMI demonstrates a strong relationship with body fat. In 1972 Keys et al. proposed the use of the term Body Mass Index to identify this ratio. They indicated that this metric was preferable to other weight-to-height indices tried previously (144). BMI has since demonstrated strong associations with estimates of TBF and %TBF by skinfolds and by DXA in adults (r^2=0.68 to 0.83) and by DXA in children and adolescents (TBF r^2=0.85 to 0.89) (63).

BMI cut-offs corresponding with excess body fatness in adults are identified as 25 kg/m^2 for overweight and 30 kg/m^2 for obesity. The associations between BMI and fatness in children and adolescents are different and are reliant on age and maturation, as the linearity of the relationship between weight and height changes as a result of normal growth and development (69). Adult cut-offs of OWO are inadequate for use in children due to these fluctuations, and so pediatric BMI-for-age reference charts have been developed. There are currently three different sets of reference values. The set of references developed by the Center for Disease Control and Prevention (CDC) are based on American national survey data collected between 1963-1994 (145). The set developed by the WHO is considered the "gold standard" in growth up to 5 years, as it was based on a cohort of children raised in optimal conditions. This set was released in 2006 followed by a supplementary set for 5 to 19-year-olds in 2007 (146).

The final set of cut-offs was produced by Cole et al. (2000) for the International Obesity

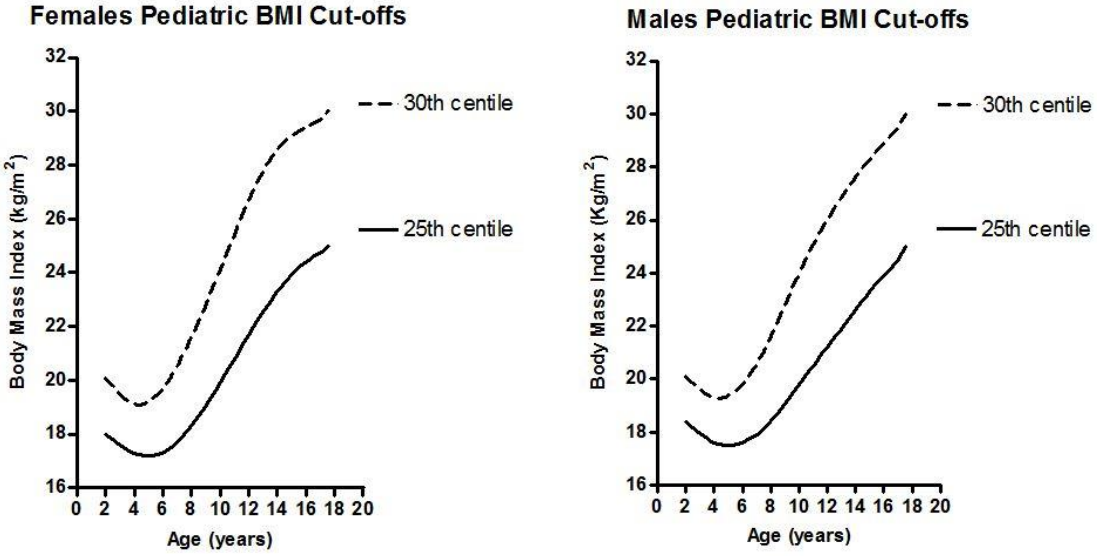

Figure 2.8 Pediatric cut-offs for overweight and obese by age and sex defined to pass through a BMI of 25kg/m2 and 30kg/m2 respectively at 18 years of age. (Figure adapted and redrawn from Cole et al. 2007. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*, 320{7244]).

Task Force (IOTF) (Figure 2.8) (101). This set was developed to transition smoothly into adult

cut-offs assigning pediatric BMI cut-off values that were statistically equivalent to adult, 25 kg/m^2 (overweight) and 30 kg/m^2 (obese) (65,101). IOTF reference curves are based on growth reference data - a large international sample with values describing the growth of a population - rather than on growth standards - growth in optimal conditions as seen with the WHO cut-offs (3,64).

Adult BMI cut-off values are constant across studies and countries, while any of the three cut-offs (WHO, CDC, IOTF) can be used for children and adolescents. This makes prevalence estimates and comparisons between studies, and countries complicated and difficult. The IOTF references underestimate obesity in Canadian children compared to the WHO and CDC as its cut-offs are at higher values of BMI, likely due to the use of different samples and different curve construction methods (146). Again, the WHO curves represent the way children should grow, and the IOTF curve represents the way children in specific populations did grow, suggesting Canadian children are likely bigger than they should be. The largest discrepancy between references is seen between the ages of 5-11 (2).

The Dietitians of Canada, the Canadian Pediatric Society and the College of Family Physicians of Canada recommend that the WHO growth charts be used for individual tracking of growth and tracking of the prevalence of OWO in Canadian, due in part to the underestimation by IOTF classification. This practice is used in multiple regions in Canada, including in the province of Saskatchewan (147,148). Conversely, the IOTF curves are the reference of choice for many academic and clinical studies, as well as scientific pediatric journals (e.g. International Journal of Obesity).

Pediatric BMI cut-offs are a major advancement for nutritional health monitoring of children and adolescents; however, there are still concerns regarding the validity of BMI as a

measure of body fatness or adiposity. BMI correlates not just with FM but also with LM, skeletal muscle mass and bone mass and is unable to parse weight into these respective components (65,149,150) . Changing mineralization and water content of lean and bone in children further complicates the ability of BMI to estimate fat (65,141) . Although BMI has a strong correlation to %TBF in children, the strength of this relationship is reliant on the tendency for children with low BMI levels to have low levels of FM and children with high BMI levels to have high levels of FM. In children with mid-range BMI, the levels of FM can vary drastically (65). Freedman et al. (2009) illustrate this in findings that a BMI over the 95th centile demonstrates 70-80% sensitivity (true positive) and a 95% specificity (true negative) for excess adiposity in children, while the sensitivity and specificity at lower values of BMI (85th-95th centile) are less accurate (99). With that said, the correlation between a BMI over the 85th centile and adiposity is high enough to have notable health implications for both male and female children and adolescents. This is illustrated in the diagnostic performance of BMI to identify metabolic syndrome (MetS; clustering of CVD and diabetic risk factors) and other cardiovascular health risks. Laurson et al. (2014) found that in children identified as having "normal weight (NW)" by CDC BMI standards, only 1.7% of females and 0.8% of males presented with MetS, compared to 9.2% of females and 6.8% of males identified as having overweight, and 24.6% of females and 35.4% of males identified as having obesity (151). These results also illustrate sex differences in the ability of BMI to identify FM, likely because of sex difference in body composition development; for example, from 5-18 years, BMI will increase in males by 50%, but most of these gains are due to FFM accrual. The relative contribution of FFM in females is notably lower (99). The consequences of this sexual dimorphism are also illustrated in the study by Laurson et al. (2014) whose finding indicate that with the same BMI classification, females have a greater health risk

than males (e.g. higher MetS in NW females than NW males). BMI increments are more likely associated with LM in males and FM in females, and FM will have greater health implications. This is likely why Freedman et al. (2009) suggest that while BMI in children is moderately sensitive and specific for excess body fatness, the use of alternative or additional measures to BMI may be essential for discerning actual adiposity and for identifying the associated risk (99) .

2.3.4.1 Critique of BMI for defining OWO

Obesity is a condition in which the accumulation of FM surpasses threshold values and begins to negatively affect one's health (152). A substantial body of research now documents the associations between OWO and numerous health consequences including Type II diabetes, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and stroke. Yet the strength, or even the direction, of the association between OWO and health can be altered depending on the criterion being used to classify OWO. This is because the risk associated with OWO has a stronger association with FM and to the distribution of fat, than with BMI or lean mass.

BMI can be extremely accurate and, in some cases, more accurate at predicting health risk than more specific measures of body fat. For example, in a recent study from the Mayo Clinic, BMI was associated with a higher hazards ratio (2.7) for CVD mortality than %TBF or FM index (fat to height indices) (1.6 and 2.2, respectively) from hydrostatic weighing and skinfolds (153); however, on an individual level BMI is still flawed, providing insufficient or even incorrect evidence of health concerns. For example, a recent study by Tomiyama et al. (2016) examined the classification of CMR by stratifying over 40,000 participants' data by standard BMI classifications. Of those classified as OW, over 33% were metabolically healthy (e.g. no dyslipidemia, insulin insensitivity, etc.) as were 29% of OB and 16% of OB type II and III individuals. Furthermore, over 30% of those classified as NW were cardiometabolically

unhealthy. This data implies that almost three-quarters of a million Americans have CMR that is misclassified.

BMI measures in children can similarly draw erroneous conclusions. Lower BMI values in childhood correlate with a lower likelihood of future OWO, and yet a normal BMI does not predict the absence of future OWO or health risk (99). Assessment and tracking of FM and health risk in children would likely benefit from the inclusion of measures that can provide information about the characteristic and location of excess weight (99,154). In light of the criticisms against BMI, McCarthy et al. (2006) produced %TBF cut-offs associated with the 85th

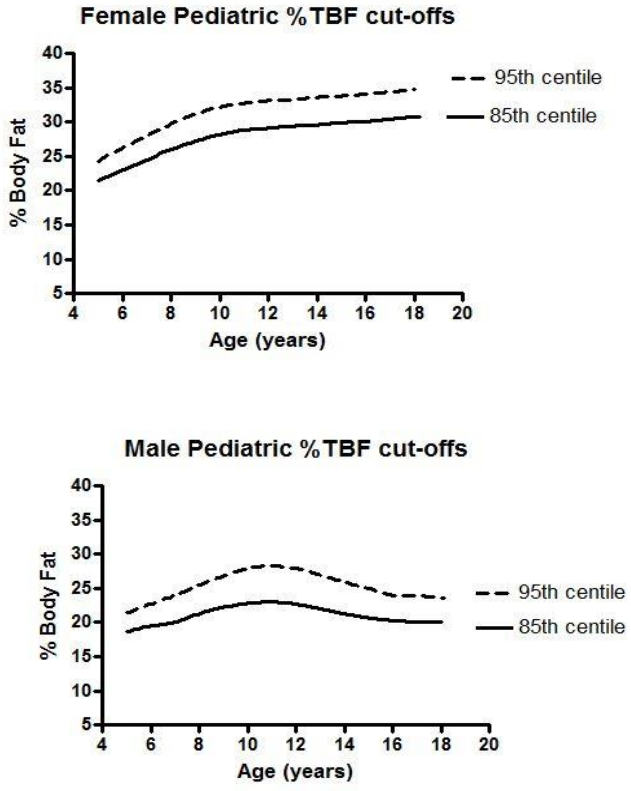

Figure 2.9 Pediatric cut-offs for overweight and obese by age and sex (Figure adapted and redrawn from McCarthy et al. 2006. Body fat reference curves for children. International journal of obesity. 30(4), p598-602).

and 95th centile from the IOTF pediatric BMI cut-offs by Colet et al. (2000) (Figure 2.9) (100,101). These cut-offs identify %TBF values indicating overweight (>85th centile) and obese

(>95th centile) and are frequently used in studies examining pediatric fat mass, especially fat mass in relation to health outcomes.

Another suggestion stemming from the criticisms of BMI is that measures that specifically identify elevated levels of abdominal (trunk) fat should be used. Abdominal fat can be estimated by waist circumference (WC), magnetic resonance imaging (MRI), skinfolds, dual x-ray absorptiometry (DXA), or indices such as waist-to-height or waist-to hip-ratios (155,156). This is important as trunk fat is strongly implicated in health risk and is associated with an atherogenic (promoting atherosclerosis) risk profile(8).

Findings by Laurson et al. (2014) demonstrate the inability of BMI to identify excess abdominal adiposity in children. Of those females identified as NW by CDC BMI cut-offs, 4.5% had WC values over the WC cut-offs linked with the National Cholesterol Education Program/Adult Treatment Panel III (ATP III) curves. Meanwhile, 37% OW and 2% of OB females did not have WC over cut-offs. In males, no NW individuals had high WC values, but neither did 87% of those classified as OW and 35% of those classified as OB (151). These results make a similar point to that of Freedman et al. (2009) that the validity of BMI to identify adiposity (and even more so abdominal adiposity) will vary with degree of BMI. This discrepancy is important to note because abdominal fat has demonstrated stronger links to MetS and CVD morbidity than BMI (157–159).

2.3.5 Prevalence of OWO in Adults by BMI

Recent world-wide estimates suggest that 37% of adults are OWO and that annual attributable deaths surpass 3 million (160,161). Canadian rates are equally alarming. The results from the Canadian Health Measures Survey (CHMS) from 2011-2012 suggested that 25% of

Canadians over 18 years are obese (about 6.3 million people) (152), and approximately 62% of adult males and 46% of adult females were OWO (26,152,160). Tracking the data from 2003 to 2014 suggest that rates of OWO have risen roughly 5% in males and 5% in females over the last decade (26). More recent estimates from the 2014 Canadian Community Health Survey (CCHS) estimate that out of almost 28 million adults surveyed, approximately 35% were considered OW (BMI over 24.99-29.99 kg/m^2) and almost 27% were considered obese (BMI $30kg/m^2$ or over) (162). As such, the most recent estimates suggest that roughly 62% of Canadian adults 18 years and over are OWO. Provincial rates in Saskatchewan are even higher than the national average with 32% of adults classified as OB (31% in Saskatoon). The most recent data from the 2015 Canadian Community Health Survey using direct measures of BMI estimate that just over 70% of Saskatchewan adults are OW or OB (162).

2.3.6 Prevalence of OWO in Children and Adolescents by BMI

Canadian data (2015) estimates that the prevalence of OWO more than doubles from childhood (under 18 years) to adulthood (over 18 years) (approximately 25% to over 60%) (25,26). Longitudinal data from the FELS study in the Unites States suggests that the most common ages for OWO onset are 10-15 years, and 20-25 years (20% of total OWO onset) in females, and 20-25 years (23% of total OWO onset) in males (107). The incidence drops from this age onward, suggesting that 50-60% of those who will become OWO in adulthood will have done so before the age of 35.

The prevalence of childhood and adolescent OWO remains high nationally and internationally despite some reports indicating that there may be stabilizing or declining trends (2,163,164). Analysis of data from 34 Organization for Economic Cooperation and Development (OECD) countries (2015) indicates that approximately 24% of boys and 22% of girls are OWO.

There appears to be a stabilizing trend in high-income countries over the past few decades but authors note that rates differed by sex, age, socioeconomic status (SES) and ethnicity (165). Other data, such as those from the Global Burden of Disease study (2013), suggests that numbers of OWO youth continue to rise even in developed countries (160). A 2013 report on Canadian preschoolers in Newfoundland and Labrador found that provincial rates of OWO had dropped between 2001/02 and 2009/10 (from 39% to 36%) and in one region the rates of OW in 2009/10 (14%) dropped below those of 1988/89 (22%); however, there was also one region (with the highest baseline OWO prevalence) which continued an upward trend (164). Canadian surveillance data up to 2013 concluded that childhood OWO had plateaued or decreased over the past 15 years. Authors acknowledge that trends differ somewhat by sex, age, SES and the method of data collection (1).

2.3.6.1 Differences in prevalence by collection method

The method used for the collection of data can alter the outcome and the accuracy of the data and make analysis of secular trends difficult. Direct measures provide the most accurate estimate of OWO in a population but these measures are more expensive, require trained personnel and tend to result in smaller sample sizes (152,166). Self-reported data such as BMI provides an inexpensive and easily conducted measure allowing for a very large sample size. As such, self-report is often used for large scale surveys such as the CCHM and CHMS. Authors of CCHM and CHMS warn readers to be aware of differences in collection methods between surveys when assessing OWO prevalence and secular trends (152). For example, comparing data from 2003 (self-report data) to 2004 (direct measure data) CCHS estimates an increase of almost 12% in the prevalence of OWO in youth 12-17 years from 14% to 26%. This type of jump is seen again between 2014 (self-report data) and 2015 (direct measure data) from 23% OWO to

45% OWO in 12-17 year. Self-report tends to under-represent OWO rates (2) . The method of collection is likely responsible for the lower prevalence in 2003 and 2014 using self-report compared to prevalence in 2004 and 2015 using direct measures. Parents also tend to misreport-over reporting BMI by underestimating their child's height. This results in an overestimation of the prevalence of OWO in young children by parental report (2,167). The 2002/03 parental reports of children 2-5 years and 6-11 years estimated 15% and 6% higher prevalences, respectively, than the directly measured estimates the following year (167). Interpreting the trend is made even more difficult as the over-report by parents in children under 12 is accompanied by an under-report by self-report in 12 to 17-year olds. A more accurate representation of secular trends can be obtained by comparing self-report to self-report, and direct measures to direct measures. When data collected the same way are compared it is apparent that there are increasing numbers of youth with OWO. It is observed that the prevalence of OWO by self-report increased by almost 4% from 2005 to 2014 in youth 12-17 years from 19% to 23% (24% to 29% in males and 15% to 17% in females).

There have been attempts by Statistics Canada and the Canadian surveys to use an adjusted self-report measure in order to compare between self-report data and direct measure data. Adjusted self-reported numbers are based on correction equations, and may provide a more accurate estimate than self-report alone without comprising the large sample size or the ease of data collection (152,166). The equation used by Statistics Canada was developed using the 2005 Canadian Community Health Survey data. A sub-sample of respondents had height and weight data collected using self-report and direct measure. The two measures were compared to identify responder bias (166). The adjusted self-report results from the CHMS 2011-2012 suggest that

26% of males, and 23% of females over 18 are OB; (an increase of 6% from self-reported data in both sexes) (152).

Although the self-reported and adjusted self-reported are lower than the directly measured prevalence, all three methods show increasing values in adult and child OB from 2003 to 2011/12 (152) and from 2004 to 2015 (162). As such OWO remains a public health concern in Canada due to the health implication of excess weight and the stability of OWO from one stage of life to the next (2,168).

2.3.7 Abdominal Fat and Health

In adults, clustering of CMR is found in those with higher TrF, even in those with a normal BMI (155). Stratifying OWO individuals by high and low waist circumference reveals disparate risk assessments; for example, high WC carries an odds ratio of the risk of MetS of 1.85 in OW women and 2.35 in OB women compared to having a low WC. Children and adolescents with more trunk or trunk-to-extremity fat often have more TBF, have higher cardiometabolic risk factors in adulthood, and are more likely to gain weight over the short term (169,170) . Conversely, lower limb fat has been suggested as being beneficial in regards to these same risk factors and has demonstrated a relationship with lower levels of blood glucose and insulin, and a lower prevalence of dyslipidemia and undiagnosed diabetes (157,171–177). Higher android-gynoid ratio (a ratio of fat on the trunk to fat on the lower body) is associated with higher CVD in NW children (178); a higher trunk-to-extremity fat by DXA is related to higher levels of CMR in NW adolescent females (179); and waist-to-height ratio was found to be a better indicator of increased cardiometabolic risk than BMI in a large meta-analysis of adult data (180).

In 2003 Health Canada adopted newly developed WC cut-off guidelines. This switch was prompted by the high correlation of abdominal fat with CMR and the inability of BMI to identify high abdominal fat (a BMI within normal weight parameters may be accompanied by a high and risk inducing WC) (181). These WC guidelines align with those of the WHO and state that there is an increased health risk associated with a waist circumference ≥102 cm in adult males, and ≥88 cm in adult females. These are the same values promoted by the Adult Treatment Panel III (ATP III). The ATP III is a set of guidelines used for prevention, identification and treatment of high cholesterol and other related cardiometabolic risk factors (182). Previous body-shape indicators of increased risk used by Health Canada included waist-to-hip ratios of ≥1 in males and ≥0.8 in females (143).

Many countries (Italy, Cuba, Australia, and Britain) have developed WC or waist-to-height/hip ratios percentile curves for children and adolescents. The purpose of these cut-offs is to identify adiposity related to health outcomes. Canadian WC percentile curves have also been developed identifying the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 95^{th} centile (183). Although those along a higher centile have greater health risk than peers with a lower centile there is no recommended cut-off. In Australian children, a WC value over the 85^{th} centile identified those with the highest percentiles for %TBF, TG and systolic blood pressure (SBP) (184). Authors of these papers all identify the need for a WC reference for children like that created for BMI by Cole et al. (2000) (101). The preference would be for one that is based on longitudinal data with the ability to link WC during childhood to health outcomes in later life (183). One attempt to create this type of "health-related" cut-off in Spanish youth found that the 70^{th} percentile of WC identified elevated metabolic and cardiovascular risk outcomes during childhood and adolescence. Authors suggest that the 70^{th} percentile was the optimal threshold (185). A

Canadian threshold of the 75th centile would yield cut-off values ranging from 66.5 cm for 11-year-old males, to 79.6 cm for 18-year-old males; and from 64.2 cm in 11-year-old females to 73.8 cm in 18-year-old females (183). These WC cut-off values are much lower than those developed by Joliffe & Janssen (2007) based on the adult cut-offs from the ATP III and International Diabetes Federation (IDF), but not dissimilar from the mean WC of Canadians ages 12-19 identified by Janssen et al. (2011) from 2007-2009 CHMS data, particularly the 18-year-old cut-off. Janssen et al. (2011) identified a mean WC of 77.5cm (95% CI, 74.9cm, 80.1cm) in males, and 74.8cm (95% CI, 72.8cm, 76.7cm) in females.

2.3.8 Overweight and obesity trends by abdominal fat indicators

Over the past 30 years, the secular trends in adult BMI has been accompanied by increasing cardiometabolic risk factors such as fasting glucose and diabetes prevalence (186,187). The data is more discrepant in children regarding the relatedness of BMI to other health risk factors. It is unknown the degree to which CMR factors are dependent on BMI and BMI trends. The known risk of abdominal obesity over and above BMI suggests that OWO prevalence and trends may not provide the full picture of current and future health risk (8,9,154). Trends in high blood pressure in American children appear to be declining while incidence of Type II diabetes is increasing and both are co-occurring with increasing BMI, abdominal obesity and skinfold thicknesses (188–190). In British youth, the prevalence of OWO is higher in children when using indicators such as WC and waist-to-height ratio than when using BMI (191). While BMI prevalence appears to have plateaued in British youth, the "at risk" by waist-to-height and obesity by WC have not (191). Similarly, the prevalence of MetS (excluding high WC criteria) in adults is higher in those who surpass NIH WC cut-offs (>102cm in men; >88cm in women) than in those who are categorized as OW by WHO BMI cut-offs (MetS prevalence 19

% versus 22% in men; 23% versus 18% in women) (192). A major public health concern may go unnoticed if only BMI trends are followed. Increases in abdominal obesity are potentially mediating or masking the relationship between BMI and health risk. While BMI may be beginning to plateau in Canada, other measures such as WC and their comorbidities may not be (193) and, as such, an assessment of WC or other measures of abdominal obesity should accompany BMI (194).

Waist circumference has increased even more than BMI since the 1980's in Canada, and observed increases in adult WC cannot be accounted for by increases in BMI alone (194,195). Pediatric WC percentiles in the UK increased more than BMI percentiles from the 1970's to early 2000's, with greater increases in centiles for girls than for boys (196,197). Canadian WC and skinfolds are higher at a given BMI than they were in the 1980's (194). Specifically, comparing WC data from the CHMS 2007/9 to those from 1981, WC measures at a BMI of 25 kg/m^2 (or pediatric equivalent) demonstrated a 1.1 cm increase in men, a 4.9 cm increase in women, a 1.6 cm increase in boys, and a 4.1 cm increase in girls. Skinfolds were similarly higher by 9% in men, 12% in women, 14% in boys and 14% in girls between 1981 and 2007/09 (194). The positive linear relationship (slope) between BMI and WC was higher in 2007/9 than in 1981 in males and females, as was the median value of each age group (194). These secular changes have resulted in 14.6% of Canadian males and 30.6% of Canadian females aged 12-19 years having WC at levels considered to have increased-risk in 2007/2009 according to WC cut-offs linked to the adult ATP III criterion (198,199). American data suggests an independent increase in WC (over and above changes in BMI) of 0.86 cm (0.53-1.19), with greater gains in adults <49 years than >49 years, males more than females, and in OB more than NW or OW populations (197). Similar secular trends were observed in developmental curves of adolescent BMI and

skinfolds using two Saskatchewan longitudinal studies conducted 30 years apart. The Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) data from the 1990's demonstrated significantly greater skinfold thickness (including abdominal SF) but not BMI in comparison to the Saskatchewan Growth and Development Study (SGDS) data from the1960's while controlling for height, maturity and sex (200). Again, this suggests that fat indices are increasing, independent of BMI; and, while ½ to ¾ of the secular trend of increase in youth WC may be explained by increases in BMI, there are trends in WC that are independent of BMI (193).

2.3.9 Summarizing OWO measures

BMI use is widespread and will likely continue to be the tool of preference because of its population level correlation with health concerns, the ease and low cost of application, the consistent use across time, and the ubiquitous use internationally. These characteristics allow for optimal analysis of health in large data sets, for trend analysis, and for comparisons between populations. With that said, the inability of BMI to parse FM from LM, and total (or lower) body fat from TrF cannot be ignored. This is especially important during the years of growth and development. The years of childhood and adolescence see changes in body composition, sexual dimorphism, and changes in BMI that do not relate equally to changes in fat mass, lean mass and bone mass between sexes or between individuals (69,201). This is important to note because it is not just weight or BMI gains *per se* that are cause for concern but rather fat mass gains and specific fat depots that contributes to the comorbidities of OWO. There is also a suggestion that the age at onset of OWO may have different implications on health.

2.4 *OBESITY AND CARDIOVASCULAR DISEASE*

2.4.1 Overview

In recent history, the onset of OWO was solely in adulthood. More recently the onset has moved to childhood and adolescence, although this still remains less common than adult onset (69). The prevalence of OWO increases with age and those with more FM at an earlier age tend to put on more FM and become larger in adulthood than those with less FM at an earlier age (25,26). Metabolic dysfunction and CMR factors that were once the concern of older adults are being found in children and adolescents. Stability of lifestyle factors and weight status (OWO) contribute to increasing CMR levels as the child with OWO grows into an adult with OWO (202,203). The evidence is clear that CVD and metabolic risk factors can, and do, arise during the developmental years (204,205). According to The International Diabetes Federation (IDF) criteria, 2% of Canadian and 9% of American youth have MetS, with an estimated 50% of American and 38% of Canadian children and adolescents having at least one risk factor for CVD and MetS (49,206,207). The prevalence in adults is much higher, with between 11% and 22% (depending on the definition used) of Canadians and 22% to 34% of Americans over 18 years presenting with MetS. The prevalence increases with increasing age (49,206). The most common risk factors in Canadians are low HDL's and high abdominal fat or high WC (49).

2.4.2 Definitions of Cardiovascular disease, Metabolic Syndrome and Cardiometabolic Risk

The direction and strength of the association between BMI and health remains controversial, whilst the literature on the association of abdominal fat with health is unequivocal. The type of fat mass and its location are critical in the etiology of OWO related disease (see Section 2.4.1). Disease is not an inherent property of FM *per se*; rather, the clustering of cardiovascular and metabolic disease risk factors that often accompany OWO are consequent of

adiposopathy (inflammation and dysfunction adipocytes) (155). OW adults can be metabolically healthy and NW adults can present with cardiometabolic abnormalities. These metabolic differences have been attributed to differences in PA levels, physical fitness and waist circumference (131,155,208,209), factors which exert their influence independent of BMI or FM. Nonetheless, CVD risk factors such as hypertension, hyperglycemia, IR, and morbidity such as diabetes and liver disease are far more common in OB adults than in NW adults (133).

There are a variety of mechanisms by which obesity relates to these risk factors and to CVD (7). One of the most significant and direct links between obesity and CVD is the development of atherosclerosis (46). Atherosclerosis is the hardening of the arteries and plaque formation on the inside or lumen of the blood vessels. Plaque formation is the result of genetic predisposition, sedentary lifestyle, poor diet and/or inflammation. Each of these factors correlate with OWO (Figure 2.1). Unaddressed atherosclerosis will almost inevitably lead to CVD (e.g. coronary heart disease, myocardial infarction, hypertrophic cardiomyopathy) (210–213). CVD risk is often expressed in mathematical terms as seen in the Framinham Risk Assesment score and similar metrics. Equations are developed in which presence/absence or level of risk factors (age, cholesterol, smoking, etc.) are assigned a numerical value. Values are summed and the total points are associated with a percent risk over a score of zero. The percent risk identifies the elevated risk of experiencing a cardiovascular event, such as coronary heart disease or stroke, attributable to current risk factor status (214,215). Older individuals, males and those with a smoking history are at higher risk.

There is an interplay between the risk factors and the presence of CVD and Type II diabetes (T2DM) such that one condition is often complicated by the presence of the other, and magnified by the presence of additional risk factors (46). Type 2 Diabetes Mellitus (T2DM) is a

progressive condition of IR resulting from chronic hyperglycemia and insulin insensitivity. It is linked with myriad contributing factors, many of which are the same as those contributing to CVD including sedentary lifestyle, genetics, obesity and poor diet (216–219). There is an increased relative risk of both CVD and T2DM when a clustering of risk factors are present (46). The term and concept of MetS (a subgrouping of cardiovascular and diabetic risk factors) is used to express this relative risk. The presence of MetS is predictive of IR (and thus T2DM), and is linked to abdominal obesity which is the highest risk morphology of OWO.

The criterion for Mets includes visceral obesity (measured by WC), dysglycemia, hypertension, elevated TG and low HDL-C (Table 2.1) (220). The specific cut-offs for each

Table 2.1 Definition of the Metabolic Syndrome- Criterion for diagnosis. (Table adapted and redrawn from the International Diabetes Federation consensus worldwide definition of the metabolic syndrome, 2006. https://www.idf.org/e-library/consensus-state

Elevated waist circumference*	Population- and country-specific definitions (IDF uses ≥94cm for Caucasian men and ≥80cm for Caucasian women)
Elevated triglycerides (on treatment for elevated triglycerides is an indicator ŧ)	≥150mg/dL (1.7mmol/L)
Reduced HDL-C (or on treatment for reduced HDL-C is an indicator ŧ)	<40mg/dL (1.0 mmol/L) in males; <50mg/dL (1.3mmol/L) in females
Elevated blood pressure (on antihypertensive drug treatment in a patient with a history of hypertension is an indicator ŧ)	Systolic ≥ 130 and/or diastolic ≥85 mmHg
Elevated fasting glucose ŧ (drug treatment of elevated glucose is an indicator)	≥ 100mg/dL

*It is recommended that the IDF cut points can be used for non-Europeans and Europeans until more data are available

ŧ Patients taking fibrates or nicotinic acid or high doses of ω-3 fatty acids can be presumed to have high triglycerides and low HDL-C.

ŧ Most patients with type 2 diabetes mellitus will have the metabolic syndrome by proposed criteria.

factor varies by definition (WHO, IDF, National Center for Environmental Prediction-NCEP: ATP III), but a recent harmonized set of criteria has simplified and universalized the interpretation and diagnosis of MetS (221). According to the IDF, the waist circumference cut-

offs for elevated risk are ≥ 94 cm for males, and ≥ 80 cm for females. The values are the same for Asian, South Asian, South and Central American and African females but 4 cm lower for African men (220). The IDF also notes that the inclusion of additional metabolic measures such as Homeostasis-Insulin Resistance (HOMA-IR; fasting insulin/fasting glucose), and the presence of inflammation (C-reactive Protien) can increase the predictive power of MetS risk for CVD and T2DM (46).

The presence or absence of risk factors are considered dichotomous, and the presence of 3 or more factors indicates MetS. While the IDF previously considered an elvated WC to be obligatory for a MetS diagnosis, recent harmonization of diagnosis receommendations now suggest that while it is a useful screening tool and MetS risk component, it is no longer a mandatory criterion (221). The presence of MetS increases the relative risk of both CVD and diabetes; and the presence of MetS in conjunction with other traditional CVD and diabetes risk factors (obesity, age, sex, smoking, inactivity, unhealthy eating) indicates one's cardiometabolic risk (CMR). CMR is the result of the global CVD risk determined from traditional assessments like the Framingham Risk Assessment, combined with additional risk present in those with MetS. The term CMR was developed to encompass and capture the presence of all CVD and T2DM risk factors of which OWO is one (46). CMR profiles provide an overall picture of health rather than an absolute risk measurement. These profiles are clincially important for identifying patterns and potential for disease (46).

Children and adolescents rarely meet the entire criterion of MetS or CVD. Because risk factors are not present at high enough levels to constitute a diagnosis of MetS, many authors have begun to use a continuous metabolic risk score to identify an elevated risk of MetS in the absence of the full constitution (169,222–224). This method regresses metabolic variables of

blood pressure, TG, cholesterol, HOMA-IR, and waist circumference onto CA and smoking status. The standardized residuals are saved and summed to create a continuous risk score. BMI z-score can be added, or WC taken out of the equation depending on the research question (225). A high score is indicative of a greater CMR risk factor profile (169,223).

The following will discuss what is known about the pathophysiology of obesity which leads to CMR factors of elevated blood pressure, cholesterol, blood sugar and insulin, and how these CMR factors contribute to CVD.

2.4.3 Biology and Pathology of Adipocytes and Obesity

Adipocytes are the fat cells of the body. Their primary use is as a collection facility for energy, stored in the form of TG. Fat cells cluster in the body as fat depots; for example, as subcutaneous fat (under the skin), and visceral fat (around organs). These clusters are held together by connective tissue structures made of collagen. Clusters are well innervated and vascularized. In addition to energy storage, adipose tissue is also an important endocrine organ responsible for secreting beneficial hormones such as leptin and adiponectin for growth, appetite, immune function and metabolism (47).

Adipocytes follow four stages of differentiation. The first stage of adipoblast, or precursor adipocyte cell, is formed during the embryonic stage. Adipoblasts differentiate into pre-adipocytes and then to very small adipocytes, at which stage small lipid droplets are present (69). The final stage of differentiation is the mature adipocyte. Newborns are estimated to have approximately five billion adipocytes with a diameter of about 30-40 μm. During childhood and adolescence, adipocytes increase in number and size to approximately 30-50 billion with a diameter of 80-100 μm in a non-obese adult (69). Hyperplasia and hypertrophy of adipocytes occur with increasing body size and are essential to adequately meet the high energy demand of

growth; however, when caloric intake exceeds demand, pathological increases in size and number of adipocytes can ensue. Altered growth hormones can also lead to pathological processes affecting adipocytes; for example, elevated insulin will lead to increased adipocyte size and number in addition to excess fat mass (69,226). Elevated growth hormone will increase number and total mass but not the size of adipocytes, whereas a deficiency will result in an increase in cell size and total mass but not number of adipocytes (226).

When growth is not occuring (adulthood) or not occuring as rapidly (mid-childhood), an excess of caloric intake to caloric expenditure ratio is easily attained. Adipose tissue accomodates excess calories (stored as TG) by enlarging (hypertophy) or by multiplying (hyperplasia) (69). Many of the detrimental metabolic consequences of weight gain can be mitigated if the adipocytes are able to proliferate as many small adipocytes tend to be more metabolically healthy than fewer large adipocytes; however, in a portion of the population, adipocytes are unable to effectively multiply. In some individuals (more so in males than premenopausal females) there may also be an inability of subcutaneous fat to exapand adequately, and so fat deposition favors deep (visceral) depots (158) .

The distribution of adipocytes in the body is partially under the control of genetics with high correlations for visceral fat and abdominal fat between family members (see section 2.3.1). Candidate genes have been identified that upregulate visceral fat accumulation through increased number of deep glucocorticoid receptors, or alternatively by promoting peroxisome proliferator-activated receptor-y (PPAR-*y*). PPAR-y are agonists which promote hyperplasia of subcutaneous adipocytes (69,133,227). Treatment with agonists of PPAR-y increase hyperplasia of subcutaneous tissue, decrease inflammation (C-reactive protien levels), and lower ectopic liver fat (133,227). These findings suggest that genetics play a role in adipocyte health.

Hypertrophied adipocytes will at some point reach a tipping point or a ceiling for size. When this capacity is exceeded, inflammation begins. Enlargment of adipocytes from chronic overfeeding strains the mitochondria and the endoplasmic reticulum of the enlarging adipocytes, eventually damaging these cellular structures. Furthermore, adipocytes produce adipokines like leptin, adponectin, vistafin, and resisten, all of which modulate metabolic processes and alter endocrine function. Levels of these adipokines are altered when adipocytes are stressed and, most often, high levels of adipose tissue are accompanied by adipocyte stress. This is demonstrated in the positive correlation between adiposity and levels of inflammatory adipokines and inverse correlation between adiposity and anti-inflammatory adipokines (i.e. adiponectin) (124). Metabolic and endocrine dysfunction, and adipocyte damage lead to dysfunction of body systems, and precede chronic diseases leading some authors to propose that obesity is in fact a disease of adiposopathy - an endocrine disease of the fat cells (47,228).

When adipocytes are damaged, an inflammatory cascade is initiated. Characteristic of all cell damage is the release of cellular stress factors. In the case of obesity related inflammation, pro-inflammatroy cytokines such as IL-6 and TNF-alpha are released from the oversized-overstressed adipocytes (229). These cytokines interfere with insulin signalling and further aggravate the inflammatory process. Additional damage is done by Reactive Oxygen Species (ROS) which are released during excessive feeding (230). These ROS's initiate a further cascade related to IR.

Eating induces thermogenesis and the release of glucose into the body due to the activation of the Sympathetic Nervous System (SNS). Over-activation of the SNS leads to a chronic stress response in the body which is linked to inflammation through the HPA-axis, and insulin and glucose dysregulation. Overeating leads to continual activation of the SNS,

inflammation and the excessive release of free fatty acids (FFA) into circulation. Levels of circulating FFA relate linearly with FM and even more so with visceral fat than subcutaneous fat (133). Central and visceral adipocytes are very metabolically active with elevated responses to catecholamines such as epinephrine, a stress hormone related to and released during inflammation, and SNS activation of β-adrenergic receptors throughout the body. Catecholamines in turn stimulate hormone sensitive lipase (HSL) which breaks down TG to release additional FFA into the blood (7). Visceral adipocytes are also problematic because they produce greater amounts of pro-inflammatory cytokines such as TNF-a and interleukins, in comparison to fat in other depots. The pathological cascade relating to obesity originates with an accumulation of excess body fat. In those who are genetically predisposed or epigenetically at risk, adipose tissue has an even greater liklihood of becoming pathogenic - hypertrophying and becoming inflammed. It is this adiposopathy and inflammation which is central to the disease processes related to CVD (47).

2.5 *DIET*

2.5.1 Energy Intake and Fat Mass

Fat mass accumulates when there is a caloric imbalance between caloric intake and caloric expenditure. A prolonged imbalance of 100-200 kcal/day can lead to the development of OWO in children (231,232). The literature suggests the contemporary calorically dense “Western” diet has played a pivotal role in the secular trend of increasing OWO rates; however, controversy remains as whether or not OWO trends are accompanied by changes in energy intake (233,234).

It is clear that a reduction in caloric intake can be effective in lowering body weight (234). A Cochrane literature review of children aged 6-11 suggests that interventions that include dietary changes are effective at reducing BMI or BMI z-score in children, although the authors

suggest that the quality of the evidence is low (91). Longitudinal evidence suggests that caloric intake is not directly linked with acquiring OWO. One study demonstrated that caloric intake decreases from the age of 13 to 27 years but the odds ratio of OWO at 27 years was 0.37 for total caloric intake. This suggests that those who acquire OWO consumed fewer calories during adolescence (118).

There are two large studies which convincingly implicate total calorie consumption in the etiology of OWO. The study by Berkley et al. (2000) tracked 10,000 9 to 14-year-olds for one year and found that children with larger increases in BMI had higher total caloric intake. Specifically, an increase of 0.0059 and 0.0082 kg/m^2 in females and males respectively, was found for each 100 kcal/day increase (235). The second study by Ong et al. (2006) demonstrated that in almost 900 infants, an increase of 100 kcal/day at 4 months increased the risk of OWO at 3 years by 1.46 and at 5 years by 1.25 (236). This suggests that diet during infancy can influence future OWO risk. A review of both longitudinal and cross-sectional studies of dietary intake in children and OWO concluded that "with the exception of infants, there are no conclusive associations between energy intake or diet composition and later overweight development in children" (232), whereas an earlier review of ecological data concluded that recent increases in energy intake is a "major contributor" to increases in weight (233). Evidence for the success of lowering caloric intake for weight loss is more cogent than that for sustaining a lower caloric intake to prevent OWO onset. These discrepancies may be attributed to the diversity of dietary patterns and macronutrient compositions possible in iso-caloric diets (234).

2.5.2 Dietary pattern and fat mass

The WHO continues to implicate diet in the etiology of OWO; however, it is important to note that the WHO specifically implicates change in dietary pattern rather than increasing energy

intake (237). The type and timing of food ingestion may be more salient than total calories. This idea is suggested in a study of 13 to 18-year-olds dietary habits in which having a morning and afternoon snack, and a slower speed of eating were significantly related to lower FM and abdominal fat, while there was no significant relationship between total caloric intake and FM (238).

Cross-sectional findings suggest that eating while watching television and skipping breakfast are risk factors for OWO (239). Longitudinal studies have found that while total caloric intake does not significantly increase the risk of OWO, sugar sweetened drinks, snacking, fast food, and portion size are related (232,240). For example, data on children aged 4-8 years found that patterns of high fried-food intake were consistently associated with higher levels of FM (kg), and high intake of dark-green and deep-yellow vegetables were associated with lower levels of FM. These relationships were independent of PA, age, sex, size and sedentary time, and were adjusted for total caloric intake (241). Similar cross-sectional findings from adolescents indicate a significant positive relationship between proportion of fat in the diet with BMI, and TrF (242). Authors of this study found that mono- and poly- unsaturated fats were inversely related to fat and TrF, while saturated fat was not related. They also acknowledge contradictory literature and suggest that the specific role that subtypes of fat may play requires further investigation. Variation in other macronutrients may also influence FM. Diets low in carbohydrates and high in fat have shown to selectively decrease abdominal fat in addition to lowering total fat mass better than low fat diets in obese men and women (243). It has been suggested that low carb diets may be more effective in reducing visceral fat than a low calorie/high carbohydrate diet, at least in obese subjects with T2DM (244).

2.5.3 Diet and CMR

A meta-analysis of weight loss interventions by Zomer et al. (2016) found that weight loss decreased CVD risk irrespective of whether the intervention employed PA, diet or both (245). Conversely, dietary counseling of children 5-15 years resulted in a lower presentation of 2 or more CMR risk factors (TG, low HDL, glucose, BP) in children with OW compared to control children with OW, despite the finding that the intervention did not affect the prevalence of OWO between groups (246). These findings suggest that diet can influence disease risk independent of any influence on FM.

The nutrient composition of the diet may be also be relevant to cardiometabolic health; for example, cardiometabolic health improves in OB children when vegetable protein and whole grains consumption is increased (247). Diet may also improve health by affecting the distribution of fat, or through other means independent of fat loss or location. For example, low-carbohydrate high fat diets increase insulin sensitivity (243) and lower C-reactive protein (an inflammatory marker) (248) in OB adult participants, independent of loss of intra-abdominal fat. Also in OB participants aged 21-62, a low-carbohydrate versus high-carbohydrate diet demonstrated greater decreases in blood lipids and systemic inflammation and a greater increase in HDL cholesterol and adiponectin, with similar changes in body weight and composition (same change in hip-to-waist ratio) (248). High fat diets remain controversial, and although some clear metabolic benefits have been documented, conclusive evidence has not (249), and findings are based primarily on interventions with adults, not children. It is also important to note, as mentioned by Kosinski and Jornayvaz (2017), that much of the literature on high fat diets often incorporate lifestyle interventions, and exercise itself is known to confer cardiometabolic improvement.

The amount of activity or inactivity one accumulates may mediate the relationship between diet and FM. Sedentary time was found to significantly relate to CMR in adolescence independent of dietary intake; however, authors of this study suggest that more work needs to be done to isolate the role of dietary intake (250). It is more likely that activity and diet work together. Longitudinal data from the Amsterdam Growth and Health Longitudinal Study (AGAHLS) suggests that those with metabolic syndrome at 36 years had a trend towards higher energy intake throughout the time course from 13-36 years, concomitant with decreasing levels of high intensity activity (251). The extent to which diet alone could maintain improvements in cardiometabolic health in the absence of physical activity (PA) could be substantially less than when the two positive lifestyle behaviors operate together.

2.5.4 Physical Activity Overview

The health benefits associated with PA are well documented in the literature. A dose response is also identified between PA and health even at very small increases in PA level (252,253). Inadequate levels of PA are found in most Canadian adults. Only about 15% of adults meet the criteria of 150 minutes per week of moderate-to-vigorous PA (MVPA). These low levels of PA are in accord with secular trends of increasing BMI and WC (254,255). Sedentary time continues to increase in adults and in children despite the known association between sedentary behaviors and health, and there is increasing concern over the association of sedentary time and health consequences (256,257). Increasing sedentary time found in children and youth is concomitant with secular trends of decreasing active transport, time in physical education classes, and minutes of free play (258). These trends are particularly concerning considering the evidence of the link between PA in childhood, and PA and health in adulthood (259–261). The pathways by which childhood PA influences adult health can be either direct or indirect.

Adequate PA during earlier life may delay the onset or slow the rate of development of health risk factors, thus directly improving adult health status. Adequate childhood PA may increase the likelihood of individuals maintaining adequate PA into adulthood and thus indirectly influence adult health (205). The mechanisms behind these pathways may be mediated by lower body fatness throughout the lifespan which is often associated with higher PA (52,259,262–264). Body fatness and PA are each independently related to CMR factors.

2.5.5 Physical activity and Fatness

The question of whether PA prevents OWO has been heavily researched. While findings remain discrepant, most studies suggest a correlation between PA and FM. Many studies suggest that PA is inversely related to FM gains. One large cross-sectional sample including over 6000 children from 12 different countries found that moderate PA (0.49), vigorous PA (0.41) and sedentary behaviour (1.19) were all significant predictors of OB (265) . Findings from a randomized control trial of a PA intervention with 900 12-year-olds followed for 4 years also highlighted the importance of PA. At the end of the four years, the school that received the intervention had higher levels of PA, lower prevalence of OWO students, and lower gains in FM indices in those adolescents who were NW at baseline (266). A review of 32 longitudinal studies of adolescent PA and concurrent fat gains similarly concluded that PA or decreased sedentary behaviour is protective against FM gains and OWO onset. This supports a growing emphasis on PA education and intervention. PA can establish beneficial lifestyle habits and prevent OWO and early onset of CMR.

There are also contradictory findings which suggests that there is no relationship between PA and OWO, or that BMI predicts declining PA but low PA rarely predicts increasing BMI (267–269). One study of over 8,000 young women tracked over 4 years found that self-reported

PA had no relationship to change in BMI (270). Findings from a longitudinal study of 8 to 11-year-olds found that a higher Fat Mass Index at baseline predicted lower PA and higher sedentary time, but not the other way around (271). In a 1-year follow-up of 421 young adults, those with lower levels of PA had the highest body weight at base line and the largest increase in FM after controlling for change in moderate-to-vigorous PA. This suggests that high BMI begets high BMI irrespective of PA level or PA change (272). The relationship between PA and fat mass may be bi-directional (205). On the one hand, low PA and high energy intake creates a caloric imbalance leading to fat gains. On the other hand, carrying a an excess of body mass may be more physically and psychologically strenuous and relate to a greater perception of barriers to exercise in comparison to the perception of non-overweight individuals (205,273). Additional factors such as social expectation, self-esteem and judgment are related to OWO and PA behaviour, especially in youth (274).

Explanation for differences in the directionality and significance of findings may again be dependent on the type of measurement used. BMI is a surrogate for fatness, but this metric also includes LM. Muscle mass can increase with PA interventions whereas adiposity and abdominal FM often decreases with PA interventions thus confounding findings of a relationship between fatness (by BMI) and PA. This is seen in findings from the AGAHLS in which adolescent PA was significantly associated with skinfolds but not with BMI (275). This study also found that adolescent skinfolds were better predictors of adult fatness by DXA than adolescent BMI (276). There is also often a stronger association when measures of PA are objective, such as those collected by accelerometer, and when metrics of fatness such as abdominal fat/WC are used rather than using BMI as a proxy for fatness (205).

The intricacies of the relationship between PA and fat mass add to the complexities of the relationship between PA and CMR. Indeed, PA is associated with body composition and CMR, which are also independently related (277,278).

2.5.6 Physical activity and Cardiometabolic Health

There is a general belief that a decrease in FM is found with increased PA. But the relationship between PA and FM is only one facet of the relationship between PA and health (279).

PA elicits beneficial changes in multiple body systems including the musculoskeletal, cardiovascular, endocrine, immune and metabolic systems (264). As such, normal levels or loss of BMI underrepresents the health benefits of PA. Specific examples of the benefits of regular PA include: increased mitochondrial size and function, which elevates fatty acid oxidation; improved oxygen transport to working tissues; improved glycemic regulations by mobilizing GLUT4 transporter to cellular membranes for glucose uptake and use; stronger myocardium and vasculatures, which improve cardiac output, cardiac contractile and volumetric properties; and up regulated antioxidant defenses and possible improvements in the number and function of innate immune cells (280–285).

Physiological adaptations to regular exercise improve CMR. While many of the improvements may be greater when accompanied by weight loss, there is much evidence to suggest that PA mitigates CMR independent of weight loss. Changes in body composition may contribute to these improvements. Indeed there are numerous studies, longitudinal, cross sectional and systematic reviews, suggesting that PA has the ability to target visceral and abdominal fat even in the absence of weight loss (169,202,205,264,279,286). PA also improves individual and clustered metabolic risk factors (278,281,287,288). PA has demonstrated an

inverse association with SBP, TG, total cholesterol, Total/HDL ratio, IR, sum of four skinfolds, and T2DM. For example, in a literature review by Ross and Bradshaw (2009) it was found that in 17 randomized control trials of exercise interventions of varying age groups, only modest weight loss was reported; however, the majority of the studies found significant reductions in visceral fat (289). A systematic review of the pediatric literature found similar results, with vigorous PA having the strongest association with body fat, abdominal fat and cardiorespiratory fitness (278). Although the review did not find the association between levels of PA and clustered CMR to be significant, 1/3 of the studies featured did find a significant relationship with one or more risk factors (278).

Finally, cardiorespiratory fitness is a strong predictor of all-cause and CVD mortality (278,290,291). Obese-unfit men carry a higher risk ratio of all-cause mortality (odds ratio=1.9) and CVD mortality (odds ratio= 4.1) than lean-fit men. Obese-high fit men have a lower odds ratio of all-cause mortality than lean-unfit men, and of CVD mortality than lean and NW-unfit men (290). There is a general agreement that cardiorespiratory fitness (CRF) can be attributed to a combination of inherited factors and individual PA behaviors, and that vigorous PA likely has a stronger association with CRF than does light to moderate PA (277,278,290,291). It is also important to consider the implications of the bi-directional relationship between fatness and PA/fitness, and how this relationship influences cardiometabolic health. Those with a higher genetic ceiling for CRF (healthier mitochondria and more muscle mass) may participate in more PA; and higher PA levels can lead to lower fat mass, greater fitness and thus better cardiometabolic health (277,292).

With technology has also come burgeoning evidence suggesting a common genetic etiology between cardiovascular health, PA behaviour, fatness and fitness (293,294).

Specifically, a negative genetic correlation was found between aerobic fitness and %TBF; grip strength and CVD; obesity associated (FTO) gene and PA; and FTO gene and grip strength. The relationship between fitness (grip strength) and CVD was highest in those with the greatest genetic risk of CVD. The evidence also suggests that fitness is causally related to CVD and that maintaining physical strength may mitigate future CVD events, especially in those individuals most at genetic risk (293,294). This common origin linking behaviour and physiology may also explain why most data places low PA chronologically before fat accrual, but there is other data suggesting that fatness comes first (271). A bi-directional relationship or common underlying genetic basis suggest that preventative efforts should likely focus equally on weight status and lifestyle behaviours.

Despite large amounts of evidence supporting the association of adult PA with adult health, and child PA with child health, there is a dearth of evidence linking child PA with adult health. Within a life course perspective, there is a logical unanswered question: Does PA and health in earlier life carry any long-term health benefit into adulthood and are adult benefits reliant on adult lifestyle and fat mass? The following section will provide an overview of findings relating PA to FM during critical periods, health in later adult life, and potential moderators and confounders.

2.6 *CRITICAL PERIODS – THE INTERPLAY BETWEEN GROWTH AND DEVELOPMENT, FAT MASS, PHYSICAL ACTIVITY, AND CARDIOMETABOLIC DISEASE THROUGHOUT THE LIFE COURSE*

Exposure to stressors during critical periods are more likely to lead to chronic dysfunction than exposure at other times due to the high malleability of systems, tissues and organs during these periods (121). There is clear agreement in the literature that there are critical periods of development for OWO, and growing support for the link between early FM gains and OWO onset during critical periods, and later cardiometabolic diseases (12,16,295). What has been less explored is if mitigating factors of FM, PA, and diet during critical periods can operate as an antagonist to the onset of OWO, and by association CMR factors (121); for example, can the plasticity of body systems during these periods offer an opportunity in which PA can improve function and have a heightened and lasting influence on body composition, adult weight status and health (121). PA can act in opposition to fat accrual and promote optimal development and function of these tissues and systems, for example by assisting in glucose uptake, lowering stress hormones and inflammatory cytokines, and decreasing adipogenesis (121,264). PA may be able to "set a trajectory" for later life health, both habitually and physiologically, although this is less understood (121). There is also discrepant information on whether the influence of PA is strong enough to counter pathological trajectories of FM and CMR set earlier in life.

2.6.1 Prenatal life - maternal health and physical activity

The role that early life exposures have on life course health trajectory is demonstrated in the associations between BW and later life disease (296). Fetal growth and the intrauterine environment are profoundly influenced by maternal characteristics (296). Some of the first studies illustrating this were based on data from the Dutch famine during WWII. Fetal outcomes such as elevated CVD, glucose intolerance and obesity were documented in the offspring of those exposed to the famine while pregnant (297–299). A large pool of evidence now suggests that maternal nutrition, BMI pre-pregnancy, parental obesity (both mothers and fathers),

gestational weight gain, and parental metabolic health (insulin sensitivity) are influential in the healthy development of fetal organs and tissues, as well as in infant growth patterns, offspring risk of OB and metabolic consequences (296,300–302). Regular PA is an essential component to preventing OWO and promoting health in a variety of populations. PA is also recommended for pregnant mothers. Physically active pregnant women (before and during pregnancy) gain less gestational weight and are less likely to develop gestational diabetes mellitus (GDM) or hypertension, regardless of pre-pregnancy weight (83,303,304). PA during pregnancy is linked with a reduction in the risk of small or large for gestational age infants and reduced infant FM without compromising infant FFM (305,306). Specifically, resistance training and aerobic activity of pregnant mothers can reduce offspring fat mass and increases lean mass at 1year and at 18-24 months as seen in findings by Chu et al. (2012), and Mattran et al. (2011) (301,307). Fetuses of mothers who were given a PA lifestyle intervention had a healthier fat distribution than fetuses of the control group; specifically, fetuses had greater thigh fat mass, and slower fat deposition in the subscapular region *in utero* (308). Alternatively, offspring of obese and (gestational) diabetic mothers have up to 4x the OB risk during childhood, higher levels of fat mass (g), %TBF, and BMI, as well as an increased risk of IR, and reduced β-cell (pancreatic insulin cells) capacity predisposing to diabetes (236).

OWO is related to elevated levels of myriad inflammatory proteins (levels of TNF-a, IL-6, IL-10, C-reactive protein). Maternal inflammatory levels (often associated with OWO) can have negative implications for the infant (309). Maternal PA in turn, relates to lower levels of these same inflammatory agents, improved IR in mothers and improved offspring outcome such as improved fetal nervous system maturation and long-term cardiovascular health (309,310) (264,283,311–313). PA during pregnancy may also relate to better control of maternal blood

sugar and insulin levels and thus lower levels of fetal exposure to FFA, glucose and insulin, and better insulin sensitivity in the offspring (14). In the presence of optimal nutrition, the placentae of physically active mothers have higher vascular volume and surface area, and higher rates of perfusion and thus improved blood flow and gas exchange between the mother and the fetus (314). Fetal exposure to norepinephrine and other exercise induced catecholamines improve fetal development of the cardiac autonomic system (315).

In accordance with the developmental origins hypothesis of life course epidemiology, these findings suggests that maternal PA exposes the fetus to positive stimuli (e.g. placental blood flow, decreased glucose, exercise induced catecholamines), inducing physiological adaptations in the fetus that yield greater health advantages during subsequent stages of life (310). These advantages can directly affect cardiometabolic health; for example, through improved insulin sensitivity. There are also indirect links between maternal PA and offspring health as seen in rodent models in which offspring of active mothers had a greater lifelong propensity for PA, as well as greater fat loss induced by exercise interventions (316). The different physiological response to PA in offspring of active versus inactive mothers suggests that maternal PA can alter the offspring phenotype or expression of the genome if not the genome itself, and that the physiological or genomic foundation of PA and fat metabolism are related.

The thrifty genotype hypothesis first introduced by Neel (1962) suggests that negative fetal exposures to inadequate maternal nutrition permanently impair vital organs and systems, such as the endocrine and metabolic systems, resulting in the onset of diabetes in later life (317). Neel proposed that evolutionary genetic modifications interact with the modern environment resulting in a mismatch between development and external environment. This mismatch

manifests as IR and other metabolic abnormalities such as diabetes (79,318–321). Hales and Barker (2001) expand on this theory and propose a thrifty phenotype in which permanent physiological adaptations once meant to conserve calories when food was scarce are now a liability when food is available in excess and PA is dropping, leading to the obesity epidemic (81). It is proposed that these hypotheses also underlie the unequal prevalence of OWO and diabetes in ethnic groups who were, up to recently, undernourished or a part of hunter-gatherer societies with periods of feast and famine: Australian aborigines, Amerindian, Native Americans, Canadian Indigenous, and South East Asians (322,323). These groups of people have undergone rapid "westernization" and the genetics are at a mismatch with the environment (322). The final addition to these hypotheses is the hefty fetal phenotype hypotheses by Dyck (2001) (81). Dyck suggests that in Canadian Indigenous peoples (as well as Pima Indians of the USA), the thrifty genes interact with obesogenic environment even before birth. A high birth weight represents a survival bias (thrifty gene) that is mismatched with its external environment (intra-uterine) and the current prevalence of maternal obesity, gestational diabetes, and obesogenic environment after birth (high calories, low PA). High birthweight (BW) infants are at an increased risk obesity but also of T2DM diagnosis in later life (81).

2.6.2 Birthweight and Infancy

BW is one of the first indices of healthy growth and development and is a surrogate measure for fetal growth and the intrauterine environment (296). BW and infant growth are indicators of maternal health, child health and child survival (322). One of the first studies to identify a relationship between BW and morbidity and mortality was carried out with a cohort born in 1911 in Hertfordshire, England. In the study of over 5,000 male babies, those with the lowest BW had four times greater death rates from ischemic heart disease than those normal and

high BW (324). Since then studies have repeatedly demonstrated a relationship between size at birth and later life health and weight status. Evidence remains discrepant as to direction and shape of the relationship- a positive linear, negative linear and U-shape curve between BW and long term health consequences have been demonstrated.

High BW infants have an increased risk of OWO in childhood and beyond (325). The odds ratio of OWO at age 7 increases 1.03-1.07 per 100 g of BW (302). Seidman et al. (1991) found that in infants with BW over 4500 g there was a 4x greater risk of severe OW (>27.8 kg/m^2) in adulthood compared to BW of 3000-3499 g (326). Similarly, a meta-analysis by Yu et al. (2011) revealed that a BW >4000 g was associated with an odds ratio of OB of 2.07 compared to BW <2500g. One reason for this discrepancy may again be the choice of BMI as OWO metric. Indeed, all studies included by Yu et al. (2011) used BMI or deviation from ideal weight. While high BW relates to high BMI, a different relationship emerges when measures such as WC or DXA are used. High BW is almost always associated with higher LM but rarely with high FM or high abdominal fat as suggested in the literature review by Ong (2006) (236,322,327). A higher BW may also be protective against metabolic disorder in OWO children. In OB children, those with high BW had higher adiponectin (an anti-inflammatory), higher IR and lower hepatic IR, lower FFA and insulin during glucose tolerance test, and lower TrF compared to low BW obese children. (328). Alternatively, when high BW is a consequence of mothers' polycystic ovarian syndrome, gestational diabetes, or high glucose levels the offspring has an increased likelihood of excess fat accumulation, childhood OB and diabetes (81,295,322). While some argue that the relationship between BW and later life disease and OWO is dependent on excess childhood weight gain, other findings such as those by Wei et al. (2003) found an increased risk of T2DM in high BW children after adjusting for current BMI (236,329). With that said, Wei et

al. (2003), also indicated that high BW children with T2DM had higher BMI, blood pressure and family history of diabetes compared to those with low BW suggesting that concurrent weight may amplify the risk conferred by high BW coincident with familial risk (329).

Low BW consistently demonstrates a relationship with disease but there are different suggestions as to the mechanism. Many studies have demonstrated that low BW is linked with later life IR, CVD and type 2 diabetes (318,321,322,329). These diseases may have their origins in pathological changes to organs and systems occurring *in utero* such as reduced nephron number or beta cell function seen in low BW babies (296). Additional risk may be conferred by preferential fat over lean tissue accrual, and more specifically abdominal fat, found in low BW infants. For example, Gale et al. (2012) showed that in elderly men, a low BW was associated with lower levels of LM and higher levels of FM relative to current weight (330). Similarly, adolescents with low BW were shown to have increased levels of abdominal fat, specifically visceral fat, in addition to higher IR, even after adjusting for BMI, PA, and socioeconomic status (331). Low BW consistently demonstrates a relationship with high %TBF and higher abdominal fat compared with NW infants, but this may be a result of excess fat or low LM and can co-exist with a low body weight. As such, a high fat-to-lean mass ratio may underlie the pathways to disease in what Wells (2007) describes as a high "metabolic load". Wells posits that normal growth is characterized by optimal LM accrual whereas poor growth (indicated by low BW) constrains LM and is often expressed as high %TBF (296). Suboptimal fat-to-lean ratio can be considered a high metabolic load which predisposes an individual to CMR in later life.

The metabolic load theory clearly has links to the thrifty (hefty) phenotype theory previously discussed, as a mismatch between intra-uterine and genetic programming, and the post-natal environment will often lead to excess FM, either leading to or consequent of IR and

other cardiometabolic irregularities (79,81,82). Such a mismatch is found in those born with low BW who become OB in later life. Findings from McKeigue et al. (1998) showed that in 70-year-old males born with low BW, the relationship between glucose intolerance and IR with size at birth was only significant in those who were OB in adulthood (332). McKeigue et al. (1998) also found that insulin sensitivity was better in HBW infants when adult weight status was also high (OW) suggesting that continuity of being big may be protective (332). Other studies have found that there is a U-shaped relationship between BW and CMR. Specifically, after adjusting for age, sex, BA, PA, socioeconomic status, and BMI, those adolescents with either high or low BW had significantly higher IR, leptin levels, and visceral adipose tissue (331). There was no relationship with inflammatory markers or blood pressure, and an inverse relationship between BW and TG suggesting there may be different pathways by which low and high BW confer risk (331). Metabolic overload in high BW infants comes when there is continual accrual of FM over LM while in low BW infants it likely begins with catch-up growth as catch-up weight is predominantly fat (296,332,333).

Catch-up growth in low BW infants is one final pathway by which disease outcomes correspond to BW. In developing countries, catch-up growth is associated with LM and less so with FM in later life; however, in industrialized countries this is not usually the case (296) . Wells (2007) suggests that fetal development and early infancy appear to be critical windows during which nutritional uptake is earmarked for LM development. As these critical windows close, energy intake allocation switches to FM accrual (296). The same is suggested in findings from a large epidemiological meta-analysis by Dulloo et al. (2006) in which it is demonstrated that catch-up growth is characterized by an affinity for fat accrual, and even more so, abdominal fat accrual (333). Authors suggest the term “catch-up fat” phenotype to embody this concept.

The partitioning of energy from lean to fat is consequent of reduced insulin sensitivity coincident with catch-up growth; hyperphagic compensatory drive preferring energy dense foods; and a shift to a more efficient metabolism, that is, suppression of thermogenesis for energy conservation. This "thrifty metabolism" and catch-up fat phenotype are involved in physiological mechanisms whereby early insulin and leptin resistance develops leading to later life obesity, T2DM and CVD (41,333).

There is substantial evidence that being big and growing fast in infancy and the toddler years carry with it a higher risk of adult OWO regardless of BW (334–336). Longitudinal data from the FELS study found that rapid weight gain from 0-2 years was associated with risk of OB (odds ratio 4.1), higher body fat, %TBF, visceral and subcutaneous fat and %TrF in adulthood (336); however, Jones-Smith et al. (2013) found that it was size, not velocity, of growth from 0-2 years that was most associated with OBO in childhood (337). Larnkjoer et al. (2010) found that the strongest predictor of adolescent %TBF was weight gain from birth to 9 months and that weight gain from 0-3 months was negatively associated with adiponectin (an anti-inflammatory adipokine), even after adjusting for %TBF (338). A meta-analysis by Baird et al. (2005) supports the findings that rapid growth in infancy confers a higher odds ratio of later obesity (odds ratio from 1.17 to 5.7); but that being OB as an infant also increases the risk (odds ratio; OR= 1.35 to 9.38) (339). Finally, findings from Giles (2013) similarly indicate that both size (BMI z-score at 9 months), and rapid growth (change in BMI z-score from 9 to 12 months), are significantly related to %TBF in later childhood (85).

There does appear to be a difference in outcomes between catch-up growth and rapid infant growth. Catch-up growth is contingent on an initial LBW. Longitudinal data from the Avon study demonstrates that both rapid growth in the first year (OR =1.0 - 1.10 per 100 g) and

catch up growth (OR= 1.09- 6.16) have an increased odds ratio of OWO in childhood (302). The study by Bourhours-Nouet et al. (2008) found that in OB children, rapid weight gain from 0 to 2 years was positively related to insulin sensitivity but the strongest relationship was seen in those with a HBW suggesting that rapid growth in HBW infants may be metabolically protective in the presence of childhood obesity (328). Alternatively, in the same study those children with LBW who became OB by 10 years, and had undergone catch-up growth, had the lowest insulin sensitivity, suggesting that rapid growth which constitutes catch-up growth in LBW infants is metabolically detrimental (41,328). Interestingly, findings from the longitudinal Stockholm Weight Development Study of eutrophic BW infants demonstrated that weight gain from 0-6 months and 3-6 years were related to adult OB, but only weight gain from 0-6 months was associated with young adult CMR (334,335). This suggests that rapid infant growth favors FM, predisposing an individual to a greater metabolic load in adulthood; whereas, toddler and early childhood gains favor lean mass, creating a more balanced metabolic load in adulthood, even in the presence of adult OB (334). Postnatal factors that increase LM and decrease FM could decrease the metabolic load and thus mitigate the risk of later life OWO and CMR conferred by BW and early rapid growth.

Prior to ambulation, crying comprises the greatest caloric expenditure. As such, the temperament of the child may be relevant to the rate of fat accrual. Babies who cry use a substantial amount of energy and thus may compensate by eating, indicated by infants who are easily soothed being leaner (340). There is also a growing body of evidence suggesting an inverse relationship between breastfeeding and OWO in childhood, adolescence and adulthood. Cross sectional data of German 5 and 6-year-olds found that the prevalence of OWO (BMI >97th centile) in breast fed babies was almost 2% lower than in formula fed babies with a clear dose

response related to the length of breastfeeding (341). Similarly, longitudinal data from American children indicated that being breastfed at 1 month, and for more than 6 months (versus never) was related to a reduced risk of OB at grade 6 by 47% and 42% respectively (342). Breastfeeding for longer than 4 months and 12 months decreased the likelihood of OWO at 3 years, and 1-8 years respectively; and introducing milk other than breast milk before 6 months increases the likelihood of OWO at 20 years (343). The mechanism behind the protective effect of breastfeeding involves the body's metabolic response to the milk's composition which promotes slower growth, as opposed to formula which stimulates rapid growth in infancy. Recall that rapid growth trajectories in infancy correlate with FM gains and OWO later on (333,343).

PA has the ability to alter rapid trajectories of fat mass growth (264). There is general agreement on the benefits that PA has for children of all ages (344–346). Guidelines for infants under 1 year and toddlers 1-2 years have been developed by PatrticipACTION Canada (347). ParticipACTION is a national non-profit organization supported and funded in part by the Public Health Agency of Canada. They suggest that tummy time for infants and energetic play for toddlers is important for healthy growth, motor development and higher fitness levels. There are very few studies of PA in infants and what little evidence there is suggests that infant/parent PA interventions do little to improve subsequent PA level, CMR or FM (348). Fortunately, the incorporation of PA later in life shows promise in mitigating the risk conferred by altered BW and infancy status (349).

2.6.3 Adiposity Rebound and Preschool years

The next critical period for growth and intervention is the adiposity rebound (AR) - the point in early childhood at which a declining adiposity reaches a nadir and begins to increase again into adulthood (350). AR typically occurs around the age of 5. There is extensive literature

suggesting that an early AR predicts adult OWO and CMR independent of adult BMI and that the risk of adult disease decreases with increasing age at the AR (19,351).

Using longitudinal data, Guo et al. (2000) found that earlier BMI rebound is related to having a higher BMI at the age of the rebound. Authors also found that an earlier BMI rebound and a higher BMI at the BMI rebound were related to higher maximum velocity of BMI gains in adolescence and to maximum BMI values in young adulthood. In turn, maximum BMI velocity and maximum adolescent BMI conferred an increased odds ratio of OW from 35-45 years of age (87,352). Gardner et al. (2009) found that the weight gained during the preschool years (ages 0-5) and weight z-score at 5 years contributed to the prediction of composite CMR score and weight z-score at 9 years (353). Similarly, Dulloo et al. (2006) and Rolland-Cachera et al. (2006) suggested that having a higher BMI z-score at the rebound, or experiencing rapid weight gain immediately following the rebound predict adult fatness, BMI, skinfolds, hypertension, glucose intolerance and T2DM (106,333). Metabolic consequences are worse when poor weight gain in infancy is accompanied by rapid weight gains following the nadir (106,333). This may be explained again by Dulloo's "catch-up fat phenotype" as rapid gains after the rebound act similar to catch-up growth by stimulating a disproportionately high rate of fat over lean mass gains (333).

Age at AR may be an early indicator of the timing of maturation (early or late), as earlier AR is associated with early menarche and early skeletal maturation (106). Early rebounders also have faster rates of fat gains than late rebounders, and OB children tend to have accelerated growth of all tissue in comparison to non-obese children (106,354). Alternatively, the characteristics of early maturation and excess FM may be phenotypes of a shared origin. Adrenarche is the age at which the adrenal cortex becomes matured, usually between 5 and 8

years, and is the beginning of the androgen rise that precedes pubarche (pubertal onset) (355). Marakaki et al. (2017) demonstrated that premature adrenarche corresponds with greater height, more adipose tissue and advance BA at age 7 and 8, and that those with premature adrenarche had an earlier age at AR (355). It is important to note that children with and without OB can have premature adrenarche. Thus, the authors suggest that an early AR indicates earlier maturation rather than OB risk and that accelerated maturation is in turn associated with increased fat mass accrual in adulthood (14). Authors also make note of the potential contribution of endocrine factors and the impact of altered endocrine functions. The HPA axis controls adrenocorticotropic hormone which is responsible for adrenarche but also contributes to IR and OB (42,137). Genetic risk determined by the presence of OB-related SNPs, contribute to a cluster of growth patterns including rapid weight gain in early childhood, earlier AR and higher BMI at AR. In turn, these patterns are known to predict subsequent OB (352). Interestingly, findings by Rolland-Cachera (1987), indicate that both children with OB, and adults who had OB but did not have OB as children have an earlier AR (356). These findings support the idea that genetic variations that impose obesity risk operate through accelerating growth rate and maturational timing in the early years (352).

Literature has repeatedly related PA level with adiposity level during childhood (115,119,264). Having a greater fat mass around the age of AR (5 years) is related to lower PA and increased sedentary time and over half of preschool children who have OWO are more likely to remain so in adulthood (115,357,358). In a recent study of Canadian preschool children it was found that a clustering of factors including sleep, sedentary time and PA were associated with BMI z-score; however, moderate-vigorous PA was not a significant predictor when controlling

for the other factors (359). Evidence is more consistent regarding the relationship between PA and health.

A systematic literature review of the health implications of PA in children 0-4 years identified 96 relevant studies representing over 70 000 participants (346). The review by Carson et al. (2017) found that PA was consistently associated with positive health outcomes including fitness, adiposity, and cardiometabolic health, and that more PA is better (346). Using pooled accelerometry data from over 20,000 children and adolescents (4-18 years), Ekelund et al. (2012) found that more time spend in MVPA was related to better CMR outcomes (WC, BP, HDL, insulin, TG) regardless of sedentary time (52). Similarly, a systematic review of the literature by Janssen and LeBlanc (2010) found that PA was associated with numerous health benefits for children 5-17 years and that there was a clear dose-response with more PA conferring greater health benefits (344). Finally, a 12 month longitudinal study of young children found that higher levels of PA at 4.5 years was related to higher FFM, BMI (potentially due to higher FFM), cardiorespiratory fitness, and lower %TBF (unadjusted means) at follow-up (360). Authors suggest that promotion of PA in the younger years may carry into later childhood and have long-term benefits on body composition and health. This age is especially critical as those who will be OWO children and youth are likely to become so before the age of 8, with the majority of weight gained before 5 years; furthermore, those who will become OWO have higher weights by age 2 or 3 than those who will remain NW children and adolescents (57,353,361).

In summary, the contributing factors to OWO in early life include maternal characteristics (OWO), BW early feeding habits, early BMI or AR rebound, PA habits, and rapid weight gain. These factors also contribute to fat mass and health in subsequent periods.

2.6.4 Childhood and Adolescence

PA during childhood and adolescence has a protective effect against FM gains (362). As PA declines from childhood through adolescence, fat mass correspondingly increases (118). Low PA levels are also inversely related to TrF trajectories in adolescence (169). These correlations correspond with findings that there is a significantly lower prevalence of adolescent onset of OWO in active children than in inactive children (363). Data from a prospective study revealed that a lower level of fat mass at 14 years was found in those with higher levels of PA, especially moderate/vigorous PA, at age 12 (364). PA has demonstrated a similar inverse relationship with %TBF in 8-year-old males and in 13 to 27-year-old males and females (118,365). In one study of Australian children with similar caloric intake, the differential factors between children with and without OW was PA, and those children who reduced their PA over four years had the greatest increases in %TBF (366). There is also evidence that PA during childhood and adolescence has protective effects against OWO. The Young Finns Study followed participants for 21 years and found that persistently low levels of PA or declining levels PA from 9-18 years carried a risk of OWO and abdominal obesity from 30-39 years that was over two times that of those who maintained high levels of PA (367). These relationships persisted in women but not in men after adjustment for childhood fatness and other confounders.

PA during childhood and adolescence also enhances cardiometabolic health, even in children and adolescents who have OWO, likely because of its ability to target abdominal and visceral fat, improve insulin sensitivity and strengthen the cardiovascular system (208,264,283). In youth between 4 and 18 years, time spent in MVPA and frequent interruptions in sedentary time are significantly associated with cardiometabolic outcomes such as SBP, TG, HDLs and fasting insulin (52,225). Elevated BMI over one's peers, even one that is "normal" in

adolescence predicts coronary heart disease in adulthood even when controlling for adult lifestyle and BMI (368). It is also known that fitness, which is related to higher levels of activity, decreases the likelihood of OWO in addition to lowering CVD factors such as WC, BP, TG, IR and cholesterol in both adolescence and adulthood (69,369).

As discussed previously, the stability of PA behaviour and fitness may be the link between childhood and adulthood health; for example, data from the Oslo Youth Study found that the maintenance or increase of adolescent PA levels into adulthood was associated with a significantly lower odds ratio of acquiring OWO (117). Jekal et al. (2010) concluded that BMI in adolescence had a positive relationship with CMR in adulthood; and fitness in adolescence had an inverse relationship with CMR in adulthood (370). Eisenmann et al. (2009) similarly found that change in fitness correlated with change in body fatness from adolescence to adulthood ($r = -0.24$ to -0.46). Declining levels of PA from childhood to adulthood have repeatedly demonstrated a negative effect on health. For example, those with lower levels of fitness and PA in childhood, and those with larger declines from childhood to adulthood are at an elevated risk of adult OB and IR leading to T2DM (371). Similarly, data from the Young Finns Study demonstrated that adult abdominal obesity was related to youth PA, although the relationship was indirect via tracking of PA into adulthood (372). Unfortunately, it has been shown that tracking of PA between childhood and adulthood is weak to moderate at best with higher coefficients between the closest age intervals (27,373,374). The tracking of sedentary behaviour and obesity are stronger than that of PA suggesting that the link between adolescent PA and adult OB is more likely through adolescent fat mass than through PA stability (372,374). Similar suggestions are made by Eisenmann et al. (2005) who concluded that while fitness, fatness and clustered CMR all demonstrate tracking coefficients between 0.4,0.6, it is adolescent fatness not adolescent

fitness that is related to adult CMR. With that said, there is some evidence that intense PA in adolescence, such as involvement in vigorous sport, has the potential to independently influence adult MetS. Yang et al. (2009) found that sustained participation in intense sport for 3 years or more from 3-18 years significantly and independently reduced the risk of MetS in adulthood (375).

Adult weight status and health have antecedents in childhood and adolescence. Preventing childhood and adolescent fatness may be key to preventing, or at least delaying, the onset of adult cardiometabolic diseases either indirectly, through tracking of PA and fatness, or directly, by limiting exposure to adiposity and early onset of CMR (208). There is also evidence that even in the presence of childhood and adolescent OWO, the long-term risk of CVD and MetS are not inevitable but are reliant on tracking of OB across the lifespan (62,140). Furthermore, most OWO adults were not OWO in childhood and adolescence. This suggests one final window at which interventions preventing adult OWO and disease can be employed.

2.6.5 Emerging Adulthood

Emerging adulthood is a term first proposed by Jeffrey Arnett in the field of psychology (28). This period has somewhat arbitrary boundaries, "from late teens through the twenties," but is conceptualized as occurring roughly between 18 and 25 years. This final developmental period is characterized by geographic and psychosocial changes - moving out of parent's home, transitioning out of high school and into college and career, and new independence (28). Self-identity includes characteristics relating to health and health behaviors. Formation of one's identity as "exerciser/non-exerciser" or "healthy eater/eat whatever I want" can be tried out and subsequently adopted or rejected during this time (28,376,377). This viewpoint may correspond to viewpoints from childhood modeled by parents and caregivers or may be novel as this period

is one of new ideas. According to the "habit discontinuity hypothesis" behavioural habits that are altered alongside a change in context or a life course change (as is seen during EA) are likely to be more successful and permanent (28,378). This is cause for concern as EA is characterized by adverse changes in PA and eating habits which can contribute to FM gains also seen during this period (32,121,379–382). Furthermore, there is ongoing debate as to whether or not child and adolescent FM and behaviour have any independent effect on adult health once adult adiposity is controlled (383). This, in combination with the large body of evidence demonstrating that NW children and adolescents become OWO adults, suggests that EA may be a crucial period influencing the trajectory of life course health.

There is a scarcity of data on the somatic changes occurring during the period of EA (18-25 years) despite clear trajectories of BMI and FM that continue (rather than plateau) past the age of 18. Longitudinal data from the CARDIA study demonstrated that 5 year weight gains in young adults age 18-30 years at baseline were greater from 18-24 years than from 25-30 years in males (384). Suglia et al. (2013) followed 8,000 16-year-olds until the age of 29 and found that approximately 15% gained weight, 20-35% remained OWO from adolescence, 7-9% lost weight, and 50% were NW and stayed NW. Findings from Racette (2005) are even more discouraging as authors found that 70% of college students gained weight (90,385). The actual amount of weight gain across four years of college is reportedly only 2 to 5 kg; however, most of the weight is FM. Bone mass accrual has generally ceased by 18 years and studies have demonstrated that beyond the age of 20, it requires a greater than 3 kg flux for significant change in FFM to occur (110). Less than 3 kg is predominantly fat mass (97,380,386). Specific to college changes, Gropper et al. (2011) found that %TBF changes over the freshman and sophomore year were positive in both males and females (~+2%) while change in %FFM were negative (~-2%) (387). Over 4

years, gains equalled 2.3kg (2.9%) fat mass in females and 4.9 kg (5.2 %) FM in males, accompanied by a loss of almost 1kg FFM in female and a gain of 1.3 kg FFM in males (388). In light of the ubiquity of weight gain (and specifically FM gain) during this period, it is not surprising that many who enter college with a healthy weight become OW, and adolescents who are OW often become OB young adults (17,152,387–390).

National survey data from the United States (1991-1998) identified that the ages 18-29 years had the greatest increase in OB prevalence (30). Longitudinal data from 1996-2009 found that the 5 year incidence (new cases) of OWO in American youth (baseline 13-20 years; follow-up 19-26 years) was 13%, while only 1.6% shifted down from OWO to not OW (31). While some data suggests that those with NW at 20 years are able to maintain weight, those with BMI categorized as OWO experience substantial increases between 20 and 30 years of age (87). One factor likely contributing to maintenance of weight status or increasing FM is PA.

Levels of PA in adolescence and EA correlate with FM and longitudinal data from the AGAHLS suggests that high PA confers an odds ratio for high FM of 0.81 (116,118,391). In university students (18-22 years), participation in light, moderate and vigorous PA is significantly related to BMI and TBF with 58% of the variance in female TBF explained by low levels of vigorous PA (392). Unfortunately, there is a clear pattern of decreasing PA during EA confluent with the same pattern in adolescence. The AGAHLS demonstrates a decrease in energy expenditure of 1500 Mets per week between the ages of 13 and 27 years (393). PA declines even further with the experience of early adult life events such as moving in with a partner, getting married and having children (391). Once these major life events have occurred there is little change in PA levels through mid-adulthood suggesting that EA may be pivotal in establishing lifelong PA habits that mitigate potential FM gains (118,393).

Altered dietary intake has also been indicated in EA weight gain. For example, fast food consumption, which is linked with weight gain, is highest in the 20 to 39-year-old age group of Americans (394). In a one week recall, over 50% of Missouri college freshman had consumed fried or fast food three times (385). Sugary drinks have similarly been linked with FM gains in 7 to 20-year-olds, and have the highest consumption levels in 19 to 39-year-old Americans (395,396). Furthermore, the intake of beneficial foods for weight and health such as vegetables and fruit are extremely low in those entering their freshman year (70% eat fewer than 5 servings per day) and in 20 to 29-year-old Americans (average of <1 serving/day) (385,397). Steep declines is fruit and vegetable consumption coincide with the 5 year transition from high school into college and career (385,397). Dietary habits formed during childhood and adolescence do not track well into adulthood. Data from the PBMAS cohort found that between the ages of 13-18 and 18-27, only 40% of females and 30% of males remained in the same dietary patterns, i.e. a pattern of vegetarian diet - high fruit and fiber - or western - highly processed (398). Although there is potential for the adoption of new healthy food habits during EA, the data on college dietary habits above does not show much promise. The tracking of dietary patterns high in cheese, desserts, dressings and sauces were higher than those of leafy greens, eggs and non-refined grains during the transition from adolescence to young adulthood. A similar trend may yet be identified through EA into adulthood (398).

FM and PA are irrevocably linked with CMR and CVD during EA just as they are in preceding periods. The AGAHLS has demonstrated that PA relates to FM from 13-27 years and that PA during young adulthood (21 years) relates to CVD risk factors (118,393). FM accrual during EA also demonstrated a correlation with CMR in longitudinal data from the Saskatchewan Growth and Development Study (SGDS). While adolescent adiposity failed to

significantly predict adult CMR, those with the highest CMR from 50-60 years accrued 62% more adjusted TBF percentages from adolescence to adulthood than those with the lowest CMR (399). Other studies have found that PA habits in EA (18-24 years) mitigated cardiovascular risk (carotid artery elasticity) 21 years later, even after adjusting for current BMI and change in PA (400). There also appears to be cumulative benefits (or risk) attributable to PA and adiposity; for example, data covering the period from 16-29 years demonstrated higher risk of hypertension at 29 years in chronically OWO compared with persistently NW. Furthermore, those who became OWO during transition from adolescence to adulthood had an intermediate level of risk supporting the idea of cumulative risk (90).

A similar intermediate risk relating to stability or transition is illustrated in findings from the Harvard Alumni Study (401). A lower risk of CVD was found for college athletes who transitioned to non-athletes compared to those who were never athletes, but a higher risk was found in those who transition compared to those who remained an athlete or became an athlete after college. Finally, those who became active after college had the same risk as those that maintained activity (401). These findings suggest that PA has a cumulative and concurrent effect on cardiovascular health although the authors emphasize the importance of habitual exercise post-college to ensure low risk (401).

Fortunately, educational-behavioral interventions focusing on healthy lifestyle (including PA, fitness, dietary intake) show some promise in limiting weight gain in NW university students although the mechanisms are less clear and interventions have failed to produce significant changes PA levels or caloric intake (72).

2.7 *CROSS SECTIONAL AND LONGITUDINAL STUDIES*

2.7.1 Characteristics of Cross-Sectional and Longitudinal Studies

Growth research attempts to answer questions pertaining to changes in human characteristics over time and human biological variation, particularly from conception to full maturation (69). There are two basic types of study designs that can address such questions: cross-sectional and longitudinal. Cross-sectional studies collect data at one time-point on large groups of participants from different age cohorts. This allows for the identification of common changes with age and the approximate age at which these changes occur (69). For example, PA and body composition can be measured simultaneously in 4 age cohorts: 10-year-olds, 11-year-olds, 12-year-olds and 13-year-olds. The mean BMI (kg/m^2) can be identified for each of a low, moderate and highly active group for each cohort, and a curve developed to represent the pattern of BMI change over the time course. A cross-sectional study can identify independent variables that may be associated with outcome variables but cannot speak to the intra-individual developmental patterns of factors. Cross-sectional studies can only find correlations (69). For example, dietary habits, and PA levels in adulthood can be assessed alongside FM or OWO status, but stability of PA levels or continuity of dietary intake from childhood to adulthood cannot be assumed.

Longitudinal studies typically consist of a smaller number of participants measured serially over time with a minimum of three measures (402). Longitudinal studies consider systematic changes observed across time and identify the within and between individual variance of the change (69,403). For example, the BMI of a single cohort could be measured from age 10-13 years, providing a representative curve of change (in BMI) over time (age). Analysis methods

appropriate for longitudinal data analysis (such as multi-level analysis) can account for the effect of multiple "predictor" variables on the outcome variable such as BMI. Longitudinal analysis also allows for the identification of between-individual variability by allowing the regression coefficients of predictors to differ between individuals and between time points (69). For example; the influence that age, and PA levels at each age has on BMI growth can be explored. Findings based on longitudinal data can infer causation (69).

2.7.2 Advantages and Disadvantages

Cross-sectional studies are often preferable to longitudinal design because they have lower participant burden, less researcher turnover, shorter duration and less participant attrition than longitudinal studies. The disadvantages of longitudinal design include higher attrition, higher cost, and concerns over reliability of measures over time; yet, this design remains superior to cross-sectional design for growth studies because of its ability to reflect individual differences in growth patterns, identify rate or velocity of change, and incorporate time-dependent variables.

Cross-sectional and longitudinal studies are used to address similar questions and can provide similar conclusions. For example; cross-sectional data collection of females aged 8-27 suggests that TrF increases with pubertal stage (404). Longitudinal data from the AGAHLS on participants followed from 13 to 36 years also found increases in TrF with age, but these findings are more valid than cross-sectional findings because the data is derived from serial measures of the same individuals while accounting for differences between individuals and between time-points within individuals (275). The longitudinal AGAHLS study was also able to identify that daily PA from adolescence to young adulthood had a beneficial effect on adult body fatness (275). These types of findings cannot be produced with cross-sectional data because there is no

data (other than retrospective questionnaires) on occurrences or exposures prior to the measurement occasion.

There is an alternative to the cross-sectional and longitudinal design. A mixed-longitudinal design, or accelerated longitudinal design, is a compromise between the two, and may be preferable because it mitigates some of the disadvantages of both the pure longitudinal design and the cross-sectional design by using overlapping cohorts. The Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) is an example of a mixed longitudinal study design and is the study from which the data for this dissertation is utilized. The PBMAS has generated a unique data set that is able to explore the growth based research questions of this dissertation (232,402).

2.8 *SASKATCHEWAN PEDIATRIC BONE MINERAL ACCRUAL STUDY*

In 1989 Bailey et al. determined that the peak in annual incidence of fractures in Saskatchewan youth corresponded to the age of PHV (405). Authors concluded that the incidence could not be explained solely by PA and suggested that different rates of linear growth of bone and bone mineralization may contribute. In order to address this hypothesis, Dr. Bailey initiated the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) (1991-2017). Between 1991 and 1993, 253 children (aged 8-15 years) were recruited from elementary schools in Saskatoon, Saskatchewan, Canada (406). Measurements were taken bi-annually for the first 6

years, annually between 2002 and 2005, 1-2 times between 2009- 2011 and once more in 2016-2017. The final wave of measures included a participant age range of 33 to 41 years. Each measurement occasion included the collection of dietary and physical activity information along with dual-X-ray absorptiometry total body scans. The 2010/11 and 2016/17 waves also included blood samples for determining cardiovascular and metabolic profiles. Informed consent and child assent were acquired prior to the collection of any data. Consent was also re-obtained for any new measurement protocols such as the addition of blood collection. The PBMAS was approved by the University of Saskatchewan Biomedical Research Ethics Board (Bio#. 88-102).

Physical activity was determined using the age appropriate physical activity questionnaires for children, adolescents or adults (PAQ-C, PAC-A, PAQ-Ad) (407–409). Over the first 6 years of the study, the questionnaire was administered at least three times per year for the first three years and two times per year thereafter. Annual visits after 1997 included one administration of the PAQ questionnaire. This family of questionnaires provides general information on the frequency of PA and intensity. For example, children are asked if they are physically active at recess and after school, while adults are asked about participation at lunch hour or after work (See Appendix K for questionnaire). A level of intensity is indicated using a 5-point Likert scale for each PA occasion where PA is described as "sports, games, gym, dance or other activities that make you breathe harder, make your legs feel tired and make you sweat." A higher number indicates a harder level of intensity. The mean score of all items comprises a composite activity score. When there was more than one assessment in a year, the mean of all assessments was used.

The dietary intake and nutrition information of participants was assessed using a

24-h recall questionnaire. The recall was self-administered with the exception of particpants in grade 2 and 3 for which the researcher wrote down verbal answers. A training session on food portion sizes was conducted prior to the administration of the recall, and participants were given life-size pictures of food items to assist with accurate estimates. Recalls were administered three to four times in the first four years and twice a year thereafter (1994–1997, 2003–2006). Only one recall was completed in 2010/11, and two were completed in 2016/17 (one in person and one over the phone). Yearly averages were calculated for the data analysis. Data from 1991-1997 was analyzed using Canadian compatible nutritional assessment software (NUTS Nutritional Assessment System, version 3.7 Quilchena Consulting, Victoria, BC, Canada). Total energy ($kcal \cdot d^{-1}$), was calculated. Food Processor version 8.0 and revisions (ESHA Research Inc,. Salem, OR, USA, 2003.) was used to estimate total energy and nutrition after 1997.

DXA scans were performed annually over the first 6 years, and once per assessment thereafter. A QDR 2000 scanner (Hologic, Waltham, MA) in array mode was used for all scans until 2007. After 2007, the QDR 4500 (Hologic, Inc., Waltham, MA) replaced the QDR 2000. Test-retest for validity of the QDR 4500 was carried out using 20 healthy male and female university students with two scans on the same day for short-term precision, and over four weeks for long-term precision. The precision for total body LM and FM was 4.09% and 2.95% respectively. Conversion factors were developed to correct for differences between QDR 4500 and QDR 2000 machines using results obtained from 9 men and 15 women (410). Analysis of total body scans was carried out using global software version 7.10 and body composition was analyzed using software version 5.67.

Since its inception, there have been numerous researcher assistants, graduate students and faculty who have contributed to and benefited from involvement in this study. Data collected

from the PBMAS participants have generated over 61 published journal articles, and over 100 conference abstracts and presentations. The clinical significance of the findings from these papers is substantial. For example, in key papers by Bailey (1997) and Baxter-Jones (2011) it was identified that approximately 26% of bone mineral will be laid down in the 2 years surrounding PHV during adolescence, and that the bone laid down during the 4 years surrounding the adolescent growth spurt is more bone than most people will lose in their lifetime (406,411). Baxter-Jones et al. (2011) identified that total body bone mineral content will reach a plateau at +6 years from PHV (110). This is relevant to this dissertation as +6 approximates the age at onset of emerging adulthood (18-20 years), and a plateau in bone mineral content suggests that bone will not contribute to subsequent weight gain. Descriptions of BA-related LM and FM (kg) demonstrate continual gains in both males and females from -4 to +4 year from PHV indicating that weight gain prior to emerging adulthood can be comprised of fat, lean or bone mass (412).

Other important and relevant findings from the PBMAS include dietary and PA patterns with age. A recent paper by Movassagh et al. (2017) suggests that healthy dietary habits formed earlier in life are moderately stable into adulthood and that a "western-like" dietary pattern was associated with higher fat mass in childhood and adolescence, and lower total caloric intake but higher fat mass in adulthood (398). A vegetarian-style diet was associated with lower caloric intake, lower FM and higher levels of PA. Alternatively, PA level in PBMAS participants was not related to sugary drink intake, and sugary drink intake was not related to FM development (413). PA levels do; however, demonstrate a positive relationship with LM accrual in males and females from 8-15 years, and a negative relationship with FM development from 8-19 years in males but not in females (412,413). The PBMAS data has demonstrated that levels of PA

decrease across adolescence in males and females with moderate tracking across two-year intervals and that the most active adolescents had significantly more bone mineral content in early adulthood (23-30 years), controlling for height and weight (373,414). The findings of these three studies combined suggests that PA is lower in EA than in adolescence although there is some stability in level of PA across time; and that higher PA in adolescence has implications in adulthood. This also suggests that in early adulthood, a similar BMI may not represent the same body composition as those who were active youth have higher relative total bone content and lower FM.

Finally, Sherar et al. (2011) demonstrated that trajectories of TrF mass in PBMAS participants from 11 to 26 years was positively related to dietary fat, and negatively related to PA in males but not in females (169). Authors propose that this may be because females' body composition changes occur naturally with maturation, and not necessarily because of lifestyle factors. This paper also found that blood pressure risk was related to greater TrF accrual in males and females, but CMR was related to greater TrF accrual only in females. It was suggested that lack of significance of some of the variables could be due to the relatively young adult age of participants. This suggestion led to the research purpose for the final paper of this dissertation, as authors acknowledged that follow-up at older ages when CMR is higher may improve the ability to identify childhood/adolescent risk factors in the development of cardiometabolic morbidity.

2.9 *SUMMARY*

OWO and cardiometabolic diseases continue to be a public health concern in Canada. There is extensive literature suggesting that many of the antecedents of these diseases have their

onset in early life during critical growth periods. Fat mass trajectories at any point in life are also influenced by myriad factors including genetics, intrauterine development, environment, and lifestyle choices such as PA, all of which in turn drive the relative risk and progression of cardiometabolic outcomes. Trajectories of FM may, in turn, express underlying genetic risk linking the observations of rapid growth in infancy to early AR, rapid childhood FM, and early maturation. Analysis of trajectories of FM and identification of early antecedents of distal outcomes requires longitudinal data collection and the interpretation of data through from a life course perspective.

Early-onset OWO is often very stable and, as such, much attention had been given to prevention of childhood and adolescent OWO; however, there is also evidence that individuals who maintain a NW through these years of development become OWO at a later age. As such, the focus of prevention efforts may need to shift to encompass the stage of transition from adolescences into adulthood as this may represent a period of changing lifestyle, changing environment and cessation of growth. EA is a window in which FM can continue to accumulate and one in which the prevalence of OWO does indeed increase; and yet there is little research on this period and the factors relating to it.

In conclusion, to understand how to prevent life course OWO and comorbidities, there must be a clear picture of the longitudinal trajectories of FM and their predictors during the EA period. Both FM and PA have been identified as predictors of cardiometabolic health during every stage of life. There may also be an association between childhood factors of PA, FM and health, and adult health.

The overall purpose of this thesis is to examine the patterns and predictors of FM accrual in EA, with a focus on concurrent and earlier life predictors of PA and diet. All studies were conducted using data collected from participants of the PBMAS.

The specific aims are to: (1a), identify if EA is a critical period for fat accumulation and onset of OWO; (1b) compare metrics between and within sexes to categorize OWO status; (2) investigate lifestyle predictors of OWO in EA, including childhood and adolescent predictors; (3) identify effects of EA fat accrual trajectories on subsequent CMR in young adulthood (35-40 years of age).

To address these aims, the first study is an observational study illustrating in paper 1a the increase in rates of OWO in EA, highlighting the age when this group of NW children became OWO by BMI and %TBF cut-offs. Expanding on paper 1a, paper1b explores the age at OWO onset in this group by different metrics of BMI, %TBF and WC. This highlights differences in the timing of OWO onset by sex and by metric, commenting on the usefulness of each cut-off at identifying those at future risk of becoming OWO.

The second study explores predictors of total and TrF accrual over EA, specifically looking at concurrent and childhood/adolescent lifestyle, and childhood/adolescent fat mass accrual to address the question of whether adolescent FM, PA and diet have any independent effect on FM in later life once concurrent FM in included.

The third and final study investigates FM accrual during EA with the purpose of identifying differences in trajectory of TBF and TrF between those with high and low CMR profiles and the contribution of concurrent PA and diet on FM accrual.

Overall, this collection of studies attempts to address the gap in the literature surrounding fat mass accrual in EA. This dissertation will provide information to researchers, clinicians and

health policy advisors on the risk imposed by FM (specifically TrF), and elevated FM trajectories in EA on cardiometabolic health in adulthood and the times and factors that should be targeted to avoid the setting of a detrimental trajectory.

CHAPTER 3

Study 1- Paper 1a: Longitudinal patterns in BMI and percent total body fat from peak height velocity through emerging adulthood into young adulthood.

3.1 *DECLARATION OF CONTRIBUTION*

I, Erin Barbour-Tuck, am the primary author of this manuscript and was responsible for data cleaning, analysis, and interpretation; and writing, editing and formatting the manuscript.

3.2 *REFERENCE*

This document has been reformatted from the original version for inclusion in the thesis and has been included with permission according to the Copyright Transfer Agreement. Minor grammatical changes have been made to improve readability and relationship to the larger document. See Appendix O.

Longitudinal patterns in BMI and percent total body fat from peak height velocity through emerging adulthood into young adulthood. Barbour-Tuck E, Erlandson M, Muhajarine N, Foulds H, Baxter-Jones A. Am J Hum Biol. 2018 Jan;30(1). doi:10.1002/ajhb.23056. Epub 2017 Sep 13. PMID:28901657

3.3 *INTRODUCTION*

It has been suggested that fat mass accrual during key or "critical periods" of growth contribute to OWO status in subsequent critical periods (17,168,415,416). These periods include intrauterine growth (indexed by birth weight); post-natal catch up growth; the period of adiposity rebound; and the period of adolescence. Late adolescence and the period of emerging adulthood, has been less studied, despite a tendency for individuals to gain weight and fat mass during this time regardless of weight status during childhood and adolescence (28,379,385,388). Thus, currently, emerging adulthood is not identified as a critical period for weight gain.

The relationship of fat mass accrual during critical periods to adult OWO status gets stronger with each subsequent critical period. For example, adolescent obesity conveys a greater odds ratio of adult obesity than early childhood obesity (34). With the observed increase in childhood obesity (55,64,152,160,417) the concern is that adult obesity will also increase. Although emerging adulthood may be an additional critical period for the subsequent risk of adult OWO status (379–382), there is scant longitudinal data describing trends in fat accrual from adolescence through to young adulthood. Emerging adulthood is a dynamic time for many lifestyle behaviors. Changes in physical activity, eating and drinking habits are common and possibly lead to weight gain (387,388,390). Studies which encompass the first years of college indicate that body mass index (BMI) increases in both males and females (385,386), with a concomitant increase in the prevalence of OWO status. The literature suggests that many of those who enter college at a healthy weight acquire overweight (387,388,390), whilst those who enter with overweight have an increased risks of acquiring obese (17,152).

Identifying weight status in childhood and adolescence is problematic, due to the fact that body composition changes due to both normal growth and development, and environmental exposure. In adults, OWO status is defined using static BMI cut-offs. During growth, BMI

increases from birth to 4 to 6 years of age, drops (adiposity rebound) before rising again and only reaches adult values by 19 years of age. This indicates adult cut off values cannot be used during growth. Instead, childhood BMI-for-age reference charts have been developed which transition smoothly with the adult cut-offs, using the 85^{th} and 95^{th} centiles (101). Since BMI does not distinguish between fat mass and fat free mass changes, percent total body fat (%TBF) cut points have also been developed (100).

The timing and magnitude of growth is highly individualized (104), particularly during the pubertal period. Because of this, it is recommended that individuals are aligned by maturity rather than CA (418). Alignment by maturity is important as maturity status has a major influence on fat mass accrual and shows sex differences. To adjust for pubertal confounders within CA bands it is common in longitudinal growth studies to align individuals around the age of attainment of peak height velocity (PHV). Since this milestone occurs in females at approximately 12 years of age and in males at 14 years of age, alignment around PHV provides an ideal way to make sex comparisons over time.

The purpose of this study is to describe the longitudinal trends in BMI and %TBF accrual in a group of males and females from PHV to 15 years past PHV (+15) and to examine the prevalence of OWO status with age and sex. The secondary purpose is to investigate the relationship between weight statuses at different ages from PHV into young adulthood.

3.4 *METHODS*

3.4.1 Participants and Procedures

Participants were drawn from the University of Saskatchewan's Pediatric Bone Mineral Accrual Study (PBMAS; 1991-1998, 2002-2011), details of which have been described in detail elsewhere (110). In brief, between 1991 and 1993, using a mixed longitudinal cohort design, PBMAS recruited 251 children, aged between 8 and 15 years, into 8 age cohorts (8,9,10,11,12,13,14 and 15 years). Participants were measured annually from 1991 to 1998, and from 2002 to 2005, and 1-2 times more from 2009-2011; by 2011 the oldest participants were 35 years of age. Informed consent and assent were obtained initially from participants and their parents, respectively, of whom 95% were of European descent. To be included in the current paper, participants required a measure of PHV and a minimum of one complete anthropometric measure and a DXA scan in adolescence (PHV), late adolescence (5 years after PHV) and young adulthood (between 22 to 30 years of age). One hundred and eighteen participants (59 males) fulfilled these criteria and are included in the present analysis.

The median number of measurement occasions was 11 (range 3 to 14). Due to the mixed longitudinal cohort design, and missed measurement occasions, not all individuals were included in each age grouping. Table 3.1 shows the number of participants at each age. This study was approved by the Research Ethics board at the University of Saskatchewan.

Table 3.1 Number of participants measured at each biological age (BA)

BA	Male (*N*)	Female (*N*)	Total (*N*)
0	59	59	118
1	52	53	105
2	47	50	97
3	35	45	80
4	27	33	60
5	58	58	116
6	12	14	26
7	10	13	23
8	18	18	36
9	24	21	45
10	23	25	48
11	26	32	58
12	23	30	53
13	20	27	47
14	15	23	38
15	22	22	44

3.4.2 Anthropometry

Measures taken at each visit included standing height, sitting height (in childhood/adolescence) and weight using the protocol outlined in Ross and Marfell-Jones (35). Participants were instructed to wear loose fitting gym attire with no shoes or jewelry. Stretch stature and stretch sitting height were obtained using a wall mounted stadiometer and were rounded to the nearest 0.1 cm. Weight was measured on a calibrated scale and rounded to the nearest 0.1 kg. Body Mass Index (BMI) was calculated from recorded height and weight (kg/m^2) at each measurement occasion.

3.4.3 Biological Age

Individual curves were fitted to an individual's annual height velocity data (GraphPad Prism version 3.00 for Windows; GraphPad Software, San Diego, CA). Additional height data, in some instances, were provided by the schools for data collected prior to 1991. A cubic spline was then fitted to the data. The cubic spline procedure preserves the precision of longitudinal data by using individual statural data to create a smooth curve with which to identify an individual's age at attainment of PHV; age when greatest statural velocity occurs. A biological age (BA) was calculated as the difference between CA at measurement and age at PHV. BA groups were assigned by one-year intervals such that the +1 years BA group included those between the BA of 0.50 and +1.49 years past PHV. Individuals could only appear once in each BA group.

3.4.4 Body Composition

Percent total body fat (%TBF) and lean mass were measured by Dual-energy X-ray Absorptiometry (Hologic QDR 2000 and 4500; Hologic, Inc., Waltham, MA, USA). %TBF was obtained from a total body DXA scan. Between 1991 and 2007, scans were obtained using the Hologic 2000 scanner; after 2007, scans were obtained using a Hologic 4500 scanner. *In vivo* coefficients of variation in our lab for body fat measures are 3.0% and 3.4% (195,419). To correct for differences between instruments *in vivo* determined precision across the two different Hologic instruments was undertaken using results obtained from 9 men and 15 women. From these data, conversion factors were developed so that all outcomes used for analysis represented Hologic 2000 equivalent values (410).

3.4.5 BMI and Percent Body Fat Categories

Participants were classified as either normal weight (NW), overweight (OW) or obese (OB) at each measurement occasion using both BMI and %TBF cut-offs for children and adolescents (100,101). BMI classifications ≥ 18 years were as follows: (i) normal weight (NW) = BMI < 25 kg/m^2; (ii) overweight (OW) = BMI ≥ 25 kg/m^2 < 30 kg/m^2; and (iii) obese (OB) = BMI ≥ 30 kg/m^2. Percent total body fat classifications ≥ 18 years were as follows: NW = %TBF < 20.1% in males and < 30.8% in females; OW = %TBF ≥ 20.1% < 23.6% in males and ≥ 30.8%< 34.8% in females; and OB =%TBF ≥ 23.6% in males and ≥ 34.8% in females (100). %TBF references by McCarthy et al. were validated against Lunar DXA measures which have been found to be significantly lower but highly correlated ($R^2 > 0.9$) with Hologic 2000 DXA measures of absolute and percent body fat in pediatric populations (< 40.0 and > 40.0 kg) and in adult samples (> 40.0kg) (420). Although the term 'weight' encompasses all components of mass (fat or fat free), BMI and %TBF classifications are referred to in this paper as weight status categories for ease of reference. Due to low numbers in the obese category, OW and OB groups were combined for analysis.

3.4.6 Statistical Analysis

Descriptive statistics were calculated for participants at each BA category including means and standard deviations (SD) of %TBF and BMI. Missing measures at PHV and +5 were interpolated using linear regression procedures; BMI and %TBF with BA was plotted for each individual, a line fitted and the missing values extrapolated from the individual's curve. (GraphPad Prism version 3.00 for Windows; GraphPad Software, San Diego, CA).

Pearson correlation analyses were used to assess relationships between BMI and %TBF at PHV and subsequent BA's of +5, +10, +15 and +20 years. Independent-sample t-tests were

used to assess sex and group (NW versus OW/OB) differences in height, weight, BMI, and %TBF at +5, +10, +15 and +20 years after PHV; and between sex and within-sex group differences in PA and diet at PHV. Dependent t-tests were conducted to assess differences in BMI and %TBF between BA categories within each sex. Bonferroni corrections were used to control for family-wise error. Chi-squared analysis was used to test for differences in the prevalence of NW and OW/OB categories (categories determined by both %TBF and BMI cut-offs) at each BA between sexes. Logistic regression analyses were conducted to estimate the associations between NW and OW/OB at PHV and OW/OB at +5, +10, +15 and +20 years after PHV. All statistical analysis was performed using The Statistical Package for the Social Sciences (version 22.0; SPSS, Inc., Chicago, IL, USA). Significance level was set at $p<0.05$.

3.5 *RESULTS*

3.5.1 Participant characteristics

Participant characteristics at PHV are summarized in Table 3.2. Females attained PHV approximately 1.6 years earlier than males ($p<0.05$). Males were significantly taller and heavier at PHV ($p<0.05$). Females had significantly higher %TBF than males ($p<0.05$) at PHV. There was no significant difference in the prevalence of NW and OWO categories between males and females at PHV for either BMI ($p>0.05$) or %TBF ($p>0.05$) categories.

3.5.2 Patterns of BMI

The pattern of BMI development from PHV (BA=0) to +15 years post-PHV is shown in Figures 3.1a and 3.2a. During this time, males increased from 19.5 kg/m^2 to 26.8 kg/m^2, whilst

females increased from 18.4 kg/m^2 to 23.8 kg/m^2. BMI significantly increased from PHV to 8 years post-PHV ($p<0.05$) in both sexes. In males, there were no significant changes between 9 and 15 years post-PHV ($p>0.05$). In females, there were no significant changes between 9 years

Table 3.2 General descriptive characteristics of male and female participants at peak height velocity (PHV).

Variable	Males (n=56)	Females (n=57)
APHV (years)	13.6 (0.9)	12.0(0.9)*
Height (cm)	163.7 (7.4)	153.4(7.91)*
Weight (kg)	52.2 (8.5)	43.8(9.3)*
BMI (kg/m^2)	19.5 (2.4)	18.4(2.8)
%Total Body Fat	19.1 (7.5)	26.8(8.2)*
Prevalence of NW BMI Category (%)	91.1%	86.0%
Prevalence of NW %TBF Category (%)	71.4%	66.7%

APHV= age of peak height velocity; %TBF= % total body fat; NW= normal or low risk category by BMI and %total body fat cut-offs respectively. Mean (SD); * indicates significant difference between sex ($p<0.05$)

and 13 years post-PHV ($p>0.05$). Figures 3.1a and 3.2a also show the BMI cut off lines for overweight. Males did not become overweight until 7 years post-PHV (~CA 21 years); in females, it was 10 years post-PHV (~ CA 22 years).

Table 3.3 shows the changes in BMI from PHV to +15 years post-PHV and the correlations between the time points. With increasing BA, correlations between BMI at PHV and subsequent BMI decreased in males with a slight increase at terminal years: between BA 0 and +1 years ($r = 0.78$, $p<0.05$), BA 0 and +5 years ($r = 0.79$, $p<0.05$), BA 0 and +10 years ($r = 0.60$, $p<0.05$), BA 0 and +15 years ($r = 0.66$, $p<0.05$). A similar pattern was seen in females: between

BA 0 and +1 years ($r = 0.96$, $p<0.05$), BA 0 and +5 years ($r = 0.813$, $p<0.05$), BA 0 and +10 years ($r = 0.793$, $p<0.05$), BA 0 and +15 years ($r = 0.769$, $p<0.05$). Significant differences (in both sexes) were found between BMI values at BA 0 and +5 years after BA 0 (males t (55) = -17.28, $p<0.05$; females t (56) = -13.89, $p<0.05$); and between 5 and 10 years post-BA 0 (males t (22) = -4.35, $p<0.05$; females t (24) = -7.02, $p<0.05$). No significant differences were found between 10 and 15 years post-BA 0 in either sex ($p>0.05$).

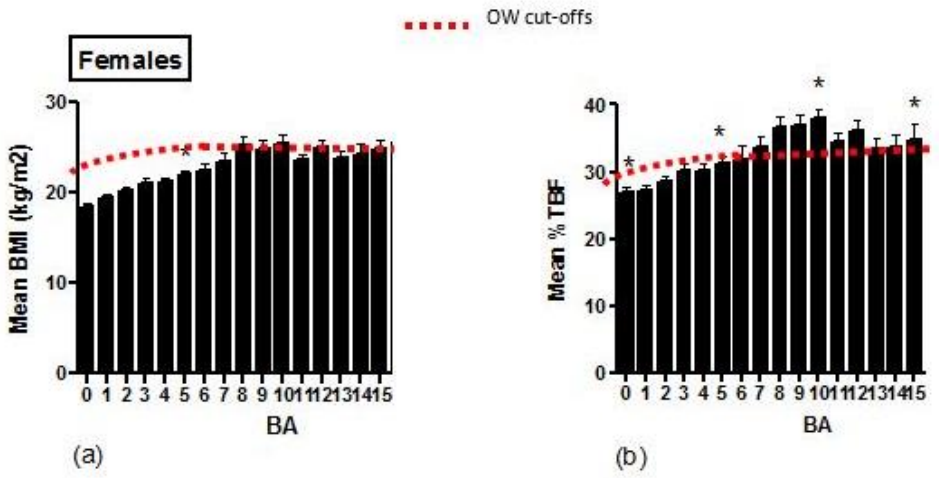

Figure 3.1 Group means for (a) BMI and (b) %TBF in females by BA with respective OW cut-offs. * significantly different mean from males at the same BA, $p<0.05$.

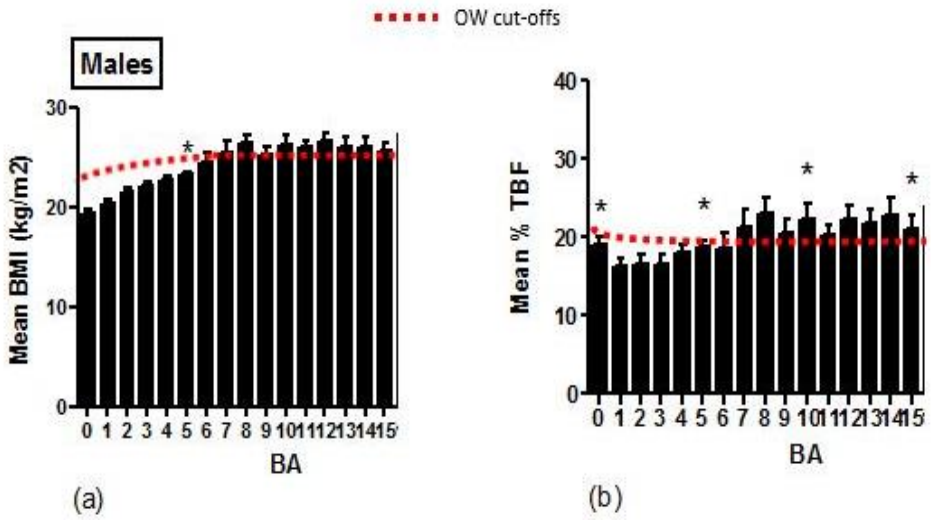

Figure 3.2 Group means for (a) BMI and (b) %TBF in males by BA with respective OW cut-offs. * significantly different from females at the same BA, $p<0.05$.

3.5.3 Pattern of %TBF

Patterns for %TBF development are shown in Figure 3.1b (females) and 3.2b (males). The pattern is similar to that seen with BMI development (Figure 3.1a and 3.2a). However, in contrast to BMI, females maintained higher values than males throughout the measurement period. These sex differences were significant at BA 0, +5, +10, and +15 years ($p>0.05$). At BA

0, the mean %TBF for females was 26.8%, which climbed to a high of 37.9% at BA +10 years before plateauing at approximately 35%. Males exhibited a lower mean of %TBF than females with values continuing to climb from a low of 16.3% at BA +2 years to a high fluctuating between 20 and 24% from BA +7 to +15.

In females, %TBF increased significantly from BA 0 to +5 years (t (56) = -6.21, $p<0.05$) and from +5 to +10 years (t (24) = -5.70, $p<0.05$) but there was no significant increase from +10 to +15 years ($p>0.05$) (Table 3.3). In males, the only significant increase in %TBF between time points was from +5 to +10 years (t (22) = -2.334, $p<0.05$). With increasing BA, correlations between %TBF at BA 0 and subsequent %TBF decreased in males: BA 0 to +1 years ($r = 0.89$, $p<0.05$), BA 0 to +5 years ($r = 0.68$, $p<0.05$), BA 0 to +10 years ($r = 0.49$, $p<0.05$), BA 0 to +15 years ($r = 0.52$, $p<0.05$). A similar pattern was seen in females: BA 0 to +1 years ($r = 0.93$, $p<0.05$), BA 0 to +5 years ($r = 0.75$, $p<0.05$), BA 0 to +10 years ($r = 0.65$, $p<0.05$), BA 0 to +15 years ($r = 0.64$, $p<0.05$).

3.5.4 Weight Status

Figures 3.3a and 3.4a show prevalence of weight status categories by BMI cut-offs. NW is the most prevalent category (>50% of participants) in females from BA 0 (PHV) (NW = 86%) to +7 years and in males from BA 0 (NW = 91%) to +6 years. From this point to young adulthood, the OWO categories made up between 15% to 60% in females (40.0 ± 13.7%) and 44% and 91% in males (62.0 ± 12.9%).

Assigning weight status categories by %TBF displayed a different pattern than that seen with BMI (Figures 3.3b and 3.4b); females had higher prevalence of OWO than males. The percentage of NW females dropped almost continuously from 67% at BA 0 to +10 years with a low of 16%.

Table 3.3 Body mass index (BMI) and percent total body fat (%TBF) changes with increasing biological age (BA).

	Male					Female 1				
	N	Change BMI	*r*	Change %TBF	*r*	*N*	Change BMI	*r*	Change %TBF	*r*
PHV	56		1	−2.8866	1	57		1	0.1363	1
1	50	0.8777	.923**	−0.1229	.894**	51	0.9178	.957**	1.7247	.927**
2	45	1.0527363	.872**	0.5251	.823**	48	1.0066827	.918**	1.4726	.881**
3	33	0.7526	.859**	2.1129	.848**	43	0.7803	.824**	1.647	.734**
4	25	1.0555	.672**	0.0324	.751**	32	0.7209	.714**	0.2491	.686**
5	56	0.2942	.791**	0.6904	.683**	57	0.2554	.813**	1.7134	.748**
6	11	0.5941	.858**	2.6126	.796**	13	0.791	.579*	0.117	.710**
7	10	0.8746	.946**	−0.4731	0.567	12	0.6433	.692*	0.5746	.612*
8	16	0.345	.811**	−1.1072	.573*	17	1.0575	.706**	1.1925	.644**
9	23	0.1565	.688**	0.2658	0.330	21	0.5044	.715**	0.6259	.690**
10	23	0.0912	.600**	−0.2379	.492*	25	0.0606	.793**	0.7989	.649**
11	26	0.0182	.519**	1.7062	0.365	32	0.234	.700**	0.929	.515**
12	24	0.7544	.681**	0.4131	.542**	29	0.6789	.520**	−0.1072	.556**
13	20	0.0929	.699**	−1.4088	0.356	26	−0.2398	.780**	−0.253	.741**
14	15	−0.4087	0.452	3.308	0.433	22	−0.179	.553**	0.9662	.569**
15	22	0.9002	.655**	6.3191	.519*	22	−0.1594	.769**	2.3705	.635**

Change BMI= change in BMI from previous year; Change %TBF = change in %TBF from previous; *r* = pearson correlation between current value (BMI or %TBF) and value at PHV; **Correlation is significant at the 0.01 level (2-tailed).*Correlation is significant at the 0.05 level (2-tailed).*.

Levels then rose slightly, plateauing with a mean of only 32% (66.0 ± 12.0% OWO) from BA +10 to +15 years. Males maintained levels similar to those at BA 0 (71% NW) for longer than the females, beginning to drop at +7 years. From this point to +15 years the NW category declined slightly (47.0 ± 12.7%).

When comparing BMI between weight status groups (NW or OWO), females' BMI was significantly different between groups at BA 0, +5 years and +10 years ($p<0.05$) but not different at +15 (Figure 3.3a). In males there were significant differences between groups at BA 0, +5 years and +15 years ($p<0.05$) but not at +10 ($p>0.05$) (Figure 3.4a). BMI in the PHV OWO

group actually had a lower mean than the NW PHV group at +14 years (results not shown) ($p>0.05$). Comparing %TBF between weight status groups (NW or OWO) by %TBF cut-offs, there were significant differences in %TBF between groups at PHV and +5 in males and females ($p<0.05$), but differences were no longer significant at +10 or +15 ($p>0.05$) in either sex.

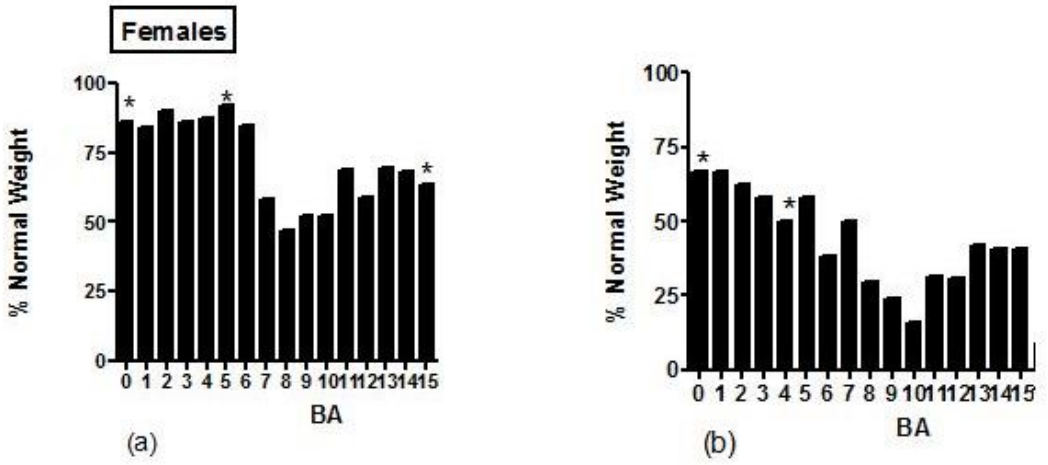

Figure 3.3 Prevalence of Normal Weight in female participants by (a) BMI and (b) %TBF. *significantly different mean values of (a) BMI and (b) %TBF between NW group and OWO, $p<0.05$.

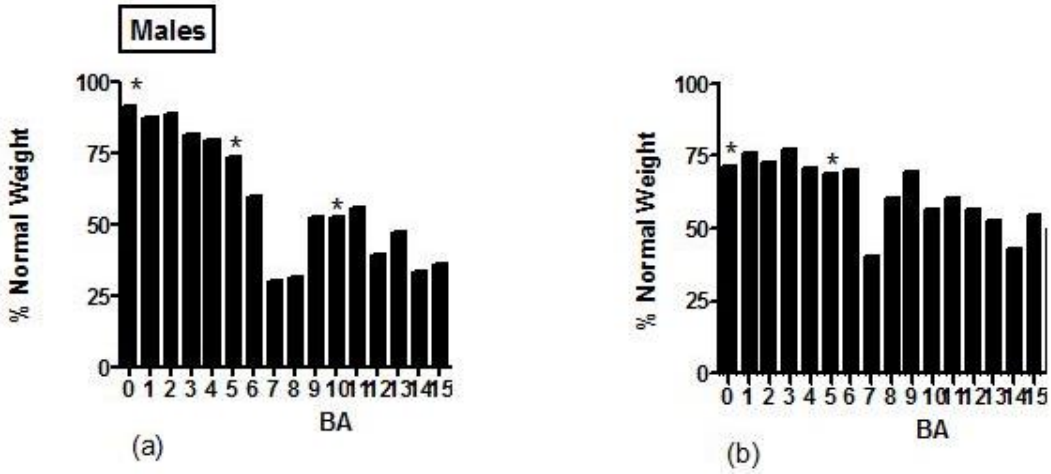

Figure 3.4 Prevalence of Normal Weight in male participants by (a) BMI and (b) %TBF. *significantly difference mean values of (a) BMI and (b) %TBF between NW group and OWO, $p<0.05$.

The results of the logistic regression indicated that those classified as OWO at PHV by BMI cut-offs were not at a significantly greater risk of being OWO than those classified as NW

at PHV, at +5 years, or +15 years ($p>0.05$). Significance was found only at +10 years with an odds ratio of 0.1 ($p<0.05$). Similarly, those classified as OWO at PHV by %TBF cut-offs are not at a significantly greater risk of being classified as OWO at +10, or +15 years ($p>0.05$). Significance was found only at +5 years with an OR 0.04 ($p<0.05$).

3.6 *DISCUSSION*

This study has shown that on average, fat mass increases after PHV for 8 years (20 years of age in females and 22 years in males); it then stabilizes for 5 to 7 years (between 25 to 29 years), with some indication of a forthcoming increase. The study results suggest that emerging adulthood (18 to 22 years of age) is an important time for fat accrual and could be a potential critical period for weight gain. The results highlight differences in weight status attributed to BMI versus %TBF cut-offs. Finally, it found that being NW at PHV is not protective against being overweight in early adulthood. This study of body fat measurement in the same group of individuals over time highlights a potentially critical period of weight gain between adolescence and young adulthood.

We have previously reported that the heights and body mass of this cohort were within normal reference standards ranges during adolescence (413). This paper indicates that the prevalence of OWO at PHV are lower than those reported in other studies (64,101,122,160,421,422). Longitudinal studies of European youth have found similar values of BMI's (117) and %TBF (335) during puberty to those found in the present study. Of interest is the fact that within a few years of attainment of PHV, the prevalence of OWO was substantially higher than those found in other similar aged cohorts (118).

3.6.1 Pattern of fat mass accrual

In the present study, a plateau in fat mass accrual was observed from the end of emerging adulthood into the late 20's. This pattern is comparable to Dutch and Norwegian longitudinal data (117,118), although the Dutch sample did not show a plateau during their 20s. Data from the Fels longitudinal study of US youth collected between 1929 and 1996 suggests that BMI increases up to a maximal value in the early 20s, and then begins to decline (87); however, at a 10 year follow up in the same study (participants in their early 30s), only the NW BMI group had maintained values. The OW group's BMI increased into adulthood (87).

3.6.2 Weight Status

Estimates of the prevalence of adult OWO using BMI in the current study are higher (60% in males; 40% in females) than American data from the Fels study (54% males and 34% of females) (87,423) and Dutch data from the AGAHLS study (118), and lower than Norwegian data from The Oslo Youth study (64% males and 35% females) (117). The adult OWO estimates by BMI were also similar to recent findings of a national cross-sectional data survey which combined sexes (34% OW and 18% OB) (424); higher than current estimates for Saskatoon (31% OB) (152); and comparable to international estimates in developed countries (55% OWO males; 45% OWO female) (160).

In regards to estimates of OWO by %TBF, there is very little longitudinal DXA data with which to compare; yet, there does appear to be a consistently demonstrated pattern of a continual increase in fat and OWO prevalence from 19 to 25 years whether measured by DXA (70), bio-electrical impedance (421), or skinfolds (118). Differences in estimated prevalence of OWO may be due to differences in sample demographics and geography but may also be due to low sample size in adulthood in the present study. In the present study, the group mean for BMI and %TBF

surpassed the cut-off for normal weight between +6 and +8 years corresponding to 18-20 years in females and 20-22 years in males, again highlighting this period of life as significant in regard to the prevalence of OWO status.

3.6.3 Emerging Adulthood

The most dramatic increase in obesity rates in the USA has been between 17 and 19 years (30). In Canada, 50-70% of University students are between 17 and 24 years of age (386), and the mean age of graduates is 22.7 years (390). The present data indicated that these are years in which BMI and %TBF continued to climb, agreeing with previous studies of college-age students and US data (379,380,382,387,388). Specifically, the sample increased by 5% in %TBF (4 kg/m^2 BMI) in males and 6% in %TBF (3 kg/m^2 BMI) in females between 18 and 22 years, similar to values found in a longitudinal study of American college students in which males increased %TBF by 5.3% (1.8 kg/m^2 BMI), and females by 2.9% (0.6 kg/m^2 BMI).

In the present study, the differences in BMI and %TBF in those classified as NW versus OWO at PHV began to disappear by the age of 20. Although those who are OWO in adolescence may be at risk of OWO in adulthood (16), those with normal BMI and %TBF for age "catch – up" during the transition from adolescence to early adulthood. This data replicates and adds to those observed in longitudinal data of American adolescents in which 22-38% of males and 24-43% of females were overweight, or gained weight from the ages of 16 to 29- some of which moved from NW status to OW status (90). Both maintaining or becoming OWO is related to an elevated health risk in comparison to maintaining a healthy weight (90).

Gains in BMI can be due to increases in lean, fat or bone tissue mass. Cessation of bone accrual occurs approximately +5 years after PHV (age 19 and 17 in males and females, respectively) (110); therefore, increases in weight seen in this study during the years of late

adolescence are likely due to fat or lean mass gains. Lifestyle behaviors such as a decrease in healthy food intake and physical activity, and increased alcohol consumption, coincide with college years and relate to fat mass gains (386). Weight, fat and BMI gains have been found in this age cohort regardless whether an individual goes to college or enters directly into the work force (30,32). Others have found that greater increases are seen in those with some college education and may be due in part to factors accompanying the transition into university which can contribute to weight gain (stress, sleep disturbances, mental health) (30,32).

3.6.4 Limitations

Although the study is small in sample size, its power comes from the fact that repeated observations are available with individuals measured over a 20 year time period. This study used BMI and %TBF from DXA to estimate prevalence of OWO. There is some evidence that breaking BMI into fat and lean mass components gives a more accurate measure; however, the literature suggests that the use of BMI (especially recently established pediatric references) are ideal for clinical practice as they are widely accessible, inexpensive and non-invasive (65). Similarly, the use of DXA has been affirmed for its accuracy and its practicality in a clinical setting (65,70,425).

The cut-off points used for this analysis are recommended for comparing data internationally and less intended for use on national datasets (101) and are perhaps more accurate when used in conjunction with World Health Organization (WHO) standards (426). With that said, the IOTF cut-off points were developed using data from six different countries and tend to underestimate the OW and OB rates compared to other reference standard such as WHO (160,427). Differences between the Lunar DXA used to establish %TBF cut-offs, and Hologic DXA used for this study's data collection, may have introduced error into estimates of the

prevalence of OWO in the sample. With that said, the Hologic 2000 and 4500 DXA tend to underestimate measures of fat compared other DXA scanners (420,428) .

This sample was almost exclusively European-descent. As such, these data can not be generalized to the more ethnically diverse population of Saskatoon. Finally, the sample size decreased substantially with age and, therefore, the inablitilty of OWO at PHV to predict OWO in adulthood should be interpreted with caution. With that said, 50% of participants were OWO by BMI in males and by %TBF in females at the last analyzed measurement between 26 and 30 years.

3.7 *CONCLUSION*

This cohort of predominatly NW status adolescents grew up to become predominantly OWO young adults. Of particular interest was the notable drop in the prevalence of NW status during the emergence of adulthood, the ages of 18-25, suggesting that emergeing adulthood could potentially be another critical period for weight gain during growth. The long-term concern is that those who become OWO are likely to remain so, or continue to grow larger, which corresponds to elevated health risks (429). The next stage of research should focus on tweezing out the independent effects of growth during emerging adulthood from the effects of environmental exposures known to influence weight gain.

3.8 *ACKNOWLEDGMENTS*

We acknowledge all the study participants and their families for their constant enthusiasm and commitment to the Pediatric Bone Mineral Accrual Study. This study was supported in part by funding from the Canadian Institutes of Health Research (CIHR; MOP 57671) and the Saskatchewan Health Research Foundation (SHRF).

3.8.1 Declaration of interest

The authors report no declaration of interest.

3.9 *COPYRIGHT TRANSFER AGREEMENT*

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LINKS BETWEEN STUDIES

Study 1 identified the period of emerging adulthood as being potentially critical in the onset and development of OWO; compared to a few participants who were OWO as children and adolescents, over half of the cohort was OWO by 25 years of age. A discrepancy between metrics of OWO was identified such that in males, BMI estimated higher prevalence and earlier predominance than %TBF, while in females it was %TBF that produced higher prevalence and earlier predominance. These conclusions led to two questions: 1) Does the age at onset of OWO differ by metric, and does the most conservative metric differ between sex? And 2) What are the factors that influence (predict) fat mass accrual during the period of emerging adulthood? Question 1 led to the design of 1b. Question 2 led to the design of study 2.

CHAPTER 4

Study 1-Paper 1b: When do normal weight Canadian children become overweight adults? Difference according to sex and metric (BMI, %FM and WC)

4.1 *DECLARATION OF CONTRIBUTION*

I, Erin Barbour-Tuck, am the primary author of this manuscript and was responsible for data cleaning, analysis, and interpretation; and writing, editing and formatting the manuscript.

4.2 *MANUSCRIPT STATUS*

This document is under revisions for the Annals of Human Biology, October 10th, 2018. This document has been reformatted from the submitted version for inclusion in the thesis with minor grammatical changes to improve readability and relationship to the larger document.

4.3 *INTRODUCTION*

Canadian rates of obesity have more than doubled over the past 40 years (2,162,430). Overweight and obesity (OWO) in both adults and children correlate with several chronic diseases including coronary heart disease and type II diabetes, as well as to risk factors for these

diseases such as hypertension, dyslipidemia, and insulin resistance. As such, obesity remains a major Canadian public health concern. The most recent estimates of OWO from Statistics Canada (2015) suggest that 34% of 12 to 17-year-old Canadians have OWO (162). This number increases slightly to 37% in 20 to 24-year-olds, but increases to 50% in 25 to 34-year-olds (162). Of interest, therefore, is the age when children with normal weight (NW) become adults with OWO.

OWO are considered by the World Health Organization (WHO) to be a condition of excess body fat to the point that health is compromised (142). The most common measure of OWO is body mass index (BMI; kg/m^2) (431); however, this metric operates on the assumption that a higher BMI will be associated with a higher fat mass. Yet at a given BMI, percentage total body fat mass (%FM), fat distribution (waist circumference (WC)) and associated health risk can vary substantially (155,191,432). Variance in the relationship between BMI and adiposity and fat distribution can be a function of sex, degree of fatness, maturation, and chronological age (99). The differences between individuals, and between sexes, become more pronounced from the onset of adolescence into emerging adulthood (EA; 18-25 years) as pubertal hormones and individual genotypes influence the relative amounts of lean and fat mass being accrued (35,69,99). Fat mass accrual comprises a greater proportion of weight gain in females, and lean mass comprises a greater proportion of weight gain in males (69). The adolescent/EA period is also typified by the conclusion of fat free mass accrual, yet continued fat mass accrual beyond this period has been recently reported (385,388,433). Many adults with OWO who had normal weight (NW) in youth transition and acquire OWO during EA; although the timing of this transition varies between sex and by metric(107,434). Using different indices and cut-points for OWO, especially during periods of body composition changes, may differentially identify age at

onset of OWO. Specifically, BMI screening for OWO may provide false negatives, overlooking those with low body weight but high body fat or WC (154).

Identifying the metric that provides the earliest identification of excess adiposity is justified by the cumulative nature of health risk imposed by prolonged exposure to OWO. The purpose of this study was to identify the sex-specific differences in the age of onset of OWO by BMI, %FM, and WC cut-points.

4.4 *METHODS*

4.4.1 Study Design and Participants.

Participants for this study were drawn from the Pediatric Bone Mineral Accrual Study (PBMAS). This longitudinal study began in 1991 with an original sample of 220 children and the addition of 31 more participants between 1992 and 1993. The PBMAS has been described in detail elsewhere (411). Participants were aged 8 to 15 at their initial measurement. After the initial 7 years of data collection, 197 participants had at least 2 two serial measurements (median = six). Between 2002 and 2005, 169 (77 males) participants returned (median 4 visits). From 2010 to 2011, 123 (49 males) were retested (median 2 visits) and between 2016 and 2017, 61 (28 males) returned for one more visit (Table 4.1). This sample is 95% European-descent (of the 94% who identified race). Inclusion criteria of participant data for this study were a minimum of two measures between 1991 and 2017. There were 237 (108 males) individuals who met the criteria and were measured between 8 and 40 years of age on a median of 10 occasions (range 2 to 15).

Table 4.1 Number of participants males (females) measured by age and year of measurement.

Age	1991	1992	1993	1994	1995	1996	1997	2003	2004	2005	2007	2009	2010	2011	2016	2017	***Total***
8	3 (7)	5 (11)	0 (2)														8 (20)
9	10 (15)	3 (9)	5 (10)	0 (2)													18 (36)
10	19 (16)	10 (18)	3 (10)	5 (10)	0 (2)												37 (56)
11	17 (12)	18 (15)	12 (18)	3 (9)	5 (10)	0 (2)											55 (66)
12	21 (18)	17 (12)	16 (15)	12 (14)	3 (10)	5 (10)	0 (2)										74 (81)
13	17 (21)	21 (16)	17 (11)	14 (16)	11 (14)	3 (10)	5 (7)										88 (95)
14	17 (16)	15 (20)	20 (15)	14 (11)	14 (16)	10 (12)	3 (9)										93 (99)
15	3 (8)	17 (15)	14 (20)	14 (15)	12 (11)	10 (16)	8 (8)										78 (93)
16		3 (7)	17 (14)	13 (12)	13 (14)	11 (7)	8 (11)										65 (65)
17			3 (7)	13 (11)	13 (12)	12 (12)	9 (6)	0 (2)									50 (50)
18				3 (6)	13 (8)	12 (11)	8 (9)	3 (3)	0 (2)								39 (39)
19					3 (6)	8 (6)	7 (8)	4 (13)	3 (2)	0 (2)							25 (37)
20						4 (3)	5 (3)	6 (13)	2 (12)	5 (4)							22 (35)
21							2 (2)	6 (9)	5 (7)	2 (9)	0 (2)						15 (29)
22								12 (9)	6 (11)	6 (10)	4 (7)						28 (37)
23								8 (10)	10 (8)	7 (9)	3 (7)						28 (34)
24								14 (14)	9 (12)	10 (7)	7 (10)	0 (1)	0 (1)				40 (45)
25								8 (6)	11 (13)	8 (14)	5 (12)	1 (1)	0 (0)				33 (46)
26								3 (5)	9 (6)	10 (11)	7 (8)	0 (4)	1 (4)	0 (1)			30 (39)
27								1 (0)	4 (5)	9 (5)	12 (11)	1 (2)	1 (3)	2 (3)			30 (29)
28										3 (3)	11 (14)	0 (2)	8 (6)	3 (7)			25 (32)
29											9 (5)	0 (2)	6 (8)	4 (4)			19 (19)
30											2 (2)	0 (1)	4 (4)	6 (4)			12 (11)
31												1 (1)	8 (10)	2 (3)	0 (1)		11 (15)
32													4 (9)	12 (7)	1 (3)	0 (1)	17 (20)
33													5 (7)	5 (7)	3 (2)		13 (16)
34													1 (0)	5 (3)	3 (1)	0 (1)	9 (5)
35														1 (1)	3 (5)	3 (2)	7 (8)
36															3 (0)	1 (1)	4 (1)
37															0 (6)	1 (0)	1 (6)
38															1 (4)	4 (2)	5 (6)

39															0 (3)	3 (1)	3 (4)
40																0 (1)	0 (1)
Total	107 (113)	109 (123)	107 (122)	91 (106)	87 (103)	75 (89)	55 (65)	65 (84)	59 (78)	60 (74)	60 (78)	3 (14)	38 (52)	40 (40)	14 (25)	12 (9)	**982 (1175)**

4.4.2 Anthropometry and Peak Height Velocity

Measures taken at each visit included standing height, sitting height (in childhood/adolescence) and weight using the protocol outlined in Ross and Marfell-Jones (35). The height data was used to develop velocity curves which were then fit with a cubic spline. A cubic spline uses the interpolation of polynomials from neighboring points to create a smooth curve. Interpolated velocity values were then used to identify age at peak height velocity (PHV) (GraphPad Prism 5, GraphPad Software, San Diego, CA, USA).

4.4.3 Chronological and Biological Age:

Chronological age (CA) was determined by subtracting the date of birth from the decimal date of measurement. CA categories were composed of 1-year intervals such that the CA category of 12 years included all those with age at test ranging from 11.5 to 12.49. Biological age (BA) was calculated by subtracting the CA of the participant at the measurement from the CA at PHV. BA groupings were constructed using 1-year intervals such that the BA of 1 included measurements occurring between -0.5 and 0.49 years from PHV.

4.4.4 Body Composition and overweight/obesity classification

Total body fat mass (TBFM), bone mineral content (TBBMC) and lean mass (TBLM) was assessed using total body dual energy x-ray absorptiometry (DXA) scans (Hologic QDR - 2000, Hologic, Waltham, MA). The coefficient of variation (%) for short-term precision *in vivo* for TBFM was 2.95% (195). Percentage fat mass (%FM) was calculated as

(TBFM/[TBFM+TBBMC+TBLM]) * 100. Age- and sex-specific cut-points for OW were used for ages 18 years and under as follows: BMI cut-points developed by Cole et al. (2000) (101); %FM cut-points developed by McCarthy et al. (2006) (100); WC cut-points corresponding to Adult Treatment Panel cut-points developed by Cook et al. (2009) (435) to identify cardio-metabolic risk, and those aligning with the Canadian 90th percentile by Katzmarzyk et al. (2004) (183). Adult OW cut-points used were as follows: BMI cut-points from WHO (Overweight ≥ 25kg/m^2) (142); %FM cut-point developed by Gallagher et al. (2000) using prediction equations developed using WHO BMI limits (20-39 years Overweight ≥ 20% in males; ≥ 33% in females) (436); WC cut-points based on Adult Treatment Panel cut-points (102 cm for males; 88 cm for females) (214).

4.4.5 Statistical Analysis

Growth curves for BMI, %FM and WC were developed using hierarchical (multilevel) linear modelling (MlwiN version 3.02, Centre for Multilevel Modelling, University of Bristol, Bristol, UK). This procedure has been described in detail previously (402). In brief, parameters (BMI, %FM and WC) were measured repeatedly within individuals (level 1 of the hierarchy) and between individuals (level 2 of the hierarchy). Analysis models that contain linked variables measured at different levels of a hierarchy are known as multilevel random effect regression models. Specifically, the following additive random effects multilevel regression models were adopted to describe the developmental changes in parameters with age.

Fixed effects:

$$y_{ij} = \beta_{0ij}\text{Constant} + \beta_{1j}\text{AgeC}_{ij} + \beta_2\text{AgeC}^2_{ij} + \beta_3\text{AgeC}^3_{ij}$$

$$\beta_{0ij} = \beta_0 + \mu_{0j} + \varepsilon_{0ij}$$

$$\beta_{1j} = \beta_1 + \mu_{1j}$$

Random effects:

$$\text{Level 2} \quad \begin{vmatrix} \mu_{0j} \\ \mu_{1j} \end{vmatrix} \sim N(0, \Omega_\mu) : \Omega_\mu = \begin{vmatrix} \delta^2_{\mu 0} & \delta_{\mu 01} \\ \delta_{\mu 01} & \delta^2_{\mu 1} \end{vmatrix}$$

$$\text{Level 1} \quad [\varepsilon_{0ij}] \sim N(0, \Omega_\varepsilon) : \Omega_\varepsilon = [\delta^2_{\varepsilon 0}]$$

Where, in the fixed effects, y is the fat parameter (e.g. BMI, %FM or WC) on measurement occasion *i* in the *j*-th individual; β_{0ij} is a constant (constant = 1); β_{1j} is the slope of the fat parameter over time (age centered around 18 years [AgeC]) for the *j*-th individual; β_2 and β_3 are the coefficients of various time dependent explanatory variables ($AgeC^2$ and $AgeC^3$) at assessment occasion *i* in the *j*-th individual. μ_{0j}, μ_{1j}, and ε_{0ij} are random effects, whose means are equal to zero. They are assumed to be uncorrelated and follow a normal distribution and thus their variances can be estimated.

Models were built in a stepwise procedure, i.e. predictor variables (β-fixed effects) were added one at a time, and the log likelihood ratio statistics was used to judge the effects of including further variables on the fit of the model. Level 1 variance ε_{0ij} indicated variance within individuals over time ($\delta^2_{\varepsilon 0}$). Age center ($\beta_j AgeC_{ij}$) was added as both a random (level 2) and a fixed variable. This permits individuals to have independent intercepts ($\delta^2_{\mu 0}$) and slopes ($\delta^2_{\mu 1}$) and a calculation of the intercept-slope covariance relationship ($\delta_{\mu 01}$). The power functions $AgeC^2$ and $AgeC^3$ were introduced into the linear models to allow for the non-linearity of growth and were retained whether or not they were significant so as to shape the fat developmental curves. The β coefficients in the final models (Table 4.2) were used to develop average growth curves for BMI, %FM and WC with accompanying level 2 variance (level 2 variance = [(Constant*Constant*$\delta^2_{\mu 0}$) + (AgeC*AgeC*+ $\delta^2_{\mu 1}$) + (2*Constant*AgeC* $\delta_{\mu 01}$)]). A total of

six independent multilevel (hierarchical) random effects models were constructed; one for each fat metric by sex. Sex- and age-specific overweight cut-points were used to identify the age at which growth curves of BMI, %FM and WC crossed over their metric specific cut-points (Figure 4.1).

4.5 *RESULTS*

A total of 2,157 (982 males) measures were available from 237 (108 males) measured on a median of 10 occasions between the ages of 8 and 40 years of age (Table 4.1). Table 4.2 summarizes the results from the six multilevel models for BMI, %FM and WC development by sex. For all models, within individuals fat metric increased with increasing age ($p<0.05$) and between individuals there were differences in individuals intercepts and slopes of the curves ($p<0.05$). In the fixed effects it was shown that, in general, age centered, age centered^2 and age centered^3 were significant independent predictors of fat metric development (BMI, %FM and WC) ($p<0.05$).

Table 4.2 Multilevel regression models for body mass index (BMI) development in males and females

	Variables	BMI		%FM		WC	
		Male	Females	Male	Females	Male	Females
Fixed Effects	**Constant (β_{0ij})**	22.99±0.31	23.5±0.39	18.45±0.72	32.85±0.67	78.28±0.77	75.41±0.87
	AgeC (β_{1j})	0.59±0.02	0.50±0.03	0.24±0.05	0.66±0.04	1.76±0.07	1.22±0.06
	AgeC^2 (β_2)	-0.02±0.001	-0.02±0.001	0.03±0.01	-0.04±0.004	-0.042±0.002	-0.07±0.001
	AgeC^3 (β_3)	-0.00008±0.00008	0.0004±0.0001	-0.002±0.003	0.0002±0.0002	-0.0005±0.0001	0.003±0.0003

Random Effects							
Level 1	**Constant ($\delta^2_{\varepsilon 0}$)**	1.17±0.04	2.04±0.07	14.72±0.75	10.68±0.49	10.21±0.45	26.19±1.07
Level 2	**Constant ($\delta^2_{\mu 0}$)**	10.31±1.45	18.98±2.42	50.57±7.33	54.39±7.07	59.34±8.55	86.88±11.47
	AgeC*AgeC ($\delta^2_{\mu 1}$)	0.04±0.006	0.07±0.01	0.17±0.03	0.13±0.02	0.37±0.06	0.26±0.04
	Constant*AgeC ($\delta_{\mu 01}$)	0.34±0.08	0.82±0.13	-0.45±0.36	0.20±0.29	2.61±0.60	3.08±0.61

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of body mass index (BMI, kg/m^2), percentage fat mass (%FM, %) and waist circumference (WC, cm). Age Centered (AgeC) is age in years centered on 18 years of age. Random effects values Estimated Mean Variance ± SEE $[BMI\ (kg/m^2)]^2$, $[\%FM\ (\%)]^2$ and $[WC,\ (cm)]^2$. Numerical values are significant at $p < 0.05$ if EMC/EMV > 2*SEE).

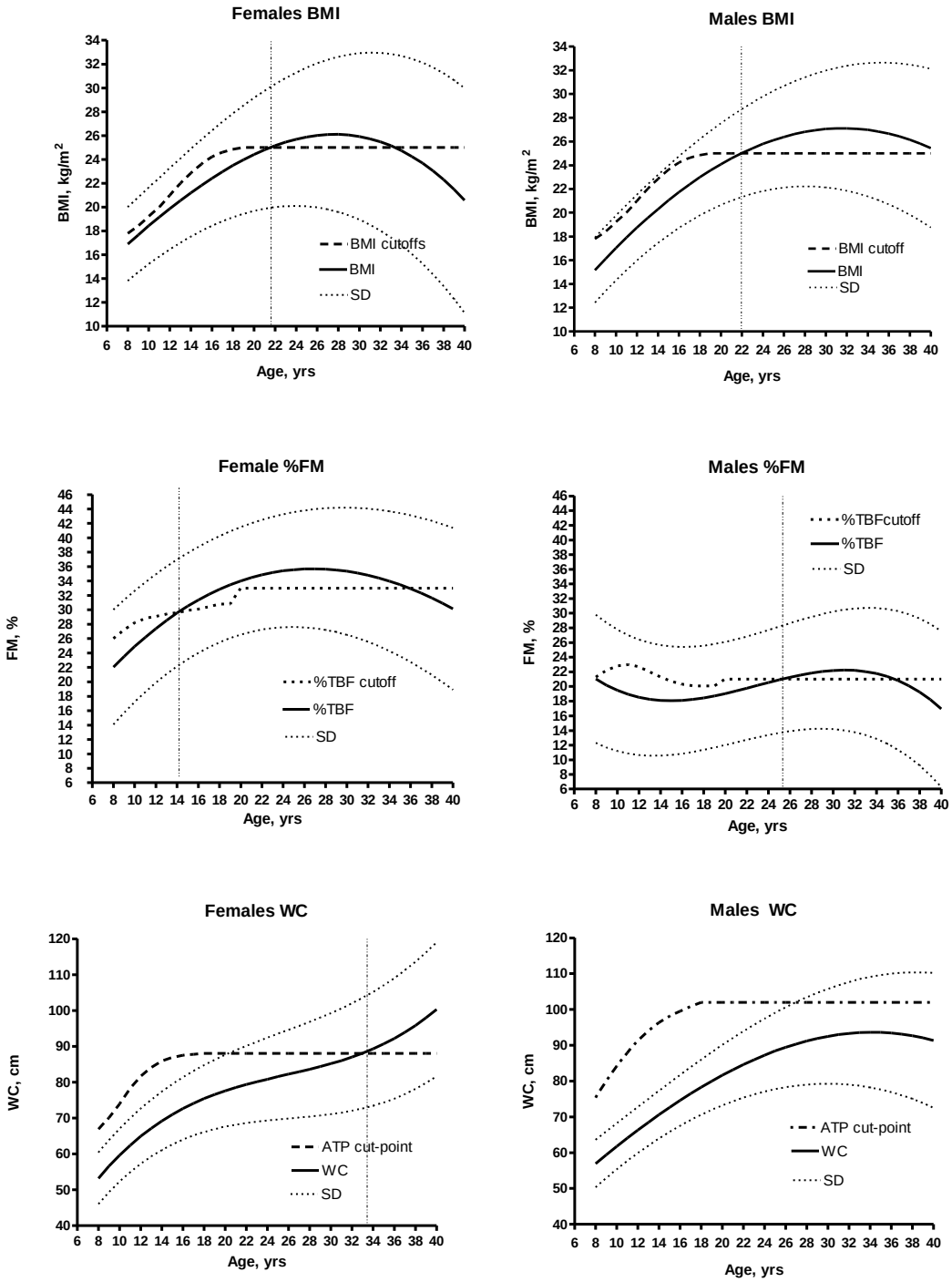

Figure 4.1 Mean growth curves and SD (Table 4.2) for body mass index (BMI), percentage total body fat mass (%FM) and waist circumference (WC) by sex against cut-offs (144,217,464) .

4.6 *DISCUSSION*

This study investigated the age of onset of overweight status in a cohort of children who were categorized by BMI as NW at study initialization (8 to 15 years). Previously it has been shown that at peak height velocity (females 11.9 years and males 13.5 years), 93% of males and 87% of females were normal weight by BMI and at 25 years of age 50% of participants were normal weight by BMI(433). In the present study, it was found that the average age of transition from normal weight to overweight status depended on age and metric used. BMI curves predicted an earlier onset in males; in contrast, percentage fat mass (%FM) predicted an earlier onset in females. Waist circumference (WC) curves had not crossed the cut-off in males by 40 years of age but had in females by 33.8 years. The implication of the results is that emerging adulthood (18-25 years) appears to be a critical time period for fat gain in normal weight youth and that the ability of metrics used to identify overweight status are not equal.

There are large individual and sex differences in body composition and, as such, having a BMI beyond cut-points does not necessarily match up with the WHO definition of OWO which specifies it as a condition of excess body fat (142). From the age of 8 to 18 years, lean mass accrual demonstrates a linear relationship with BMI while the relationship of BMI with %TBF and WC and of %TBF and WC with age are not linear (70,99,201,437). An increase in unit BMI likely corresponds to an increase in lean mass (kg) during the adolescent period; however, as sexual dimorphism arises and differences in health behavior and underlying genetics manifest, the relationship between BMI, body composition and age becomes inconsistent. The implication is that the ability of indices of OWO to identify adiposity are not equal. Differences in the observed prevalence of OWO between BMI and %FM has been previously demonstrated in this cohort with %FM identifying a greater proportion of OWO than BMI in females but a lesser

proportion in males (434). As such it was not surprising that the current study found an earlier age at onset of OWO by %FM in females and by BMI in males.

In 2017, Statistics Canada released national estimates of OWO based on self-report data indicating that 22% of 18 to 19-year-olds, and 50% of 25 to 34-year-olds had OWO (162). This suggests that a number of youth with NW become adults with OWO during the years of EA. Previously published observational data from the current cohort identifies a prevalence of OWO similar to self-reported national estimates of BMI from 12-17 years (23.1%), but lower than national estimates of youth OWO by measured BMI in 2015 (34%) (25,162). We have shown previously in this cohort, the period from 23-30 years is identified as the period when many acquire overweight. By this same period, overweight prevalence changed from 30-50% (BMI) and 60-50% (%FM) in females, and 50%-70% (BMI) and 30-50% (%FM) in males (434). National data is similar, suggesting that rates of OWO almost double between adolescence (approximately 25%) to young adulthood (approximately 50%) (1,162). It must be noted that differences between ages and metrics in this study may have arisen due to the method of analysis - longitudinal data was used but not all participants were included in every measure. With that said, the direction of the differences, by both sex and metric, have been demonstrated previously and a similar age at onset was identified by Wisemandle et al. (2000) using the FELS longitudinal data (107,434). In their cohort, the most common age at onset of OWO was the period of 20-25 years.

National estimates of the prevalence of high-risk WC from 2007/2009 Canadian Health Measures Survey place almost 20% of males and 29% of females between the ages of 20 and 39 in the high-risk category (over WHO cut-offs). This represents an increase in high-risk WC by approximately 18% from 1988 to 2007/2009 in adults in this age category (198). In the US, there

has been a similar increase in BMI and in WC but only 75% (males) and 50% (females) of WC increases can be explained by increases in BMI (193). Longitudinal data from Saskatchewan, Canada, has demonstrated that BMI has not increased in youth aged 8-16, while skinfolds (an estimate of subcutaneous fat) have (200). Looking specifically at the association between DXA derived adiposity and BMI, Sun et al. (2010) found that the correlation between measures of BMI and whole-body fat mass in 20 to 39-year-olds was significant with $r = 0.79$ in males and $r = 0.84$ in females (438). These findings suggest that BMI is correlated with adiposity but may not represent the entire picture of the prevalence of excess adiposity and may be overlooking consequential body composition.

Findings from a large cross-sectional NHANES study agreed with Sun et al. (2010) and concluded that BMI (and WC) perform well as proxies for adiposity (35,438). Results from the NHANES study indicated that both BMI and WC metrics are highly correlated with %TBF in adults > 20 years of age, such that 46% of men and 49% of woman had exact agreement between %TBF and BMI categories, and 93% of men and 94% of women had agreement within one category (35). WC had similar correlations with %TBF- 51% and 42% males and females with exact agreement, and 97% and 91% of men and women within one category (35). The agreement was highest in those 25-30 years. While these correlations seem high, it also indicates that BMI and WC failed to identify over 40% of participants who had OW by other metrics. In the 20-39 year age group, BMI under-classified almost 30% and 25% of participants with a %TBF at-risk or above overweight cut-offs. WC performed slightly better in males, but slightly worse in females. Authors concluded that BMI and WC worked well as indicators of %TBF (35). The current findings disagree and suggest that WC does not identify excess adiposity or the onset of overweight at the same time as %FM or BMI; and that BMI may be an appropriate proxy for

adiposity in males, but not in females. With that said, the cut-offs used in the current analysis to identify WC at risk were developed to correspond with BMI values at the 95th centile (OB) rather than the 85th centile (OW); while cut-offs of BMI and %BF corresponded to the 85th BMI centile (OW).

Beyond accurately representing the prevalence of excessive adiposity, using an accurate metric is important for identifying those who are at potential risk of health consequences (193). The associations between %FM and WC with cardiometabolic health have been shown to be stronger than, and independent of, the association between BMI and cardiometabolic health, suggesting that not all measures are equal in terms of risk assessment (432). Indeed, the study by Tomiyama et al. (2016) found that in a sample of over 40,000 American adults, having a BMI over 25 kg/m^2 did not confer the same cardiometabolic risk for everyone (439). One third of those classified as having OW were metabolically healthy (2/3 were unhealthy) while 1/3 classified as having NW were cardiometabolically unhealthy (2/3 were healthy). This is concerning as exposure to cardiometabolic risks (i.e. high blood triglycerides or hypertension) are known to be cumulative in their contribution to chronic disease risk such as cardiovascular disease or diabetes (383). BMI has demonstrated a similar lack of sensitivity in children for identifying excessive abdominal adiposity. The study by Laurson et al (2014) found that almost 5% of children identified as having NW by BMI had WC values over Cook's (2009) cut-points (151). With that said there is evidence that BMI is a simple method for identifying metabolic risk with associations to biomarkers of cardiometabolic risk similar to those of DXA and WC as indicated by Sun et al. (2010) (438). It is possible that these association may be different in younger individuals as the analysis by Sun et al. (2010) used data from adults over 20 years with

a mean age of 41, but beyond early adulthood any weight accrued is likely to be fat mass rather than lean mass (97,388).

It must be noted that differences between ages and metrics in this study may have arisen due to the method of analysis and the overlapping cohort design. Longitudinal data was used but not all participants were included in every measure, although the models did adjust for such missing data. Furthermore, discrepancy between measures may be due to the use of WC cut-offs corresponding with OB centiles of BMI, while the cut-offs used for BMI and %BF in this analysis corresponded with OW centile. This may have erroneously delayed the expected onset of at-risk waist circumference attainment. Had lower OW cut-offs been used, the age at onset of excess WC would have been 22 in females and 34 in males- similar to age at onset by BMI and %BF. With that said, the direction of the differences, by both sex and metric, have been demonstrated previously and a similar age at onset of overweight status identified (107,434). It has also been argued that percentage body fat is not a great measure of adiposity. However, cut-points for overweight total body fat mass are not available.

4.7 *CONCLUSIONS*

There are few longitudinal studies that follow normal weight children into young adulthood that can identify the onset of overweight status by various metrics. Our findings suggest that BMI classification in males and %FM in females are the screening tools providing the earliest indication of overweight status and that identifying onset with current adult WC cut-offs may not be applicable in childhood and emerging adulthood. WC cut-offs that align with childhood values of WC are warranted if they are to be used in younger populations for early

CMR identification. The advantage of using the appropriate tool is that individuals at risk of health consequences, owing to high fat mass, can be identified earlier, monitored more closely and have intervention programs begun earlier. Despite evidence that BMI can operate as a diagnostic of excess adiposity, its value beyond other measures such as %FM at identifying health-related information is still unclear. In this cohort of Saskatchewan Canadian children, we have found that in the 1990's the clear majority were normal weight in childhood and adolescence; however, on entering emerging adulthood (18 to 25 years) the majority became overweight. This suggests that further studies are required to determine the long-term health implications of becoming overweight during this critical period of transition from adolescence to adulthood. Given that females accrue more fat mass and less lean mass in adolescence, further work is required in discerning whether the same metrics to identify overweight status should be used when making sex comparisons.

LINKS BETWEEN STUDIES

Paper 1b from study 1 confirmed the findings of paper1a from study 1- that emerging adulthood is a period when the onset of OWO occurs in previously normal weight individuals. It also confirmed that different metrics indicate different age at onset of OWO in each sex. BMI in males and % TBF in females are more conservative estimates - identifying an earlier onset of OWO. WC cut-offs were not reached in the measurement period encompassed in this analysis (up to age 40); and yet trunk fat has demonstrated strong associations with health consequence, beyond TBF or BMI. TBF has demonstrated greater associations with health consequences than BMI, and in this study 21% and 56% of males and females respectively, were misclassified as NW by BMI when %TBF identified them as OWO. These known associations, in addition to the results of study 1b prompted the design of study 2 which sought to identify the contributing factors to total and trunk fat accrual during emerging adulthood.

CHAPTER 5

STUDY 2: The influence of childhood and adolescent fat development on fat mass accrual during emerging adulthood: a 20-year longitudinal study.

5.1 *DECLARATION OF CONTRIBUTION*

I, Erin Barbour-Tuck, am the primary author of this manuscript and was responsible for data cleaning, analysis, and interpretation; and writing, editing and formatting the manuscript.

5.2 *REFERENCE*

This document has been reformatted from the original version for inclusion in the thesis and has been included with permission according to the Copyright Transfer Agreement. Minor grammatical changes have been made to improve readability and relationship to the larger document. See Appendix P.

Influence of Childhood and Adolescent Fat Development on Fat Mass Accrual During Emerging Adulthood: A 20-Year Longitudinal Study. Barbour-Tuck E, Erlandson M, Muhajarine N, Foulds H, Baxter-Jones A. Obesity (Silver Spring). 2018 Mar;26(3):613-620. doi: 10.1002/oby.22111.

5.3 *INTRODUCTION*

Although it is well known that children and adolescents with overweight and obesity (OWO) are at a high risk of becoming adults with OWO (30), less is known about the factors to which youth with normal weight (NW) are exposed that contribute to their becoming adults with OWO (61). Statistics Canada report an almost two-fold increase in rates of OWO from adolescence (12-17 years; 23%) to young adulthood (20-35 years; 42%) (25,26). In the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) we found at peak height velocity (PHV) (11 to 14 years of age) that 9% of males and 14% of females had OWO rising to 65% and 32% respectively 15 years after PHV (26 to 29 years of age) (434).This underscores the importance of identifying contributing factors to weight gain, specifically fat mass gain, during the transition out of adolescence into adulthood - the period known as emerging adulthood (EA) (18-25 years) (28,61).

Having OWO during one stage of growth, e.g. infancy, mid-childhood or adolescence, increases the risk of having OWO at a subsequent stage. As such, much effort has been put into childhood interventions to prevent childhood onset of OWO which would track into subsequent ages (23,45). Children and adolescents with healthy or "normal weight" (NW) also become adults with OWO; however, there is a lack of data investigating contributing factors in the years beyond adolescence, emerging adulthood, during which fat mass accrual and transition to OWO occurs (31,61,434). The period of EA is characterized by both TBF and TrF gains, attributed in part to changes in lifestyle factors such as decreasing or sustained low PA and negative dietary changes (381,386,440). It is also known that having OWO in adulthood is related to elevated or accelerated fat mass accrual during critical periods of growth, accrual which is in turn related to concurrent PA and diet (16,118,121).

Some researchers suggests that a high level of PA and a healthy diet in childhood/ adolescence is essential for minimizing rapid or excess TBF and TrF accrual in subsequent critical periods (115,441); however, other studies suggest that neither PA nor diet during EA are significant once an individual's BMI or body weight in late adolescence are considered (118,386). Similarly, PA during childhood and adolescence may only be protective against later life fat mass gains if levels remain stable into EA. While OWO from childhood to adulthood tracks well, PA does not (27,45), even when controlling for fat mass during the growing years. PA in childhood and fitness in adolescence have shown an association with fat mass in EA (45,113). Youth with higher TrF mass have demonstrated greater weight gain, higher levels of TrF, and larger waist circumference in subsequent years (169,170). TrF has also been found to have a stronger relationship with health than TBF in both sexes at various ages (66) and as such the investigation of adult TrF predictors may be more urgent than those of adult TBF. The independent influence of childhood and adolescent lifestyle (i.e. PA and diet) and fat mass accrual on accrual during EA remains unclear.

The purpose of this study was to investigate the role of TBF and TrF mass during childhood and adolescence on TBF and TrF accrual during emerging adulthood, whilst controlling for the confounders of PA and diet during both childhood/adolescence and emerging adulthood. It was hypothesized that participants with greater fat mass during childhood and adolescence would have greater TFB and TrF accrual during emerging adulthood.

5.4 *METHODS*

5.4.1 Study Design

Participants were drawn from the Pediatric Bone Mineral Accrual Study (PBMAS), details for which have been described in detail elsewhere (110). In brief, this study used a mixed longitudinal study design, composed of cohorts aged 8 to 15 years. The sample was racially homogenous- 95% were of European decent. Serial measures were initially collected between 1991 and 1998, repeated between 2002 and 2008 and again between 2010 and 2011. Inclusion criterion for the present study was a complete set of PA, dietary and body composition data at a minimum of two occasions during childhood and adolescence and one measure in emerging adulthood. Of the initial 228 children (113 males and 115 females) recruited, 59 males and 67 females met the inclusion criteria for the present study. This study was approved by the Research Ethics board at The University of Saskatchewan.

5.4.2 Anthropometry

Measures included standing height, sitting height and weight, which were carried out following standards by Ross and Marfell-Jones (442). Height was measured using a wall-mounted stadiometer and recorded to the nearest 0.1 cm (Holtain Limited, Crymych, UK). Weight was determined using a calibrated digital scale and recorded to the nearest 0.1 kg (Model 1631, Tanita Corp, Tokyo, Japan). Serial height data was used to develop annual velocities and velocity curves were fitted using a cubic spline procedure. A cubic spline uses the interpolation of polynomials from neighboring points to create a smooth curve. Interpolated values from each individual's curve were then used to identify age at maximum height velocity or peak height velocity (PHV) (GraphPad Prism 5, GraphPad Software, San Diego, CA, USA).

5.4.3 Chronological and Biological Age

Chronological age (CA) was determined by subtracting the date of birth from the decimal date of measurement. CA categories were composed of 1-year intervals such that the CA category of 12 years included all those with age at test ranging from 11.5 to 12.49. Biological age (BA) was calculated by subtracting the age at PHV from the CA of the participant at the time of measurement. BA groupings were constructed using 1-year intervals such that the BA of 1 included measurement occurring between -0.5 and 0.49 years from PHV.

5.4.4 Body Composition

Total body fat (TBF, g), trunk fat (TrF, g) and total body FFM (g; bone mineral plus lean) were assessed from total body dual energy x-ray absorptiometry (DXA) scans (Hologic QDR - 2000, Hologic, Waltham, MA). The coefficient of variation (%) for short-term precision *in vivo* for TBF was 2.95% and for TrF was 4.88% (443).

5.4.5 Diet

Self-reported 24-hour recall measures of diet were administered three times per year in the first 3 years of the study and two times per year thereafter. Friday and Saturday were not included in the 24-hr recalls. Participants were given a 20-minute training session on food portion size estimation prior to reporting. During reporting sessions, the participants were provided with life-size pictures of portions for reference. Nutrient composition was estimated from the 1988 Canadian Nutrient File and analyzed with the NUTS nutritional assessment software (version 3.7; Quilchena Consulting Ltd, Victoria, Canada). Total 24-hour energy intake was expressed as an annual average in kiloJoules-d^{-1}.

5.4.6 Physical Activity

Physical activity was assessed using the Physical Activity Questionnaire for Children (PAQ-C) or Adolescents (PAQ-A), a minimum of three times per year for the first two years and two times per year for the following years of childhood and adolescence. The Physical Activity Questionnaire for Adults (PAQ-Ad) was used once per year for measures after the age of 18. This family of instruments uses a 5-point Likert scale with higher numbers indicating higher levels of PA. These tools have demonstrated good internal consistency and validity with moderate relationships with 7-day activity recall, teacher evaluations, and Caltrac motion sensors (408,409).

5.4.7 Statistical Analysis

The data was split into two-time points: childhood and adolescence and emerging adulthood. The childhood and adolescence data included measures from BA of -6 to +6 years from PHV (corresponding to CA of 8 years to 17 years) and emerging adulthood data (corresponding to CA 18 to 28 years). BA was used to align individuals during childhood and adolescence due to the large individual variability in tempo and timing of maturation and the known effect that maturation has on PA and somatic variables.

During childhood and adolescence, individual values and group mean values at each BA were used to determine an individual's z-scores at each measurement occasions. A mean composite z-score was then assigned to each participant, calculated as the sum of z-scores for all measurement occasions divided by the number of occasions. This process was used to calculate mean z-scores for childhood and adolescent TrF, TBF, PA and energy intake.

For the EA period, dependent variables were assessed for normality and violations were log transformed. Descriptive data are expressed as means by sex (SPSS version 11.5, SPSS Inc., Chicago, IL). Independent samples *t*-tests with Bonferroni corrections were used to analyze sex differences between measures at PHV and 17 years CA category (end of adolescent period) for PA, energy intake and fat mass variables ($p<0.05$).

Random effects models were developed (MLwiN version 1.0, Multilevel Models Project, Institute of Education, University of London, London, UK). This procedure has been described in detail previously (402). In brief, fat mass parameters were measured repeatedly within individuals (level 1 of the model) and between individuals (level 2 of the model). Linked variables at different levels of a model characterize multilevel random effect regression models. In the present analysis, log transformed TBF and TrF mass during EA (18-28) were described by developing gender-specific multilevel regression models as follows:

$$y_{ij} = (\alpha+\beta_j x_{ij}) +(k_1 z_{ij} + k_2 z_{ij} +\ldots+ k_n z_{ij}) + (\mu_j+ \nu_j x_{ij} + \varepsilon_{ij}).$$

Where y_{ij} is total (trunk) fat mass at the i^{th} measure in the j^{th} individual, α_j is the constant for the j^{th} individual, $\beta_j x_{ij}$ is the slope coefficient for fat mass by age (x) for the j^{th} individual at measurement *i* (in our model age is centered around 23 years), and k_1 to k_n are the coefficients for time dependent predictor variables (e.g. PA, energy intake, TBFz-score etc.) at the i^{th} measurement in the j^{th} individual. u_j, $v_j x_{ij}$ and ε_{ij} are the random parameters. These parameters are assumed to have a mean of zero and follow a normal distribution. $\varepsilon_{ij} \sim N [0, var(\varepsilon_{ij})]$ is the level one within-individual variance for the i^{th} measurement in the j^{th} individual and $\mu_j \sim N [0, var(\mu)]$ is the level two intercept between-individual variance. $\mu_j * v_j x_{ij} \sim N [0, var(\mu_j * v_j x_{ij})]$ explains the covariance of slope and intercept in the model.

5.4.8 Modelling Strategy

Predictor variables were added in a stepwise procedure and changes in the likelihood ratio statistic were used to judge significance. If variance at level 1 and 2 was reduced and predictors had estimated mean (EE) coefficients greater than twice the standard error of the estimate (SEE) ($p<0.05$) they were retained in the model. Age centered was calculated as the participants' CA age measurement minus mean CA in the EA sample (mean CA=23 years) which was added to the model as a fixed and random coefficient. Age^2 was added to the model as fixed effects to better reflect the known non-linear pattern of growth. Following age, height and total body FFM, childhood/adolescent PA, energy intake and fat mass z-scores were added followed by emerging adulthood PA and energy intake.

Completed models and significant coefficients were used to create TBF and TrF curves (Figures 5.2). The values used in construction of the curves were the maximum and minimum values of predictor variables at each CA from the current data set (i.e. PA value of 1 and 5; z-scores of -1 and +2) and the mean value of variables (i.e. height, total body FFM).

5.5 *RESULTS*

Table 5.1 provides the descriptive characteristics of males and females at the beginning (PHV) and end (17 years) of the adolescent period. This cohort was predominantly NW by age and sex appropriate cut-offs from PHV to 17 years of age (100,434).

Table 5.1 General descriptive characteristics of male and female participants at Peak Height Velocity and at 17 years

Variable	Male		Female	
APHV (years)	13.6 years*		11.9 years	
EA CA (years)	23.58 ± 3.5		22.9 ± 3.0	
EA BA (YFPHV)	3.65 ± 1.03		5.04 ± 0.72	
	PHV (n=53)	*17 years(n=40)*	*PHV(n=60)*	*17 years(n=46)*
Height (cm)	163.7 ± 6.9*	178.5 ± 7.4*	153.7 ±7.8	166.1 ± 5.9
BMI(kg/m2)	19.3 ±2.5*	22.8 ± 3.52	18.55 ± 2.7	23.2 ± 4.3
%TBF	18.6 ±7.6*	17.6 ± 7.9*	27.2 ±7.8	33.2 ± 7.3
TBF(kg)	9.8 ± 5.6*	13.8 ± 7.1*	12.2 ± 5.8	21.7 ± 8.9
TrF(kg)	2.8 ± 2.7*	5.1 ± 4.0*	4.16 ± 2.9	8.9 ± 5.3
TBFFM (kg)	41.1 ± 5.5*	59.0 ± 5.9*	31.0 ± 4.9	41.6 ± 5.09
EI(kJ)	8510.0 ± 2220.0*	11750.0 ± 4240.0*	7370.0 ± 1740.0	6530.0 ± 2780.0
PA (score)	3.0 ± 0.1	2.50 ± 0.6	3.0 ± 0.6	2.2 ± 0.6
NW Category (%)	83.4%	66.4%	78.7%	65.3%

APHV= age of peak height velocity; EA CA = emerging adulthood mean chronological age; EA BA (YFPHV)= emerging adulthood mean biological age (years from peak height velocity); %TBF= % total body fat; NW category = normal weight by pediatric %TBF cut-offs

* indicates a significant difference from females of same age ($p<0.05$)

PA scores decreased across EA from 18 years in females and from 20 years in males (Figure 4.1a). Energy intake increased slightly in females (between 7,000 and 8,000 kJ), and increased slightly more in males (10,000 to 13,000 kJ) across EA (Figure 5.1b).

Tables 5.2-5.5 report the models of TBF and TrF accrual for males and females during EA. Initial models used aggregated male and female data and found sex to be a significant predictor (not shown). Final models were run with sex disaggregated because of this significance and because of known sexual dimorphism in fat mass accrual. The coefficient for age centered was significant in each of the models indicating that TBF and TrF were significantly increasing with each measurement occasion from 18 to 28 years. The level 2 variance matrix indicated that in each model, individuals had significantly different intercepts (μ_j) and slopes of their lines ($v_j x_{ij}$). There was no significance to the covariance in slope and intercepts ($\mu_j * v_j x_{ij}$) in any of the models, indicating that the variance in intercept was not related to the slope.

The significant ($p<0.05$) fixed effects contributing to the prediction of TBF and TrF during EA included age centered, and total body FFM in both sexes. PA in males but not in females, and height in females but not in males were also significant in predicting EA TBF and TrF (Table 5.2-5.5, Model 1).

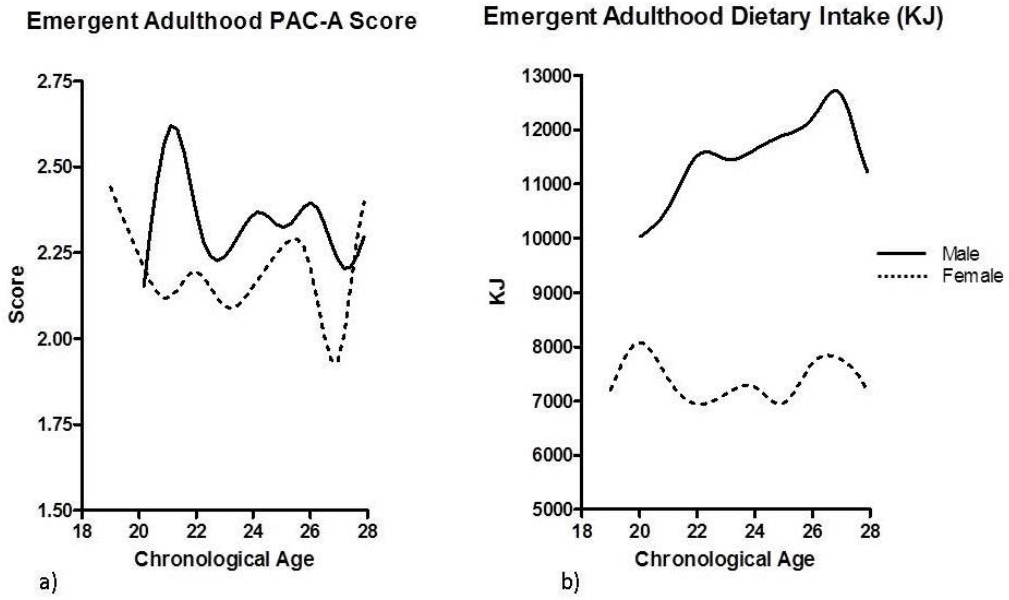

Figure 5.1 Patterns of a) PA (PAQ-A scores) and b) Energy Intake (KJ) over emerging adulthood in males and females

Table 5.2 Multilevel regression models for total body fat (TBF) in males during emerging adulthood

Variable	Model 1			Model 2		
Fixed Effects						
Constant	8.75	±	.33	8.91	±	0.32
Age Centered	0.02	±	6.63[a]	0.02	±	0.01
Age Centered^2	-1.47[a]	±	1.33[a]	-3.13[a]	±	2.94[a]
Height		NS			NS	
FFM	0.17b	±	0.05[a]	0.15[a]	±	0.05 [a]
PA	-0.06	±	0.02	-0.06	±	0.03
EI		NS			NS	
PA z-score		n/a			NS	
EI z-score		n/a			NS	
TBF z-score		n/a		0.30	±	0.05
Random Effects						
Level 1						
Constant (ε_{ij})	0.02	±	2.60[a]	0.02	±	2.80[a]
Level 2						
Constant (μ_j)	.17	±	0.03	0.10	±	0.02
Age Centered ($\nu_j X_{ij}$)	1.20[a]	±	0.41[a]	3.17[a]	±	1.24[a]
Constant*Age Centered ($\mu_j + \nu_j X_{ij}$)		NS			NS	
-2 x logliklihood (Change from previous model)					32.22	
Number of added variables					4	

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of TBF (g)
Random effects values Estimated Mean Variance ± SEE [TBF (g)]^2
Age Centered is age in years centered on 23 years.
PA and EI z-score are composite z scores from all measures from -6 to +7.
Height (cm); Fat Free Mass (FFM) (g); Total Body Fat (TBF) (kg); PA (Physical Activity -Score from 1-5); Energy Intake (EI) (KJ).

Table 5.3 Multilevel regression models for Trunk Fat (TrF) in males during emerging adulthood

Variable	Model 1			Model 2		
Fixed Effects						
Constant	7.45	±	.47	7.69	±	0.43
Age Centered	0.04	±	8.50[a]	0.04	±	0.02
Age Centered^2	-3.52[a]	±	1.92[a]	-5.40[a]	±	4.12[a]
Height		NS			NS	
FFM	0.24[a]	±	0.07[a]	0.21[a]	±	0.07[a]
PA	-0.08	±	0.03	-0.07	±	0.04
EI		NS			NS	
PA z-score		n/a			NS	
EI z-score		n/a			NS	
TrF z-score		n/a		0.40	±	0.06
Random Effects						
Level 1						
Constant (ε_{ij})	0.05	±	5.66[a]	0.04	±	6.00[a]
Level 2						
Constant (μ_j)	0.32	±	0.06	0.19	±	0.04
Age Centered (v_jX_{ij})	1.56[a]	±	0.65[a]	5.60[a]	±	2.39[a]
Constant*Age Centered ($\mu_j + v_jX_{ij}$)		NS			NS	
-2 x logliklihood (Change from previous model)					32.80	
Number of added variables					4	

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of TrF (g)
Random effects values Estimated Mean Variance ± SEE [TrF (g)]^2
Age Centered is age in years centered on 23 years.
PA and EI z-score are composite z scores from all measures from -6 to +7.
Height (cm); Fat Free Mass (FFM) (g); Trunk Fat (TrF) (kg); PA (Physical Activity -Score from 1-5); Energy Intake (EI) (KJ).

Childhood/adolescent TBF z-score was significant for TBF models, and childhood/adolescent TrF z-score was significant for TrF models (Table 5.2 -5.5, Model 2). Childhood/ adolescent PA and energy intake z-scores were not significant in any model p>0.05).

Table 5.4 Multilevel regression models for total body fat (TBF) in females during emerging adulthood

Variable	Model 1			Model 2		
Fixed Effects						
Constant	10.80	±	0.95	11.67	±	0.70
Age Centered	0.01	±	4.00a	0.02	±	4.23[a]
Age Centered^2	-0.17[a]	±	1.80[a]	-0.70[a]	±	0.95[a]
Height	-0.01	±	6.12[a]	-0.02	±	4.65[a]
FFM	0.37[a]	±	0.05[a]	0.20[a]	±	0.01[a]
PA		NS			NS	
EI		NS			NS	
PA z-score		n/a			NS	
EI z-score		n/a			NS	
TBF z-score		n/a		0.30	±	0.03
Random Effects						
Level 1						
Constant (ε_{ij})	0.01	±	1.29[a]	0.01	±	1.28[a]
Level 2						
Constant (μ_j)	0.12	±	0.02	0.06	±	9.27[a]
Age Centered (v_jX_{ij})	0.50[a]	±	0.19[a]	0.51[a]	±	0.18[a]
Constant*Age Centered ($\mu_j + v_jX_{ij}$)		NS			NS	
-2 x logliklihood (Change from previous model)					23.66	
Number of added variables					4	

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of TBF (g)
Random effects values Estimated Mean Variance ± SEE [TBF (g)]^2
Age Centered is age in years centered on 23 years.
PA and EI z-score are composite z scores from all measures from -6 to +7.
Height (cm); Fat Free Mass (FFM) (g); Total Body Fat (TBF) (kg); PA (Physical Activity -Score from 1-5); Energy Intake (EI) (KJ).

The increased TBF and TrF accrual in those with high versus low child/adolescent fat mass z-scores are illustrated in Figure 5.2. In males, the difference in low TBF z-score (-1) versus high TBF z-score (+2) resulted in a difference of 24.5 kg TBF by 28 years (Figure 5.2 a). Z-scores for TrF were very similar, resulting in a difference of 12 kg TrF (Figure 5.2 b). PA was a significant predictor in males only. Having a high (5) versus low PA (1) mitigated accrual conferred by a high fat z-score by approximately 8 kg TBF (Figure 5.2 a) and by 4.5 kg TrF (Figure 5.2 b). In females, the difference in low TBF z-scores (-1.0) versus high TBF z-scores

(+2.5) resulted in a difference of almost 12 kg of TBF by 27 years (Figure 5.2 c). Z-scores were similar for TrF, resulting in a difference of approximately 3 kg (Figure 5.2 d).

Table 5.5 Multilevel regression models for Trunk Fat (TrF) in females during emerging adulthood

Variable	Model 1			Model 2		
Fixed Effects						
Constant	9.89	±	1.35	10.70	±	1.00
Age Centered	0.01	±	5.74[a]	0.02	±	5.69[a]
Age Centered^2	-0.66[a]	±	1.37[a]	-1.36[a]	±	1.34[a]
Height	-0.02	±	8.70[a]	-0.02	±	6.70[a]
FFM	0.47b	±	0.07[b]	0.26[b]	±	0.06[b]
PA		NS			NS	
EI		NS			NS	
PA z-score		n/a			NS	
EI z-score		n/a			NS	
TrF z-score		n/a		0.40	±	0.04
Random Effects						
Level 1						
Constant (ε_{ij})	0.02	±	2.62[a]	0.02	±	2.57[a]
Level 2						
Constant (μ_j)	0.23	±	0.04	0.12	±	0.02a
Age Centered (v_jX_{ij})	0.78[a]	±	0.32[a]	0.81[a]	±	0.32[a]
Constant*Age Centered (μ_j*v_jX_{ij})		NS			NS	
-2 x logliklihood (Change from previous model)					23.66	
Number of added variables					4	

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of TrF (g).
Random effects values Estimated Mean Variance ± SEE [TrF (g)]^2
Age Centered is age in years centered on 23 years.
PA and EI z-score are composite z scores from all measures from -6 to +7.
Height (cm); Fat Free Mass (FFM) (g); Trunk Fat (TrF) (kg); PA (Physical Activity-Score from 1-5); Energy Intake (EI) (KJ).

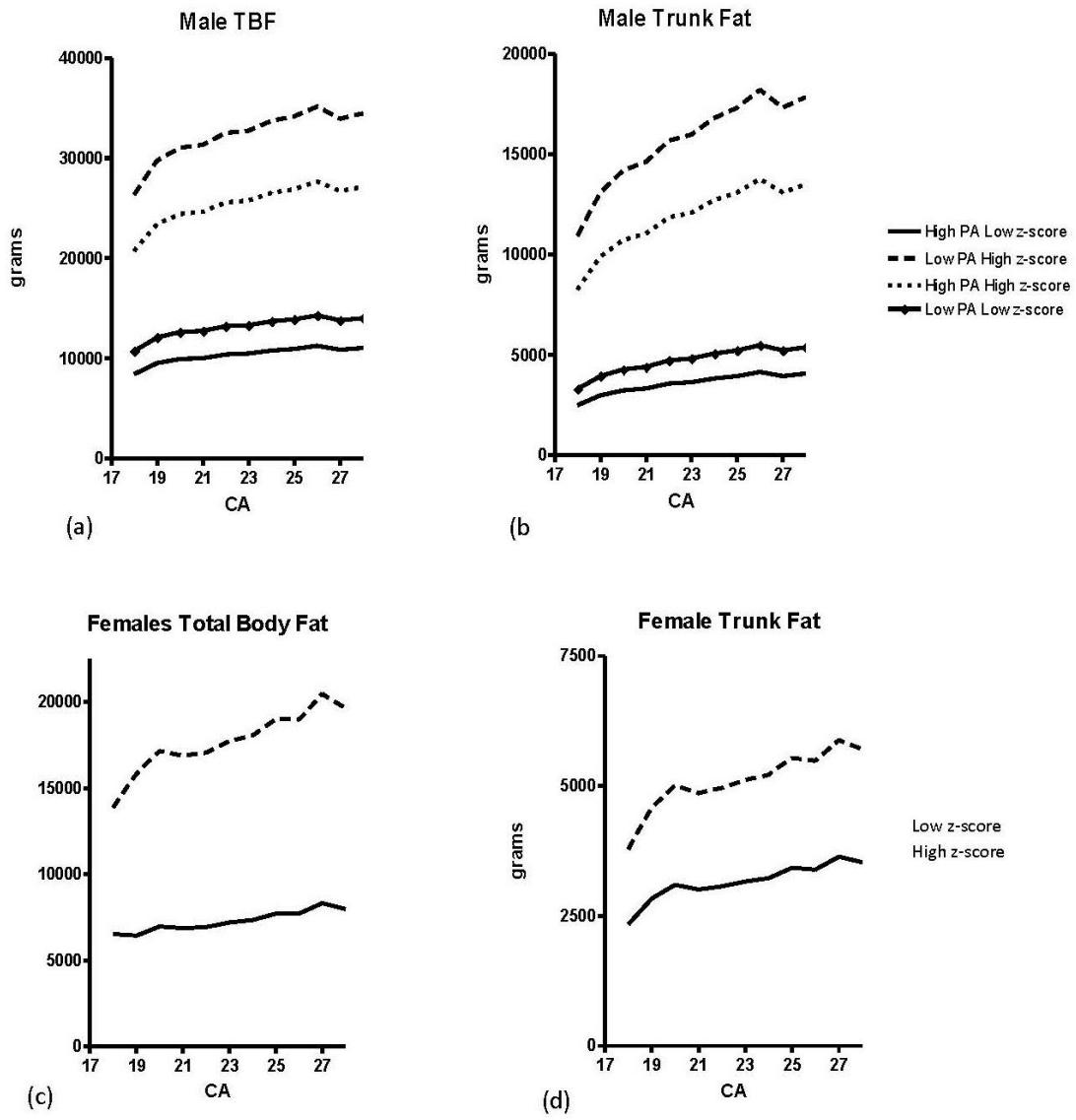

Figure 5.2 Hypothetical curves developed from multilevel model significant predictor coefficients. (a) Male total body fat (TBF, grams) (Table 5.2). (b) Male trunk fat (grams) (Table 5.3). (c) Female TBF (TBF, grams) (Table 5.4). (d) Female TrF (grams) (Table 5.5)

5.6 *DISCUSSION*

The purpose of this study was to investigate TBF and TrF accrual during emerging adulthood and the degree to which childhood and adolescent fat accrual influenced the trajectory of accrual in EA, whilst controlling for known contributing factors. It was found that the strongest predictor

of TBF in EA was childhood and adolescent TBF mass, and the strongest predictor of TrF in EA was childhood and adolescent TrF mass. PA during EA had a significant negative relationship with fat mass accrual in males but not in females. Neither childhood/adolescent nor EA energy intake were significant predictors of TBF or TrF.

It has been suggested that both females and males continue to accrue TBF from adolescence into EA with females having more TBF at 17 years and greater rate of increase to 21 years (45,118). These findings are based on skinfold measurements. The current study similarly suggests continuous gains in TBF but without sex differences. Recent waist circumference-for-age charts (NHANES) and longitudinal data suggest increasing TrF in both males and females during a period similar to EA with higher values in males than in females from adolescence into young adulthood (45,437). The present data shows similarly increasing TrF in both sexes with lower baseline values but greater gains in males compared to females. The discrepancy between studies regarding sex differences may be due to methodological differences. Unlike DXA used in the current studies which measures both subcutaneous and visceral fat, skinfolds can only account for subcutaneous fat mass. This is especially important for TrF measures, as during adolescence females tend to deposit more TrF subcutaneously while males deposit more viscerally (313,444). Skinfolds, which measure subcutaneous fat, may indicate greater fat mass in females while DXA and waist circumference, which estimates subcutaneous and visceral fat, indicate greater fat mass in males.

It has been demonstrated previously that fat mass tracks moderately well from childhood to adulthood (13,45). The current models (Tables 5.1 and 5.3) found that those with the highest measures of fat mass in childhood and adolescence also had the greatest accrual in subsequent years. The finding that higher TrF accrual in childhood and adolescence results in more TrF

accrual in adulthood may be more important than those pertaining to TBF, as TrF in adulthood is known to confer additional heath risk above TBF (66). Current models support findings by Sherar et al. (2007) which suggested that TrF mass during childhood was higher in adults with greater cardiometabolic risk (169). In addition, Maffeis et al. (2001) found that waist circumference in children with NW and OW (at 8 years) predicted weight gain over four subsequent years (170). TrF appears to persists across time suggesting that a phenotype of higher TrF during childhood and adolescence may represent an underlying polygenic risk which entrains subsequent fat mass accrual in EA (16). Indeed, genomic studies suggest that those with a genetic predisposition for adult obesity have accelerated growth (352) and an earlier pubertal onset, both factors known to relate to greater TrF during EA (445). Underlying genetics influence developmental phenotypes of obesity, and possibly more specifically abdominal (TrF) obesity (446). Fortunately, genetics and environment interact. Both factors influence fat accrual and obesity, and as such there is opportunity for lifestyle factor such as PA to alter suboptimal fat mass trajectories (121) as seen in the current models.

Emerging adulthood (18-25 years) has been highlighted as a time when TBF and TrF mass continue to increase as PA decreases (386). Previous studies have found that those with higher PA have smaller increases in weight and BMI during EA, although some suggest no effect or an effect which is dependent on fat mass before college (386). Alternatively, data of Dutch youth found that the risk conferred by high adolescent %TBF was mitigated by concurrent PA (118). Similarly, Tammelin, Laitinene & Nayha (2004) found that decreasing levels of PA or remaining at a low PA from 14 to 31 years was significantly related to having OWO at 31 years in comparison to those who remained persistently active (441). PA in the current models mitigated fat mass accrual, but only in males (Table 5.3 and 5.2). Female models support the

work of Kasparek et al. (2008) suggesting that EA weight gains may be contingent upon weight in previous growth periods (386). PA is well established as a modifier of fat mass at all ages (264), and so the lack of significance found in females may be due to a masking effect from other variables such as lean mass, or fitness (113). Females accrue a greater proportion of their adult fat mass compared to their adult lean mass during puberty (105). The effect of female childhood/adolescent PA is also likely masked by the natural accrual of fat mass and simultaneous decline in PA in females over the adolescent period (105,440). There may be sex specific effects such that PA has a weaker effect on fat mass accrual in females than in males; for example, in 17-year-old males, PA was shown to be independently related with fat mass, while in females, mothers' fat mass and education level but not PA related to fat mass at 17 years (447). It is hypothesized that PA may exert its strongest influence in females during earlier pubertal years when fat mass accrual predominates and thus PA acts as a mediator on fat mass rather than as an independent predictor. This is supported in that current models showed childhood/adolescent PA z-scores as a significant predictor of EA TBF and TrF in females (but not males) until the inclusion of TBF and TrF z-scores. Conversely, the current analysis identified EA PA to be related to fat mass accrual in males. It is hypothesized that this is due to lean mass gains which can continue into late adolescence and early adulthood and which increase energy expenditure and lower fat mass. The role of PA on fat mass accrual appears to be different in males and females, and may be masked by the effect of sex-specific tissue accrual experienced during adolescence. Regardless of sex differences, the demonstrated effect of PA on fat mass accrual during EA highlights the importance of maintaining PA not just during childhood and adolescence but throughout the life course.

Finally, it has been shown that energy intake does influence childhood and adolescent fat mass in this cohort (395). The lack of significance of childhood/adolescent diet in the current models may be due to the strength of the childhood/adolescent fat mass variable which likely encompasses and manifests the effect of diet. Energy intake was not significant during EA, suggesting that a decrease in PA rather than an increase energy intake is a more important contributing factor to fat mass accrual during this period.

This study is not without limitations. The accuracy of DXA has been questioned in growing individuals; however, validation studies demonstrate accuracy in DXA estimates of body fat for body weights between 35 and 95 kg which encompasses most body weights in the pediatric PBMAS cohort (448). PA and dietary self-report measures are at risk of recall error; however, longitudinal studies often consider using the same tools across time in spite of newer technology which may become available over the course of the study. Participants in this study were predominantly of European descent and, as such, results cannot be generalized to other ethnicities.

Our results support the argument that childhood and adolescence are important periods in which to promote healthy weight and limit fat mass accrual even in those with NW, as these periods have implications not just for childhood but also for young adulthood health and weight status. PA is a modifiable lifestyle factor capable of mitigating fat mass gain; however, consideration should be given to the optimal timing of PA interventions which may be sex specific. EA may provide an additional opportunity to alter fat mass trajectories set earlier in life.

5.7 *ACKNOWLEDGMENTS*

We acknowledge all the study participants, their families and the vast number of students and faculty for their constant enthusiasm and commitment to the Pediatric Bone Mineral Accrual Study (PBMAS) over the last 25 years.

5.8 *COPYRIGHT TRANSFER AGREEMENT*

LINKS BETWEEN STUDIES

Study 2 identified total and trunk fat mass during childhood and adolescence, in addition to physical activity during emerging adulthood to be significant predictors of fat accrual during emerging adulthood. These findings suggest that preventing fat accrual early in life will mitigate fat gains later in life. Questions remain regarding the clinical implication of accruing large amounts of fat mass in emerging adulthood. This led to the design of study 3 which investigated differences in total body and trunk fat accrual during emerging adulthood in those with higher, versus those with lower cardiometabolic risk profiles.

CHAPTER 6

STUDY 3: Fat accrual during early adulthood and continuous cardiometabolic risk score in the fourth decade: a longitudinal analysis

6.1 *DECLARATION OF CONTRIBUTION*

I, Erin Barbour-Tuck, am the primary author of this manuscript and was responsible for data cleaning, analysis, and interpretation; and writing, editing and formatting the manuscript.

6.2 *MANUSCRIPT STATUS*

This document has submitted to the Obesity Journal, June 15, 2018. This document has been reformatted from the submitted version for inclusion in the thesis with minor grammatical changes to improve readability and relationship to the larger document.

6.3 *INTRODUCTION*

Over one million Canadians report having Cardiovascular Disease (CVD) and an additional two million Canadians have diabetes, of which 90% are Type II Diabetes (449–452). Even more concerning are the rates of the Metabolic syndrome (MetS)- the clustering of 3 or more risk factors of CVD and Type II Diabetes. The prevalence of MetS in Canadian adults (18-30 years) in 2012 was 13%, just over 3 million people (453). The rates of MetS increase with age and the

risk of MetS is increased with being overweight and obese (OWO) (206). As Canadian rates of OWO remain high it is likely that the rates of MetS, CVD, and Type II Diabetes will continue to rise (162,453). Longitudinal data from our lab indicates that greater fat mass trajectories in adolescence results in higher cardiometabolic risk in emerging adulthood (18 to 25 years of age) (433). Our data has also demonstrated that during emerging adulthood the prevalence of OWO increases (434). If OWO is increasing during this period, it begs the question as to whether greater fat mass trajectories during emerging adulthood (the third decade of life) increases cardiometabolic risk in the fourth decade of life.

Cardiometabolic risk (CMR) is an umbrella term used to represent the relative risk attributed to a comprehensive list of MetS risk factors including low levels of high-density lipoprotein cholesterol (HDL), and elevated blood pressure, waist circumference (WC), triglycerides (TG), fasting glucose and insulin levels (4,182). Like MetS factors, CMR factors often accompany overweight and obesity (OWO) with a particularly strong relationship with trunk fat, even independent of total fat or OWO status (5,454). Precursors of CMR are known to arise during childhood in association with childhood OW, or in association with central adiposity or trunk fat (TrF) (84,393,455–458). Children with higher trunk fat as early as 8 years of age have higher CMR in adulthood, despite having normal weight (NW) in childhood (169).

The evidence is clear that childhood adiposity sets a trajectory of health (or unhealth), and that the highest CMR is often found in adults who were exposed to childhood OWO; however, this is likely due in part to the strong associations between childhood OWO and adult OWO (13,393,455). There is also literature suggesting and that both childhood OWO and adult OWO confer CVD risk in adulthood independent of each other (459). For example, adults with the highest CVD risk are those who remained OWO from childhood, followed closely by those

who transition from NW-to-OWO between childhood and adulthood. Those with an OWO-to-NW and NW-to-NW transition have similar and lowest risk (459). This suggests that a higher weight in childhood may act as a metabolic buffer, preparing the body to better deal with fat mass gains in the future. Those who are NW as children may be at a metabolic disadvantage during other typical times of fat accrual, particularly trunk fat accrual, such as emerging (18-25 years) adulthood (433). We have shown that fat mass gains and the transition from NW to OWO often occur during the period of EA and that this may be a key period for fat mass accrual (434). As such, the exploration of CMR in adults should optimally incorporate weight and/or body composition data from childhood and adolescence.

EA is a period of transition during which lifestyle factors such as physical activity (PA) and diet are often in flux. Both PA and diet are factors related to the onset of OWO, preferential deposits of TrF, and CMR profiles in children, adolescents and adults (243,281,447,460). Adolescent levels of PA and dietary habits have demonstrated an association with fat mass, CVD and MetS in early adulthood (60,385,400). This lab has demonstrated that higher levels of PA in males during EA can diminish fat mass gains, while the strongest predictor of both total body and trunk fat gains is the level of fat mass during childhood and adolescence (433). These findings suggest that the maintenance of healthy lifestyle habits during EA may mitigate CVD health risks in early adulthood (25-39 years); however, it remains unclear whether TrF and TBF accrual during EA and early adulthood is related to CMR later in life, and to what extent this relationship is mediated by child and adolescent fat mass accrual. There is a paucity of prospective studies encompassing the time from childhood to adulthood with the appropriate variables to examine the relationship between fat mass accrual and lifestyle across the life course.

The Pediatric Bone Mineral Accrual Study is a longitudinal growth study with over 25 years of serial data. Measurements collected include body composition parameters in addition to physical activity and dietary intake. This study is uniquely suited to investigate the role that fat mass, PA and diet during childhood, adolescence and EA has on CMR at 30-39 years of age. The purpose of this study is to examine trajectories of total body and trunk fat accrual from emerging through early adulthood in relation to CMR at the end of the early adulthood period. It is hypothesized that those with higher CMR scores at the end of early adulthood will have steeper trajectories of fat mass accrual (TBF and TrF) during emerging and early adulthood (18-39); and that those with higher CMR will have lower PA levels and higher energy intake during EA, and higher fat mass during childhood and adolescence.

6.4 *METHODS*

6.4.1 Study Design.

Participants were drawn from the longitudinal Pediatric Bone Mineral Accrual Study (PBMAS) (1991 – 2018). The details of this study have been described thoroughly elsewhere (406). In brief, the study was composed of 8 age cohorts (8 to 15 years of age at study entry). A total of 228 participants were recruited (115 females and 113 males) in 1991, of whom 220 were measured. An additional 31 participants were added between 1992 and 1993. From 1991 to 1998, participants were measured twice per year. Annual measurements were taken from 2002-2005, 2010-2011 and again in 2016/2017. After 7 years of data collection (1991-1998), 197 participants had two or more (median six) data collection points. Between 2002 and 2005, 169 (77 males) participants returned (median 4 visits). From 2010 to 2011, 123 (49 males) were

retested (median 2 visits) and between 2016 and 2017, 61 (28 males) returned for one more visit. To be included in the present study, participants had to have a blood draw and a complete set of PA, dietary and body composition data during the 2016/17 visit plus a minimum of one visit in childhood/adolescence (8-17 years) and at least 2 measures between EA and the forth decade of life (18-39 years of age); 54 (25 males) participants met these criteria and were included in the present analysis. The sample was racially homogenous; 95% of the 94% for whom race was known were white. This study was approved by the Research Ethics board at the University of Saskatchewan.

6.4.2 Anthropometry

Measures taken at each visit included standing height, sitting height (in childhood/adolescence) and weight, using the protocol outlined in Ross and Marfell-Jones (35). Height was measured using a wall-mounted stadiometer and recorded to the nearest 0.1 cm (Holtain Limited, Crymych, UK). Weight was determined using a calibrated digital scale and recorded to the nearest 0.1 kg (Model 1631, Tanita Corp, Tokyo, Japan). Age at peak height velocity was determined by fitting a cubic spline to serial height data (GraphPad Prism 5, GraphPad Software, San Diego, CA, USA).

6.4.3 Chronological and Biological Age

Chronological age (CA) was determined by subtracting the date of birth from the decimal date of measurement. 1-year intervals comprised each CA category such that 12 years included all those with age at test ranging from 11.5 to 12.49. Body composition changes rapidly during adolescence and with significant sex differences: body fat decreases and lean mass increases in males; body fat increases in females; and TrF begins to accrue more so in males than females (69,149). As such, a biological age (years from peak height velocity; PHV) was used to align

individuals up to CA of 17. BA groupings were constructed in the same way as CA groupings such that a BA of 1 included all those with a BA at test ranging from -0.5 and 0.49 years from PHV.

6.4.4 Body Composition:

Total body fat (TBF, g), trunk fat (TrF, g) and lean mass (FFM, g) were assessed from total body dual energy x-ray absorptiometry (DXA) (Hologic QDR –2000 and 4500, Hologic, Waltham, MA). Hologic 2000 was used from 1991 to 2007 after which a Hologic 4500 was used. The coefficient of variation (%) for short-term precision *in vivo* for TBF was 3.0% and for TrF was 4.9 % (195). Conversion factors were developed to correct for difference in machines using data from 9 men and 15 women (410).

6.4.5 Diet

Self-reported 24-hour recall measures of diet were administered 3-4 times in the first 4 years of the study (1-2 times over the phone), and twice per year until 2007. One recall was given in the 2010/2011 wave and 2 recalls (one in person and one over the phone) for the 2016/2017 wave of measures. Friday and Saturday were not included in the 24-hr recalls. Participants were given a 20-minute training session on food portion size estimation with life-size pictures of portions for reference. Nutrient composition for measures between 1991 and 1997 was estimated from the 1988 Canadian Nutrient File and analyzed with the NUTS nutritional assessment software (version 3.7; Quilchena Consulting Ltd, Victoria, Canada). Food Processor version 8.0 and revisions (ESHA Research Inc,. Salem, OR, USA, 2003.) was used to estimate total energy and nutrition after 1997. Total 24-hour energy intake (EI) was expressed as an annual average in Kjoules-d^{-1}.

6.4.6 Physical Activity

Physical activity was assessed using the Physical Activity Questionnaire for Children (PAQ-C), Adolescents (PAQ-A), or Adults (PAQ-AD) a minimum of three times per year for the first two years of the study and two times per year for the following years of childhood and adolescence. In adulthood, the PAQ-AD was only administered once per year. This family of instruments uses a 5-point Likert scale with higher numbers indicating higher levels of PA. These tools have demonstrated good internal consistency and validity with moderate relationships with 7-day activity recall, teacher evaluations, and Caltrac motion sensors (409,461–463).

6.4.7 Smoking Status

Participants reported on their past and current smoking history. Classification of participants was either non-smoker, past smoker (if they had quit for ≥ 1 year), or current smokers.

6.4.8 Metabolic Assessment

Blood pressure and heart rate were taken at onsite measurements, after 2002, using a standard blood pressure cuff after 5 minutes of rest. In 2016/17 five participants failed to have blood pressure recorded at a follow-up appointment and provided a physician's assessment within 6 months of their blood draw. Mean arterial pressure (MAP) was calculated using the following formula: ([{2 x diastolic blood pressure} + systolic blood pressure]/3). Participants were asked to fast for 12-hours prior to a morning blood draw and a trained phlebotomist acquired samples using standard venipuncture procedures. All samples were centrifuged for 15 minutes, within 20 minutes of blood draw and stored at –70ºC prior to analysis. All analysis took

place within 6 months of blood draw. Analysis of total cholesterol (TCHOL), high-density lipoprotein (HDL), triglycerides (TG), and C-reactive protein were conducted at the Royal University Hospital (Saskatoon, SK, Canada). Fasting glucose and insulin were analyzed in-house using EnzymeChrom Glucose Assay (Bioassay Systems) and Insulin EIA (ALPCO Diagnostics). Homeostasis model assessment for insulin resistance (HOMA) was calculated using the following formula: ({{fasting insulin(U/ml)} x {fasting glucose (mmol/l)}}/22.5) (464).

6.4.9 Continuous Cardiometabolic Risk Score

A continuous cardiometabolic risk (conCMR) score was chosen to represent cardiometabolic risk in this cohort as they are relatively young and healthy, and the prevalence of metabolic syndrome was likely to be very low. This method has been validated previously (169,223). Metabolic syndrome variables (TG, HOMA, TCHOL, HDL^{-1}, and MAP) were regressed onto smoking status and age, and the standard residuals were saved. Adding the standardized residuals provided a composite continuous risk score for each individual. These variables are consistent with those suggested by the National Cholesterol Education Program (2001) (182). As trunk fat was a variable of interest in this analysis, waist circumference was not included in the risk score. A higher score is indicative of greater health risk. High and low CMR group was determined by a median split of conCMR scores.

6.4.10 Statistical Analysis

Childhood and adolescence z-scores were used to represent TBF and TrF. This is described in more detail elsewhere (433). The childhood and adolescence data included measures from -6 to +6 years from PHV (corresponding to CA of 8 years to 17.9 years). Sex and age

specific z-scores were assigned to each individual at each measurement, from which a mean z-score for childhood and adolescence was determined.

TBF and TrF variables during the period from EA to early adulthood were assessed for normality, and violations were amended using natural logarithmic (Ln) transformations. Descriptive data are split by sex expressed as means and standard deviations (SPSS version 24, SPSS Inc., Chicago, IL). Independent samples *t*-tests with Bonferroni corrections were used to analyze differences between high and low CMR groups for PA, EI, TBF, TrF and CMR factors individually ($p<0.05$). Pearson's correlations were used to determine the relationships between TBF, TrF and individual CMR factors ($p<0.05$).

Random effects models were developed and used to construct models for TBF and TrF from EA to early adulthood in both low and high CMR groups (MLwiN version 1.0, Multilevel Models Project, Institute of Education, University of London, London, UK). This procedure has been described in detail previously (402). In brief, FM parameters were measured repeatedly within individuals (level 1 of the model) and between individuals (level 2 of the model). Linked variables at different levels of a model characterize multilevel random effect regression models. In the present analysis, log transformed TBF and TrF mass during emerging and young adulthood were described by developing multilevel regression models as follows:

$$y_{ij} = (\alpha+\mu_j)+ (\beta+\nu_j)x_{ij} + (k_1z_{ij} + k_2z_{ij} +\ldots+ k_nz_{ij}) + \varepsilon_{ij}$$

which can be reorganized to

$$y_{ij} = (\alpha+\beta_j x_{ij}) +(k_1z_{ij} + k_2z_{ij} +\ldots+ k_nz_{ij}) + (\mu_j+ \nu_j x_{ij} + \varepsilon_{ij}).$$

Where y_{ij} is total (trunk) FM at the i^{th} measure in the j^{th} individual, α_j is the constant for the j^{th} individual, $\beta_j x_{ij}$ is the slope coefficient for FM by age for the j^{th} individual at measurement *i* (in

our model age is centered around 28 years), and k_1 to k_n are the coefficients for time dependent predictor variables (e.g. PA, EI, TBFz-score etc) at the i^{th} measurement in the j^{th} individual. u_j, $v_j x_{ij}$ and ε_{ij} are the random parameters. These parameters are assumed to have a mean of zero and follow a normal distribution. $\varepsilon_{ij} \sim N[0, var(\varepsilon_{ij})]$ is the level one within-individual variance for the i^{th} measurement in the j^{th} individual and $\mu_j \sim N[0, var(\mu)]$ is the level two intercept between-individual variance. $\mu_j * v_j x_{ij} \sim N[0, var(\mu_j * v_j x_{ij})]$ explains the covariance of slope and intercept in the model.

6.4.11 Modelling Strategy

Predictor variables were added one at a time in a stepwise procedure. Significance of the predictor variables as contributors to the new model were determined by changes in the loglikelihood ratio statistic between models. A chi-square distribution was used to compare the difference in loglikelihood ratios from one model to the next considering the degrees of freedom lost by adding variables. If variance at level 1 and 2 was reduced and predictors had estimated mean coefficients greater than twice the standard error of the estimate (SEE) ($p<0.05$) they were retained in the model as significant. If these criteria were not met, the predictor was removed from the model. Age centered was added to the model as a fixed and random coefficient. Age centered was calculated as the participants' CA age measurement minus mean CA in the EA sample (mean CA=28 years). Age^2 was added to the model as fixed effects to better reflect the known non-linear pattern of growth. Total body and trunk FM were modeled and PA, dietary, and childhood/adolescent TrF and TBF z-scores were incorporated into the models and their independent effects were tested.

Completed models and significant coefficients were used to create TBF and TrF curves (Figures 6.1, 6.2, and 6.3). Maximum and minimum values of predictor variables at each BA

from the data set were used in the models to create curves (i.e. PA value of 1 and 5; z-scores of -1 and +2) whilst controlling for the other confounders by using their average values within CA bands.

6.5 *RESULTS*

The median number of testing occasions during emerging and young adulthood (18 to 39 years) was 7, with a minimum of 2 and a maximum of 10. Age centered for the models was 28 years. At mean age of 36 years, 55% of the sample was OWO by BMI. Of those who were OWO, 13 were females (8 from low CMR, 5 from high CMR) and 16 were males (6 from low CMR group and 10 from high CMR group) (26,152,160,162). Recommended criteria for MetS diagnosis according to a harmonized standard from the International Diabetes Federation, the World Health Federation, International Association for the Study of Obesity and the international Atherosclerosis Society include having 3 or more of HDL, glucose, TG, waist circumference and blood pressure above cut-offs (221). Two females and 5 males (13% of the sample) were classified as having MetS in this cohort. Males had significantly greater APHV, BW, EI, height, lean mass, SBP, and TG compared to females in adulthood ($p<0.05$); and females had greater TBF and HDL cholesterol than males ($p<0.05$). When Bonferroni's correction was made for multiple *t*-tests only APHV, BW, height, and lean mass remained significant.

Childhood z-scores and early adult descriptive characteristics (from time of CMR measures) are shown in Table 6.1 by high and low CMR groups. There were no significant differences in any of the variables between risk groups.

In females, TrF was not significantly correlated with the conCMR score but was significantly correlated with MAP (r= 0.61, p<0.0.01), HOMA (r =0 .60), HDL (r = -0.56), and SBP (r = 0.53, p<0.01). TBF was correlated with the same factors but with slightly weaker relationships. In males, TrF was not correlated with conCMR score, but was significantly correlated with HOMA (r = 0.58), HDL (r = -0.57), and SBP (r = 0.55) and DBP (r = 0.51) (p<0.01). TBF was correlated with the same factors but with slightly weaker relationships, except for HDL which was slightly higher. Childhood TrF and TBF z-scores were significantly correlated with adult values of TrF, and TBF respectively (p<0.01). Child TrF was also correlated with adult MAP, and HOMA (p<0.05) in females; and with DBP (p<0.01), HOMA, and SBP (p<0.05) in males. Childhood TBF scores were also correlated with adult HOMA in females; and with adult SBP, DBP and HOMA in males (p<0.05).

Table 6.1 Participant descriptives during childhood and at follow-up in early adulthood.

	Female	**Male**		
	Low	High	Low	High
Childhood				
N	14	15	13	12
Birthweight(kg)	3.39(0.52)	3.17(0.43)	3.65(0.54)	3.70(0.56)
TBF z-score	-0.09(1.01)	0.22(1.18)	0.10(1.25)	0.15(0.81)
TrF z-score	-0.14(1.03)	0.34(1.31)	0.08(1.26)	0.16(0.89)
PA z-score	-0.04(0.82)	0.21(0.82)	-0.16(0.93)	0.09(0.44)
EI z-score	-0.04(0.59)	0.32(0.94)	-0.14(0.57)	0.09)0.44)
Early Adulthood				
Age	36.0(2.7)	35.8(2.6)	36.0(2.4)	36.3(2.3)
BMI (kg/m2)	29.9(9.2)	26.4(7.8)	26.2(4.67)	27.8(3.37)
Height	166.50(7.89)	168.34(6.48)	180.78(7.37)	179.85(6.94)

Weight	83.45(29.13)	76.43(25.03)	85.63(14.15)	89.84(10.48)
Lean (kg)	45.66(10.00)	45.11(8.89)	63.05(6.01)	61.32(5.59)
PA score	2.15(0.75)	2.12(.49)	2.45(0.92)	2.58(0.74)
EI (kjoules)	7709.49(1892.20)	8812.29(2534.58)	10498.05(3705.50)	11055.05(4694.39)
TBF(kg)	27.24(9.19)	26.82(13.38)	19.43(9.79)	20.10(7.59)
TrF(kg)	12.43(5.01)	12.67(6.90)	10.21(6.50)	11.18(5.14)
TBF z-scores	0.02(0.81)	-0.02(1.18)	-0.04(1.13)	0.04(0.88)
TrF z-scores	-0.02(0.85)	0.02(1.16)	-0.08(1.12)	0.09(0.89)
MAP (mmHg)	93.24(6.60)	97.36(12.54)	93.44(9.11)	105.83(7.60)Ⱨ
TotChol (mmol/L)	4.45(0.87)	4.65(0.72)	4.52(0.62)	4.41(0.93)
HDLChol (mmol/L)	1.4(0.3)	1.80(.6)	1.16(0.20)	1.20(0.6)
CholRatio (mmol/L)	3.26(0.96)	2.98(0.993)	4.01(0.95)	3.92(1.31)
TG (mmol/L)	0.82(1.1)	1.00(.47)	1.19(0.56)	1.60(1.29)
Insulin (U/ml)	8.54(5.56)	12.7(10.36)	7.60(4.38)	9.90(6.0)
Glucose (mol/L)	4.50(0.68)	3.83(0.96) Ⱨ	4.31(0.82)	4.07(0.90)
$HOMA_{IR}$	1.7(1.0)	2.2(2.3)	1.4(0.7)	1.8(1.1)
CRP	3.89(5.14)	3.19(3.40)	6.62(21.21)	3.05(3.81)
ConCMR score	-0.85(0.71)	0.81(0.68) Ⱨ	-0.86(0.57)	0.93(0.79) Ⱨ

Median split used for assigning high and low CMR groups. Median score was 0.341 for females, and at -0.297 for males. * significant difference between high and low CMR groups after Bonferroni correction. Ⱨ significant difference between high and low CMR groups before Bonferroni correction. TBF(total body fat, kg); TrF(trunk fat; kg); EI(energy intake; kjoules); BMI (body mass index; kg/m^2); PA(physical activity score; from 1-low to 5-high); MAP (mean arterial pressure ; [{2 x diastolic blood pressure} + systolic blood pressure]/3); TotChol(total cholesterol; mmol/L); HDLChol(high density lipoprotein cholesterol; mmol/L); CholRatio(Total cholesterol/HDLcholesterol); TG (triglycerides; mmol/L); HOMA (homeostasis model assessment for insulin resistance; {{fasting insulin(U/ml)} x {fasting glucose (mmol/l)}}/22.5); CRP(C-reactive protein); ConCMR(continuous cardiometabolic risk score; sum of residuals of TG, HOMA, TCHOL, HDL^{-1},and MAP regressed onto smoking status and age).

Results from the multi-level model of LnTBF are summarized in Table 6.2, and LnTrF results are summarized in Table 6.3. Age centered was a significant predictor of LnTBF and LnTrF. The significance of level 1 variance indicates that TBF and TrF mass significantly increased with age from 18-39 years (E>2x standard error of the estimate $p<0.05$). The significance of level 2 variance for constant and age centered indicate that individuals had significantly different log TBF curve intercepts (constant*constant; μ_j) and slopes (age centered*age centered; $\nu_j X_{ij}$). The intercepts and slopes were not significantly related to each other in the LnTBF model as indicated by the insignificant constant*age centered random effect ($\mu_j * \nu_j X_{ij}$). In the LnTrF model however, constant*age centered random effect ($\mu_j * \nu_j X_{ij}$) was significant, suggesting that those with higher TrF intercepts had shallower slopes.

Table 6.2 Multi-level regression model for log transformed total body fat accrual aligned by chronological age

Variable	Model 2		
Fixed Effects			
Constant	10.06	±	0.11
Age Centered	1.61[a]	±	0.32[a]
Age Centered^2	-1.31 [a]	±	0.32[a]
Sex	-0.44	±	0.08
Height		NS	
CMR group		NS	
Lean	0.05[b]	±	0.02 [b]
PA	-0.06	±	0.02
EI		NS	
Birth weight		NS	
PA z-score		NS	
EI z-score		NS	
TBF z-score	0.28	±	0.04
Random Effects			
Level 1			
Constant (ε_{ij})	0.03	±	3.13[a]
Level 2			
Constant (μ_j)	0.07	±	0.01
Age Centered ($\nu_j X_{ij}$)	0.14[a]	±	0.07[a]
Constant*Age Centered ($\mu_j * \nu_j X_{ij}$)		NS	

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of LN TBF (g)

Random effects values Estimated Mean Variance ± SEE [LN TBF (g)]^2
Age Centered is age in years centered on 28 years.
Sex: Females=0; Male=1
PA and EI z-score are composite z scores from all measures from -6 to +7.
Height (cm); Lean (g); Total Body Fat (TBF) (kg); PA (Physical Activity -Score from 1-5); Energy Intake (EI) (KJ).
[a] indicates numerical values are multiplied by 10^{-3}, [b] indicates numerical values are multiplied by 10^{-4}
Numerical values are all significant, $p < 0.05$ (mean > 2*SEE). Non-significant variables are indicated as 'NS' and removed from the final model.

When age, birth weight, height and lean mass were controlled, sex was a significant predictor of LnTBF and LnTrF. Males will accrue significantly less fat in comparison to females (coded as 0), with greater sex differences for TBF than for TrF (Table 6.2 and 6.3). PA was also a significant negative predictor of LnTBF (-0.05 ±0.02), suggesting that greater levels of PA results in lower fat mass accrual (Table 6.3). PA did not significantly predict LnTrF, although it was nearing significance (-0.47±0.36). Birth weight, energy intake, PA and energy intake in childhood (z-scores) were not significant in either model ($p<0.05$). The strongest predictor of LnTBF accrual was childhood TBF z-score (0.27 ± 0.04); and the strongest predictor of LnTrF accrual was childhood TrF z-score (0.31 ± 0.05) (Table 6.2 and 6.3).

Table 6.3 Multi-level regression model for trunk fat accrual aligned by chronological age

Variable	Model 2		
Fixed Effects			
Constant	9.04	±	0.14
Age Centered	0.03	±	4.54 [a]
Age Centered^2	-1.91[a]	±	0.39 [a]
Sex	-0.32	±	0.11
Height		NS	
CMR group		NS	
Lean	0.06[b]	±	0.03 [b]
PA		NS	
EI		NS	
Birth weight		NS	
PA z-score		NS	
EI z-score		NS	
TrF z-score	0.30	±	0.04
Random Effects			

Level 1			
Constant (ε_{ij})	0.05	±	4.5[a]
Level 2			
Constant (μ_j)	0.14	±	0.03
Age Centered ($v_j X_{ij}$)	0.44[a]	±	0.15[a]
Constant*Age Centered ($\mu_j * v_j X_{ij}$)	-3.55[a]	NS	1.60 [a]

Fixed effect values are Estimated Mean Coefficients ± SEE (Standard Error Estimate) of LN TrF (g)

Random effects values Estimated Mean Variance ± SEE [LN TrF (g)]^2

Age Centered is age in years centered on 28 years.

Sex: Females=0; Male=1

PA and EI z-score are composite z scores from all measures from -6 to +7.

Height (cm); Lean (g); Trunk Fat (TrF) (kg); PA (Physical Activity -Score from 1-5); Energy Intake (EI) (KJ).

[a] indicates numerical values are multiplied by 10^{-3}, [b] indicates numerical values are multiplied by 10^{-4}

Numerical values are all significant, $p < 0.05$ (mean > 2*SEE). Non-significant variables are indicated as 'NS' and removed from the final model.

Lower childhood TBF z-scores and higher PA from 18-39 years, resulted in lower TBF accrual from 18-39 years (Figure 6.2). Figure 6.1 shows the role of PA alone. Childhood TrF z-score predicted TrF accrual from 18-39 years, while PA was not significant (Figure 6.3).

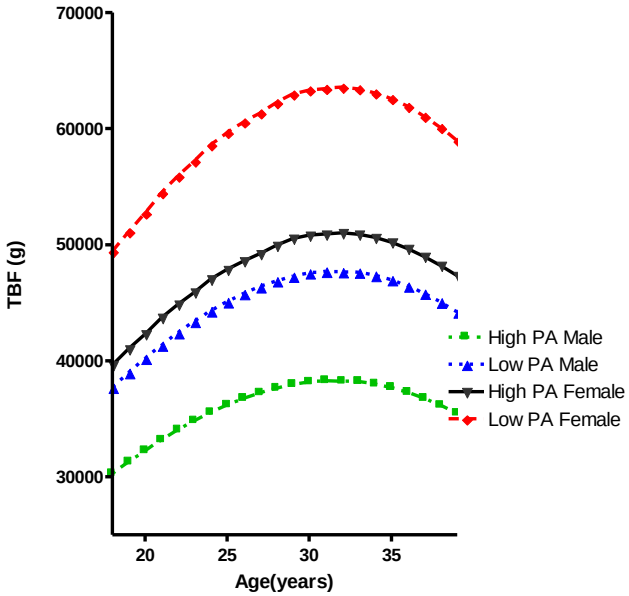

Figure 6.1 Total body fat accrual in males and females from 18-39 years illustrating the differences in trajectories attributable to physical activity and sex.

Males had less TBF accrual than females at any level of PA category; for example, high PA males had less TBF than low PA and high PA females (Figure 6.1); however, females with high PA and low TBF z-scores had lower TBF accrual than males with low PA and high TBF z-scores (Figure 6.2). Similarly, females with low TrFz-score had lower TrF accrual than males with high TrF z-score, but more fat than males with low TrF-z-score (Figure 6.3).

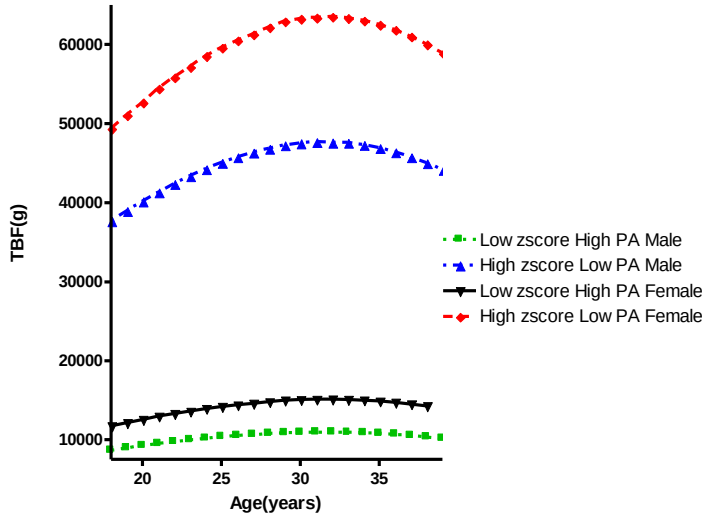

Figure 6.2 Total body fat accrual in males and females from 18-39 years illustrating the differences in trajectories attributable to sex, childhood TBF z-scores and physical activity

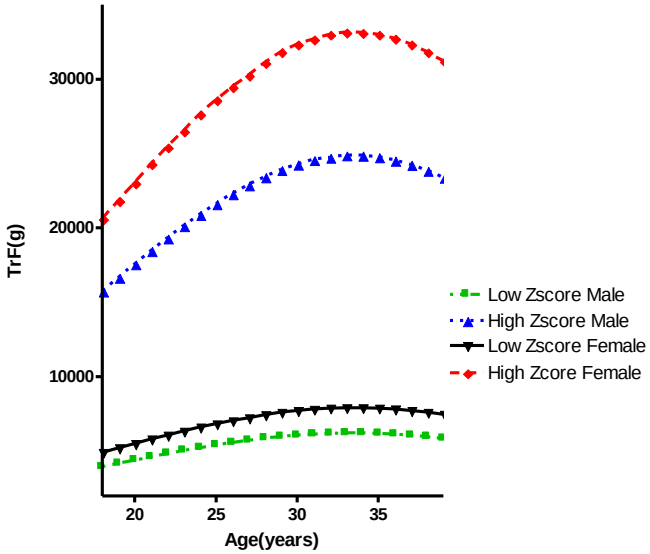

Figure 6.3 Trunk fat accrual in males and females from 18-39 years illustrating the difference in trajectories attributable to sex and childhood TRF z-score

6.6 *DISCUSSION*

This study analyzed accrual of TBF and TrF mass from 18-39 years of age and assessed if these trajectories differed between low and high CMR groups. While both TBF and TrF increased over the measurement period, CMR group did not alter the trajectories. Continuous CMR was not related to TrF or TBF; however, individual CMR components were correlated with TrF and TBF at the end of the early adulthood period. Childhood values of TrF and TBF were the greatest predictors of TBF and TrF gains. The current analysis re-affirmed previous findings from this cohort, indicating that the period of EA is important in the progression of OWO. The current findings add to the literature by suggesting that TBF and TrF continue to be accrued beyond EA and that fat accrual may relate to individual CMR factors.

Fat mass tracks moderately well from childhood into adolescence, with greater childhood fat mass predicting greater adolescent fat mass, which in turn predicts greater fat mass in adulthood (45). Previous work with this cohort demonstrated that childhood fat predicted fat gains during EA (18-28 years) (433). The coefficients for TrF and TBF z-scores in the current analysis covering EA to early adulthood (18-39 years) are significant but smaller than in previous analyses of only EA. This is likely because tracking of body composition and adiposity is stronger between chronologically closer years such that childhood and adolescent fat mass is more strongly related to late adolescent and EA fat mass than to early adulthood fat mass (455,465).

The rate of annual increase in TBF did not change (i.e. the coefficient of age centered) between the current findings (from 18-39 years) and those by Sherar et al. (2011) (from 8-28 years). EA is a period of significant fat mass gains but after EA fat mass tends to stabilize. The lack of difference observed between studies is unexpected and suggests that this cohort

continued to accrue fat mass beyond EA. The rate of predicted TrF accrual decreased in males and increased in females between the two studies. This is surprising as we and others have reported that males tend to increase TrF more than females from puberty until menopause (90,384,385).

The current study did not find any evidence that TBF mass accrual in emerging and young adulthood was higher in those with higher conCMR in adulthood. The location of adiposity can mediate the relationship between OWO and CMR (9,155,156). An example of this is NW in individuals who present with CMR clustering; or NW in youth with higher TrF values who end up as adults with higher CMR profiles (155,169). The risk conferred by TrF beyond that of TBF could explain why TBF accrual was not amplified in the high CMR group in this analysis. Yet, the analysis revealed that TrF accrual was also similar between groups.

Visceral fat, which comprises a portion of TrF, features an elevated level of lipolysis which releases free fatty acids into the blood stream, and increases the release of inflammatory cytokines (interleukins and tumor necrosis factors- alpha) (444). These cytokines contribute to the development of CMR risk factors, atherosclerosis and diabetes (47). DXA-derived measures of TrF have demonstrated a relationship with CMR factors including insulin, glucose, TG and C-reactive protein in both adults and children (5,228). Furthermore, a relationship exists between BMI and TrF in childhood, and CMR in adulthood (169,466). As such, this study, like many other recent studies, focused on TrF as a variable of interest with the expectation that TrF would differentiate high from low CMR risk (60,385,400). The current study did not find any significant differences in TrF accrual between CMR groups, contrasting previous literature

(169,466). The predictive strength of childhood z-scores in this analysis may have washed out differences by CMR group.

Childhood OWO presents an insult to the cardiovascular and metabolic systems precipitating the early onset of risk factors and a cascade of adverse processes which lead to cardiometabolic consequences in adulthood (8,383,467,468). Internal z-scores were used to express childhood fat mass in this analysis and very few of the participants were OWO children. This likely contributed to the inability of CMR to influence modeled fat curves in early adulthood; furthermore, there was increasing homogeneity in this cohort from the third to forth decade of life. This is illustrated in that previous analyses conducted with this PBMAS cohort at a mean age of 26 found that TrF was different between high and low adult CMR groups from as young as 8 years of age (169); and yet the current analysis found no difference in fat trajectories between CMR groups. In the previous analysis by Sherar et al. (2011), the high CMR group had higher child and adult fat mass values, and higher blood markers than the low CMR group; and the low CMR group had mean waist circumference (WC) values below International Diabetes Federation (IDF) cut-offs. In the current analysis, both groups have mean WC values over IDF cut-offs. It appears that the high CMR group maintained their level of "un-health" from the 3rd to 4th decade (i.e. high WC), while the low risk group became less "healthy". For example, in males, mean WC increased from 83 cm to 105 cm in the low risk group, and remained at 89 cm in the high CMR group. In females, the waist circumference increased from 74 cm to 93 cm in the low CMR group and increased from only 91cm to 92 cm in the high CMR group. As the low CMR group caught-up to their high CMR counterparts in terms of TrF mass, differences in CMR

profiles disappeared. These observations suggest that having a lower WC and by association a lower CMR in one's 20's does not preclude future CMR.

A-posteriori analyses revealed an interesting pattern in which TrF and TBF z-scores in childhood and adulthood were slightly (but not significantly) lower in the low CMR groups. Between childhood and adulthood, the high CMR females decreased in z-score while the low CMR group increased in z-score - the groups became more evenly split in terms of spread of the individuals above and below the mean. In males, both high and low CMR decreased in z-score, becoming less similar by adulthood. This suggests two things. Firstly, that in females childhood fat mass (or z-score) and in males adulthood fat mass (or z-score) may be more predictive of future fat mass and CMR. Secondly, that in females the lower risk that is likely linked with a lower z-score in childhood is almost completely offset by a greater relative gain in fat mass. Changes in fat mass have been shown to predict future CMR. For example, Chantler et al. (2015) and Tbor et al. (2011) found that in adult women, the degree of increase in TrF from adolescence to adulthood related to increased CMR independent of TrF at the follow-up (469,470). Similarly, Park et al. (2010) found that the relationship between insulin resistance and WC increments across 20 years was stronger in participants with smaller versus larger WC at baseline (471). Studies by Hanson et al. (1995) and Resnick et al. (2000) supported this idea indicating that, the risk of type 2 diabetes in OWO adults was associated is weight gain across 2 years and 10 years respectively; but that a higher risk presented in those with NW at baseline compared to those with overweight at baseline, or in the highest BMI group at baseline (472,473). Pooled longitudinal data similarly have revealed higher relative risk ratios of CVD risk factors - type II diabetes, hypertension, LDL cholesterol, HDL cholesterol $^{-1}$, triglycerides and carotid-artery intima media thickness - in NW youth (4-18 years) who became OWO adults (23-46 years),

compared to youth who remained NW, or OWO youth who became NW adults according to age-specific and sex-specific BMI cutoff points (459). These results from Juonala et al. (2011) suggested that the OWO-to-OWO group had the highest risk. The homogeneity of CMR scores in the current sample may be because the low CMR group experienced steeper increases in fat gains than the high-risk group over the last 10 years. This is also indicated in the significant constant x age centered coefficient - those with higher intercepts at 18 years had shallower slopes of fat accrual (Table 6.2 and 6.3). There has perhaps been a meeting-in-the-middle whereby the high risk conferred by high childhood fatness is matched by a situation of low childhood fatness combined with rapid gains across early and emerging adulthood.

PA during early adulthood was found to be a significant predictor of TBF but not TrF accrual. The relationship with TBF is not surprising as many studies have found similar correlations (115,275,474). What was unexpected was the lack of relationship between TrF gains and PA, as literature has demonstrated that PA can preferentially deplete trunk fat stores during PA weight loss interventions (169,202,205,264,279,286). Furthermore, PA significantly predicted TrF gain in this cohort from age 18-28 years in previous analyses, although only in males (433). In previous analysis, a separate model was run for males and females and PA was only significant in male TrF models. Sex was aggregated in the current analysis and the weaker relationship between PA and fat in females may have dominated the model. PA has previously demonstrated a weaker effect on body fat in females than in males which may explain the lack of significance (392,433,447). For example, in the study by Clement et al. (2017), female university students in the lowest, middle two and upper quartiles of percent body fat had significant differences in minutes of light PA but no difference in moderate or vigorous PA, suggesting that vigorous PA was not associated with a lower fat mass. Males in the same study with the lowest

body fat had the highest minutes of vigorous PA, moderate PA, and the 2nd highest light PA (392).

The lack of significance of PA as a predictor of TrF may also speak to the strength of an underlying genetic predisposition which upregulates visceral fat accumulation and shunts fat away from subcutaneous depots (a "healthier" fat) (129,465). Genetic underpinnings, in addition to the strong tracking of TrF suggest stability of a TrF phenotype (129,465). PA may have a greater ability to influence TBF while a body type that favors TrF deposition may manifest early in life and not be easily thwarted off its trajectory.

Diet did not demonstrate significance as a predictor in these models. It is well established in the literature, however, that a relationship exists between diet and fat mass (232,240). The lack of relationship observed in this study may be explained by recent studies that suggest the role of caloric intake is less relevant than the quality of the macronutrients (i.e. respective levels of carbohydrates and fats) (238,243,244). As this study only recorded caloric intake, we may have missed this important relationship.

6.6.1 Limitations

The PBMAS cohort included in the current analysis is not the exact same sample as the previous analysis (169). Approximately 65% of the participants from the current analysis were part of the analysis from 2011 intake (169), and those that returned for the current assessment had a mean BMI in 2011 like that of the high risk CMR group in 2011. This suggests that those included in this sample may have had higher BMI's than the entire cohort. While the prevalence of OWO in this sample (42% of females and 64% of males) was almost identical to national estimates of OWO (46% of females and 64% of males over 18 years) (26,152,160,162), the prevalence of MetS in this sample (13%) was higher than national estimates for this age group

(7.8%) (49). While a continuous CMR score has been used previously, it may not be sensitive enough to identify differences in younger participants with an absence of manifest disease. At this young age, it also appears that not all components of the conCMR score may contribute equally (or in the same direction) to the composite score. Because the analysis was modelling TrF, WC was not included in the conCMR score but TrF had strong correlations with all but TG in females, and TG and MAP in males. Future research may address this by investigating individual components of CMR and modeling fat mass trajectories each CMR factor added individually. Future longitudinal studies are required that track participants into older ages when the MetS and CVD manifest to tease out the independent contribution of childhood, emerging adulthood and early adulthood fat accrual.

6.7 *CONCLUSION*

This study added to the literature by identifying child and adolescent TBF and TrF as important risk factors for fat accrual in emerging and early adulthood, but not CMR profiles in early adulthood. Rather, findings indicated that in females, CMR may be equally conferred by higher childhood fat mass, as by low childhood fatness followed by subsequent rapid gains. In males, fat mass in adulthood is likely more important for CMR. Findings also suggested that participating in physical activity has the potential to ameliorate total body fat mass accrual in young adulthood. Interventions for preventing adult overweight need to focus on reducing childhood and adolescent fat mass without neglecting the early adult years.

CHAPTER 7

DISCUSSION AND CONCLUSION

7.1 *DISCUSSION OF STUDY FINDINGS*

Obesity continues to be a major public health concern in Canada as in the rest of the world. There has been much attention given to the period of childhood in an attempt to prevent the onset of OWO because an early onset of OWO has demonstrated strong stability into adulthood (27); however, considering discrepant rates of OWO in children and adults, it can be inferred that children with NW also become adult with OWO (1,26). Studies of young adults with OWO often focus on weight loss and treatment, with less work being done to identify contributing factors and prevent the onset of OWO in EA in previously NW youth. This dissertation sought to: 1) investigate the pattern of fat mass accrual during emerging adulthood and identify the importance of this period in the onset of OWO; and identify the age at onset by different metrics 2) identify the predictors and contributors to fat mass gains and the onset of OWO in EA, and 3) to assess the cardiometabolic consequences of fat mass gains in EA and early adulthood.

There are very few studies which attempt to identify the age of onset of OWO beyond childhood and this is the gap that study 1 attempted to fill. Paper 1a was an observational analysis using previously collected data from participants of the PBMAS cohort from the age of

PHV to the end of EA (approximately 12 to 29 years). This study found that 80% of the participants had NW at PHV, but by early adulthood that number had plummeted to just over 40% in females and just over 50% in males. OWO in childhood was unable to uniquely predict OWO in adulthood, highlighting the fact that children with NW will also become adults with OWO. The analysis identified the years near the end of adolescence and the beginning of adulthood years when the transition to OWO likely occurs. These findings confirmed those of Racette et al. (2005), Suglia et al. (2013), and Gropper et al. (2011), which found that fat mass was gained during the years of college and university (90,385,387). Paper 1b from study 1 identified that the prevalence of OWO was not identical between different metrics. Estimates by %TBF are higher in females and estimates by BMI cut-offs are higher in males. Study 1a findings generated the questions for Study 1b and 2: Is the age of OWO onset different using different metrics? What are the contributing factors to fat mass gains during this period of EA?

Study 1b asked the question: Can we confirm longitudinally that EA is a period of OWO onset? And what are the differences in age at onset and prevalence of OWO by different metrics between sexes? The findings from this study confirmed that, for many, the onset of OWO is during EA, but that the age is sex- and metric-specific. In females, %TBF is a more conservative metric, while in males BMI is a more conservative metric, the onset by both metrics occurring between PHV and 25 years. WC does not appear to be an appropriate indicator of OWO in this age group, potentially overlooking those with excess adiposity but a below-cut-off WC. BMI missed ¼ of the males and ½ the females that were "over-fat" by %TBF criteria.

Study 2 investigated lifestyle predictors of fat mass gain in EA, while controlling for childhood and adolescent fat mass and PA. Childhood and adolescent fat mass were identified in longitudinal modeling as being a very strong contributor to the amount of fat mass gained in EA.

Interestingly, children do not typically accumulate large amounts of trunk fat. Rather, trunk fat begins to accrue more so in adolescence and early adulthood; and yet, having higher TrF in childhood relative to one's peers predicted having greater TrF gains in EA. PA during EA was only significant in males, although it was proposed that some of the female participants may have been in the final years of puberty during which TBF and TrF accrual are hormonally controlled and, therefore, less influenced by lifestyle choices. While the years of EA were again highlighted as being critical for fat mass gains, maintaining a healthy weight (fat mass) in childhood and adolescence and being PA were also underscored as being potential mitigating factors. The inclusion of TrF in study 2 was primarily due to the known health implications of central adiposity. A higher TrF and TrF accrual manifest as a higher health risk which was the premise of study 3.

For study 3, PBMAS participants were invited back for a new wave of measures (2016/2017) which included blood profiles. Continuous cardiometabolic risk scores (conCMR) were used to create high and low CMR groups in both males and females. Models of TBF and TrF from 18-39 years once again identified childhood TrF and TBF z-scores as the strongest predictors of TBF and TrF accrual. The analysis did not find any difference in TrF or TBF trajectories between those with the upper half compared to the bottom half of sex-specific median split of continuous cardiometabolic risk scores. PA was also identified as having a positive effect on TBF accrual from 18-39 years. The lack of significant difference of other variables such as blood lipids, HOMA, and even waist circumference between CMR groups were likely responsible for the lack of difference in conMetS scores

7.2 *DISCUSSION OF TOPICAL FINDINGS*

7.2.1 BMI

It has been suggested that the use of BMI alone may not be adequate for discerning adiposity (99) . The findings from studies 1a and 1b support this idea, as BMI failed to identify OWO in 20-50% of individuals, with more females than males being missed. The WHO defines obesity as an excess of adipose tissue, and fat mass, more than weight, confers greater cardiometabolic health risk; as such, the recommendation from this dissertation is that a measure of adiposity such as %TBF be included in clinical assessment of OWO imposed health risk in individuals under the age of 40. Future studies with this cohort should explore if earlier onset of OWO identified by BMI, %TBF or by WC criteria provides a more accurate predictor of CMR in mid to older adulthood.

7.2.2 Diet

A large number of individuals acquire OWO in late adolescence and emerging adulthood when caloric intake remains unaltered but growth has ceased (107). This explanation of the timing of the onset of OWO is supported by findings in this thesis which identified the age at onset of OWO to be 18-28 years; however, the "calories in-calories out" theory of excess fat was not supported in the current collection of studies. While studies of caloric restriction and increased PA have demonstrated weight loss (91,119–121), studies 2 and 3 did not identify caloric intake in childhood and adolescence or in emerging adulthood as being significant in predicting fat mass accrual. The current findings support the theory that OWO is a multi-factorial disease for which there are likely metabolic, genetic, epigenetic, and endocrine contributors (15,122,123).

7.2.3 PA

The relationship between PA and fat mass was not found to be as strong as previously demonstrated (265,266). PA was identified as a predictor of TBF and TrF in males in study 2, and of TBF in males and females in study 3. This was particularly unexpected in regard to TrF as many studies have identified that PA preferentially eliminates fat from the trunk (169,202,205,264,279,286). PA in childhood and adolescence was not related to fat accrual in emerging adulthood, which was also unexpected as longitudinal data has shown that the risk of adult OWO is higher in those with low or declining levels of PA from 9-18 years (367). Finally, it was unexpected that PA was not different in childhood/adolescence or in early adulthood between those with high versus low CMR, as PA has demonstrated a positive effect on cardiometabolic health in children and adolescents and as a childhood factor improving adult cardiometabolic health (208,264,283,370,372). The findings from the current study highlight PA as a concurrent factor mitigating fat mass gains but did not find a connection between childhood PA and adult health or fat mass.

7.2.4 Critical periods for Fat mass and health

Childhood is considered a critical period for the development of OWO. Literature suggests that OWO in children is likely to remain stable into adulthood, and that those individuals who will come to have obesity have a different trajectory of fat growth, even before they have overweight (27,107). This is supported by our findings, as children with higher fat mass were also the individuals with higher fat mass accrual in young adulthood. These findings were as expected. There are fewer young adults who move from OWO to NW than there are

those who move from NW to OWO (107). Canadian statistics demonstrate the same trend - OWO increases with age (162).

OWO has demonstrated a cumulative effect on morbidity, with children with OWO in whom OWO remains are more likely to present with higher CVD risk profiles (17,20,140). What was unexpected in our study was that those with greater fat mass in childhood, adolescence and emerging adulthood, did not have higher CMR profiles - at least not by the age of 40 years. This supports the theory that higher childhood BMI may have a protective effect at a given level of adult BMI and that the health risk may be just as great for those who rapidly acquired OWO as for those with a stable (age-relative) BMI (140). This may be due to an independent risk conferred by rapid fat mass gains in the children with NW, or because this cohort was not old enough for CVD risk to manifest. There have also been findings that those with metabolically normal obesity tend to have an earlier onset, which would explain this unexpected result in Study 3 of this dissertation (131). It was also surprising that TrF trajectories were not related to EA fat accrual as this depot includes visceral fat which is more detrimental to health than either BMI or TBF (159). There was, however, a relationship between TrF and individual components of the conMetS such as HOMA-IR and MAP. It may be that levels of TrF were not yet high enough in this age of cohort to negatively impact all CMR factors, and as such the comprehensive conMetS was not representative of all risk. Also possible is that measures of TrF by DXA were unable to account for differences in visceral fat in individuals with the same TrF (which includes subcutaneous fat). These differences may account for the lack of significant difference in conMetS between those with higher versus lower TrF accrual trajectories.

Childhood and adolescence are critical periods for fat mass and OWO and this was confirmed in the current studies which suggest that if fat mass is not controlled in adolescence,

then it increases the likelihood of becoming overweight in EA. This collection of studies has also highlighted EA as the time when most of our healthy-weight youth come to have OWO, suggesting that this period of transition requires substantially more emphasis as a critical period for intervention. The instability of EA also provides an opportunity in which alterations can be made to health and lifestyle trajectories set earlier in life. According to the habit discontinuity hypothesis, positive changes made during EA, alongside a change in context and environment may be stable into subsequent periods of life (28,378). Introductions of habits such as regular PA and healthy diet are suggested as positive changes that should be encouraged and included in interventions for this age group. Although trajectories of fat mass and OWO beyond emerging adulthood are important for health, the current findings suggest that they do not predict cardiometabolic risk, at least in the short term.

7.3 *FUTURE DIRECTION*

A series of interesting observations and questions have arisen out of this series of studies and in particular study 3. In study 3 there was a pattern that suggested that the low CMR group may not have had any lower risk of CVD and diabetes than the high CMR group, despite slightly lower TrF (g), because they also had greater increases in fat z-scores from childhood to adulthood, at least in females. There was not enough power in the current analysis, nor was the group old enough (potentially) to identify clear cardiometabolic consequences; however, previous literature and the pattern seen in the study 3 suggest that this is an area that should be more closely explored. Suglia et al. (2013) identified an odds ratio of hypertension 5 times higher in those who transitioned from NW to OWO between the years of 16-29 years compared

to those who remained NW, or transitioned from OWO to NW (90). OWO to OWO had the highest risk. Petkeviciene et al. (2015) identified that a change in BMI increased the odds ratio of HDL^{-1}, elevated triglycerides and hypertension in adulthood, independent of childhood BMI (456). In adults who are OWO, an inverse association between childhood BMI and blood pressure has been demonstrated such that those with the lowest BMI in childhood who become OWO in adulthood have the greater risk than children with higher BMI (62,459), again emphasizing change in weight as the key component to elevated risk.

Having more weight or fat mass in childhood may be protective against cardiometabolic dysfunction that commences in adulthood. The presence or nature of this protection is unclear but it may operate by mechanisms similar to the thrifty genotype hypothesis and the metabolic loading hypotheses (see section 2.7.1), in which the body's metabolic and endocrine systems are "primed" early (perhaps *in utero*) to deal with a certain environment (79,296,318–321). If the future load matches the load priming, health detriments are mitigated. Alternatively, when the environment has a small initial load (low fat mass) and a high later life load (fat mass gains), the systems are ill equipped to deal with the change and dysfunction occurs. Future adequately powered longitudinal studies are needed to analyze cardiometabolic risk in adulthood while controlling for maternal and intrauterine characteristics, birth weight and early growth, childhood fat mass, and CMR risk profiles, and lifestyle characteristics such as PA and diet. This will provide further insight into the primed versus exposed load hypothesis.

Future research questions should explore if different fat distribution in childhood predicts adult CVD and diabetes, and, if so, what types of interventions (or exercises) are most effective at targeting TrF loss. Future interventions and programs need to be diligent in tailoring programs

to youth who were NW as they enter early adulthood, as they may be at even higher risk of disease if fat mass is accrued rapidly, but this also needs to be confirmed.

The lack of difference in fat mass and blood profiles between high and low CMR groups in study 3 introduced the idea that indices of cardiometabolic health and health risk that were used may be inadequate or inappropriate for this population. Different components of the conCMR score may be more salient at different ages as TrF was strongly related to individual CMR factors but not to the composite score. Cardiometabolic risk factors are known to have different growth curves in youth up to 20 years but there has been little work done on curves of CMR factors in young adulthood (435). Abdominal obesity has demonstrated the strongest relationship with risk of MetS, but in the current study 3 WC was not included in the conCMR score because TrF was being modeled (206). This may also be one of the earlier indicators of CMR in those who do not yet have MetS or CVD, arising before adverse levels of HDL's, triglycerides or glucose (206). While the model did not identify WC crossing the cut-off by 40 years, adult TrF was correlated with multiple individual CMR factors, and both high and low female risk groups (92 cm and 93 cm respectively) and low male risk group (105 cm) had WC means above recommended levels. Future longitudinal studies with CMR profile data obtained through out childhood into adulthood are needed to ascertain the earliest and most significant predictors of future CVD and MetS.

Finally, the findings suggest that the power of PA to exert change on fat mass may be contingent on sex and age. While PA was a significant predictor of both TrF and TBF accrual from 18-28 years in study 2, this was only in males. In study 3, PA was a significant predictor of TBF accrual but not TrF accrual when sex was combined in the model. While some studies cite PA as having a weaker effect on body fat in females than in males in early adulthood

(392,433,447), other studies in mid adulthood (50-60 years) demonstrate the opposite sex difference, in which males have to be more physically active to see changes in abdominal fat. For example, two recent studies in 50 to 60-year-old adults found that the percent of time spent in moderate-to-vigorous PA determined by accelerometer was more highly (negatively) correlated with BMI and WC in women than in men; and that exchanging 1 hour of sedentary time for 1 hour of light PA had a greater association with both visceral and subcutaneous abdominal fat in women than in men (475,476). There is a possibility that the effect of PA on fat mass decreases with age in males, perhaps as lean mass accrual slows and lean mass loss begins (243,281,460,477), while in females PA has an increased effect with age as biologically necessitated gains in fat mass cease (478). Future studies that incorporate objective and continuous PA assessments from childhood into later adulthood, using precise measures of biological age when appropriate, are required to tease out the effect of PA from that of hormones on changes in body composition and health related risk.

7.4 *LIMITATIONS*

This collection of studies is not without limitation. Each study has specific limitations discussed at the end of each chapter. A short summary of limitations follows.

This group was homogenous in its ethnicity, being 95% Caucasian. As such, findings cannot be generalized to other ethnicities. Specifically, there are ethnic differences in WC cut-offs (Asians have lower recommended cut-offs), amounts of TBF for a given BMI, ratios of visceral-to-subcutaneous fat at given TBF, and predisposition to cardiometabolic diseases (211,479). Furthermore, as with all longitudinal studies, participant baseline measures of characteristics that are susceptible to secular change (such as fat mass and obesity prevalence) are likely different from the current population. This discrepancy is likely to increase with

increasing length of time over which the longitudinal study is carried out. For example, the rates of abdominal obesity increased seven times in Canadian adolescents and three times in Canadian adults between 1981 and 2007-2009 (198). In 1990, the prevalence of adult obesity was 9.2% (480). In 2015, the prevalence of adult obesity was 27% in Canada and 31% in Saskatchewan (11). With that said, just over 70% of Canadians currently have OWO and these numbers are comparable to current values in the PBMAS cohort (481).

In terms of methodological weaknesses, it is acknowledged that the DXA scan analysis parameters were originally set for bone mass and not readjusted for measures of TBF. This may have underestimated the amount of TBF and TrF in our adult sample. The implication of this may be that study 1a and 1b may have demonstrated an earlier age at onset of OW by TBF metric; and for study 2 and 3, the significance of predictors may have been somewhat altered, e.g. conMetS may have been significant if differences between OW and more extreme values of OB TBF were undistinguishable.

For study 1b, WC cut-offs used had been developed to transition smoothly to adult values of OB by BMI ($30 kg/m^2$) rather than OW values. Similarly, pediatric WC cut-offs were developed to smoothly transition into adult WC cut-offs aligned with the adult OB BMI cut-offs (198,199,220). This likely delayed the identified onset of OW (or elevated risk) by WC compared to the age of onset identified by BMI and %BF for which OW cut-offs were used. Had OW WC cut-offs been used, the age at onset of elevated risk WC would have been 22 years in females and 34 years in males - closer to the age at onset by the other two metrics. This also indicates that metrics likely have more overlap in their identification of at-risk morphology than reported in study 1b.

Although these studies contained small sample sizes, the power of longitudinal analysis comes from the high level of correlation between measurements within individuals. The same individuals were serially measured over 20 years, with the majority of included participants of each study being measured between 6 and 10 times, comprising over 2000 measurement points (see Table 4.1).

7.5 *CONCLUSION*

In conclusion, through this series of studies we investigated the time course of the onset of OWO in a group of children who were predominantly NW; the potential determinants of TBF and TrF mass accrual during the years of emerging and early adulthood; and the effect of fat accrual in emerging and early adulthood on the risk factors of CVD and MetS. Our findings support the existence of multiple contributing factors in the progression of OWO and the pathogenesis of the cardiometabolic risk. Many of these factors begin to influence life course fat trajectories in early life. The findings from these studies encourage interventions targeting both children and adolescents as well as emerging adults - a previously underserved age group. Interventions that focus on maintaining a healthy weight and healthy lifestyle during the transitional period from adolescence to adulthood are recommended. Optimizing modifiable risk factors such as weight control and physical activity throughout childhood into emerging adulthood may prevent the onset of OWO and, therefore, its complications such as MetS and CVD.

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APPENDICES

APPENDIX D: DEMOGRAPHIC QUESTIONNAIRE

Demographic Questionnaire

Date: _____ Scheduled Appointment Time: _____

Name: _____ Maiden Name (if applicable): _____

Birthdate: _____

Health Number (1991): _____

PBMAS ID #:_____ SEQ#:_____

Your Current Address: _____ City: _____

Province: _____ Postal Code: _____

Telephone #: (home)_____ (work) _____

Cell Phone #: _____ E-mail address: _____

Is this correct? ❑ Yes ❑ No

Parents Address:_____ City: _____

Province: ___ Postal Code: _____

Telephone #: _____ Is this correct? ❑ Yes ❑ No

Martial Status: _____ Single _____ Married

Name of Spouse:_____ Date of Marriage: _____

Educational attainment:

What is the highest grade of elementary or high school that you have ever completed?

- ❑ Grade 8 or lower
- ❑ Grade 9 - 11
- ❑ Grade 12 diploma or equivalent

Have you received any other education that could be counted towards a certificate, diploma or degree from an educational institution?

❑ Yes

What is the highest certificate, diploma or degree that you have completed?

- ❑ Less than high school diploma or its equivalent
- ❑ High school diploma or a high school equivalency certificate
- ❑ Trade certificate or diploma
- ❑ College, CEGEP or other non-university certificate or diploma (other than trades certificates or diplomas)
- ❑ University certificate or diploma below the bachelor's level Bachelor's degree (e.g. B.A. B.Sc., LL.B.)
- ❑ University certificate, diploma or degree above the bachelor's level

❑ No

Current household income: (your household)

<$25,000 ❑ $25,00 to $35,000 ❑ $35,000 to $50,000 ❑

$50,000 to $ 90,000 ❑ >$90,000 ❑

Parental education level attained:

What level of education was attained by your **mother**?

Less than high school ❑ 2 years or less post-secondary diploma or certification ❑

University Bachelor Degree ❑ Masters or PhD ❑

What level of education was attained by your **father**?

Less than high school ❑ 2 years or less post-secondary diploma or certification ❑

University Bachelor Degree ❑ Masters or PhD ❑

Reported items:

*Father's Height _____ cm

*Mother's Height _____cm

*Birth Weight _____g

When you were a baby were you mainly **(please check circle that applies)**:
*Breast-Fed ❍
*Formula-Fed ❍

*If breast Fed, how many months were you exclusively breast fed? _____

*If you do not know these items, who can we contact for this information?

Name: _____ Telephone #: _____

APPENDIX E: BLOOD PRESSURE QUESTIONNAIRE

Blood Pressure

Please check the following conditions before taking a blood pressure reading:

Participant has:

been in a warm environment for 1 hour ❑ Yes

had no caffeine or cigarettes for 2 hours ❑ Yes

had no alcohol in the last 8 hours ❑ Yes

no heavy physical activity in the last 2 hours ❑ Yes

bowel/bladder is not full prior to reading ❑ Yes

Diastolic Blood Pressure (DBP) _____ mmHG

Systolic Blood Pressure (SBP) _____ mmHG

Resting Heart Rate (HR) _____ beats per minute

APPENDIX F: FEMALES ONLY QUESTIONNAIRE

Females Only Questionnaire

How old were you when you started to have menstrual cycles?_____ years old

Did it occur in:
Spring
Summer
Fall
Winter

Are you currently using oral contraceptives?
No
Yes

If yes, for how long have you used them? _____ Years _____ Months

What is the brand name of the oral contraceptives that you use? _____

If no, have you used them in the past?

No
Yes

If yes, for how long had you used them? _____ Years_____ Months

What brand name of oral contraceptives did you use? _____

How many periods do you have in a year?
Over 13 periods
9 to 13 periods
3 to 8 periods
less than 3 periods

Have you had a period in the past three months?
No
Yes

What is the date of the first day of your last period? _____

Have you ever had an absence or loss of periods (pregnancy and lactation not included)?
No
Yes

If yes, at what age(s) did you miss a period(s)?
_____ years old
_____ years old

For how long did your periods stop?

_____mos. _____ yrs
_____mos. _____ yrs

Legally, you cannot be scanned if you are pregnant.

Are you pregnant?
No
Yes
I don't know

How many children have you given birth to? _____ If none, go to next page

Child 1: Name: _____
Birthdate: _____Birth Weight: ____lbs oz
Did you breastfeed? ❑ No ❑ Yes

If yes, how many months? _____

Child 2: Name: _____
Birthdate: _____Birth Weight: ____lbs oz
Did you breastfeed? ❑ No ❑ Yes

If yes, how many months? _____

Child 3: Name: _____
Birthdate: _____Birth Weight: ____lbs oz
Did you breastfeed? ❑ No ❑ Yes

If yes, how many months? _____

Child 4: Name: _____
Birthdate: _____Birth Weight: ____lbs oz
Did you breastfeed? ❑ No ❑ Yes

If yes, how many months? _____

APPENDIX G: CHRONIC CONDITIONS QUESTIONNAIRE

Chronic Conditions Screening Questionnaire

Have you ever been told by your doctor that you had any of the following conditions?

Heart disease of angina	_____ No	_____ Yes	_____ Don't know
Heart attack	_____ No	_____ Yes	_____ Don't know
High blood pressure	_____ No	_____ Yes	_____ Don't know
High blood cholesterol	_____ No	_____ Yes	_____ Don't know
Stroke	_____ No	_____ Yes	_____ Don't know
Tuberculosis	_____ No	_____ Yes	_____ Don't know
Asthma	_____ No	_____ Yes	_____ Don't know
Hay Fever	_____ No	_____ Yes	_____ Don't know
Chronic colitis	_____ No	_____ Yes	_____ Don't know
Diabetes	_____ No	_____ Yes	_____ Don't know
Thyroid condition	_____ No	_____ Yes	_____ Don't know
Kidney disease	_____ No	_____ Yes	_____ Don't know
Hepatitis	_____ No	_____ Yes	_____ Don't know
Stomach ulcers	_____ No	_____ Yes	_____ Don't know
Rheumatoid arthritis	_____ No	_____ Yes	_____ Don't know
Other arthritis	_____ No	_____ Yes	_____ Don't know
Any fracture	_____ No	_____ Yes	_____ Don't know
Any cancer	_____ No	_____ Yes	_____ Don't know

APPENDIX H: GENERAL HEALTH QUESTIONNAIRE

General Health and Lifestyle

1. In general, would you say your health is:
   Excellent
   Very good
   Good
   Fair
   Poor

2. On a scale from 1-5, **compared to other people your age and sex, would you say you are**:

1	2	3	4	5
Much less active				Much more active

3. In the past 12 months how often have you drank some kind of alcohol beverage?
   Daily or almost every day
   3 or 4 times a week
   Once or twice a week
   Once or twice a month
   Less than once a month
   Never
   I don't know.

4. How often do you or did you drink any type of milk (including milk on cereal)? Do not include milk added to coffee or tea.

	Current	Teenage (13-17 y)	Childhood (5-12 y)
Never	( )	( )	( )
Less than once per week	( )	( )	( )
Once per week	( )	( )	( )
Less than once per day but more than once per week	( )	( )	( )
Once per day	( )	( )	( )
More than once per day	( )	( )	( )
More than 3 times per day	( )	( )	( )
Don't know	( )	( )	( )

5. Have you EVER smoked cigarettes regularly; regularly means more than 20 packages in a lifetime or more than 1 cigarette a day for a year?

No
Yes

If No, go to Question 12.

6. How old were you when you started smoking regularly?
_____ years old

7. Do you still smoke?

No
Yes

If YES, go to Question 9

8. If you stopped smoking cigarettes completely, how old were you when you stopped?_____ years old

9. For the entire time that you smoked, on average how many cigarettes did you smoke per day?_____ cigarettes

10. Between the years that you started and last smoked cigarettes, did you ever quit smoking for a year or longer?

No
Yes

If Yes, go to Question 11; if No, go to Question 12.

11. You may have started and stopped several times. How many years total did you quit?_____ years

12. Are you regularly exposed to someone else's smoke at work (school) or home?

No
Yes

APPENDIX I: FAMILY CARDIOVASCULAR HEALTH QUESTIONNAIRE

Family Cardiovascular Health Questionnaire

Including living and deceased, were any of your biological that is, blood relatives including grandparents, parents, brothers, sisters ever told by a health professional that they had:

1. Diabetes (excluding during pregnancy)?

Yes □ Type I □ Type II □ Both □
No □
Don't Know □

If Yes, which family member?		Age (in years) diagnosed:
Mother	□	_____
Father	□	_____
Mother's Mother	□	_____
Mother's Father	□	_____
Father's Mother	□	_____
Father's Father	□	_____
Brother	□	_____
Sister	□	_____
Other	□	_____

2. High blood pressure, excluding during pregnancy, before the age of 50?
   Yes □
   No □
   Don't Know □

If Yes, which family member?		Age (in years) diagnosed:
Mother	□	_____
Father	□	_____
Mother's Mother	□	_____
Mother's Father	□	_____
Father's Mother	□	_____
Father's Father	□	_____
Brother	□	_____
Sister	□	_____
Other	□	_____

3. Stroke before the age of 50?

Yes □
No □
Don't Know □

If Yes, which family member?		Age (in years) diagnosed:
Mother	□	_____
Father	□	_____
Mother's Mother	□	_____
Mother's Father	□	_____
Father's Mother	□	_____
Father's Father	□	_____
Brother	□	_____
Sister	□	_____
Other	□	_____

4. Heart attack or angina before the age of 50?

Yes □ No ☐ Don't Know ☐

If Yes, which family member?		Age (in years) diagnosed:
Mother	☐	_____
Father	☐	_____
Mother's Mother	☐	_____
Mother's Father	☐	_____
Father's Mother	☐	_____
Father's Father	☐	_____
Brother	☐	_____
Sister	☐	_____
Other	☐	_____

APPENDIX J: BLOOD PRESSURE QUESTIONNAIRE

Blood Pressure Questionnaire

1. Have you been diagnosed by a health professional as having high blood pressure?
Yes ☐ No ☐ Don't Know ☐

2. In the past month did you take medicine for high blood pressure?
Yes ☐ No ☐ Don't Know ☐

3. Have you adopted lifestyle changes to treat hypertension?
Yes ☐ No ☐ Don't Know ☐

4. If yes, when did you adopt these changes?

Start: dd/mm/yy _____ Finish: dd/mm/yy _____

5. Please list the lifestyle changes you have made.
_____
_____
_____
_____

APPENDIX K: PHYSICAL ACTIVITY QUESTIONNAIRE FOR ADULTS

Physical Activity Questionnaire (Adults)

We are trying to find out about your level of physical activity from ***the last 7 days*** (in the last week). This includes activities that make you sweat, make your legs feel tired, or make you breathe hard, such as team sports, running, strenuous occupational activities, and others.

Remember:
There are no right and wrong answers — this is not a test.
Please answer all the questions as honestly and accurately as you can — this is very important.

Physical activity in your spare time: Have you done any of the following activities **in the past 7 days** (last week)? If yes, how many times? (Mark only one circle per row.)

	No	1-2	3-4	5-6	7 times or more
Rock climbing	❍	❍	❍	❍	❍
Rowing/canoeing	❍	❍	❍	❍	❍
Tennis/squash	❍	❍	❍	❍	❍
Stair climber (or other similar equipment)	❍	❍	❍	❍	❍
Walking for exercise	❍	❍	❍	❍	❍
Heavy yard work	❍	❍	❍	❍	❍
Jogging or running	❍	❍	❍	❍	❍
Bicycling	❍	❍	❍	❍	❍
Aerobics (or other exercise class)	❍	❍	❍	❍	❍
Swimming	❍	❍	❍	❍	❍
Baseball, softball	❍	❍	❍	❍	❍
Dance	❍	❍	❍	❍	❍
Football	❍	❍	❍	❍	❍
Badminton	❍	❍	❍	❍	❍
Soccer	❍	❍	❍	❍	❍
Street/floor hockey	❍	❍	❍	❍	❍
Volleyball	❍	❍	❍	❍	❍
Basketball	❍	❍	❍	❍	❍
Skating (in-line/ice)	❍	❍	❍	❍	❍
Cross-country skiing	❍	❍	❍	❍	❍
Ice hockey/ringette	❍	❍	❍	❍	❍
Martial arts	❍	❍	❍	❍	❍
Weight training	❍	❍	❍	❍	❍
Other: _____	❍	❍	❍	❍	❍
_____	❍	❍	❍	❍	❍

In the last 7 days, *during the morning*, how often were you very active (for example: playing sports, exercise classes, strenuous occupational activity, strenuous household or child rearing tasks)? (Check one only.)

None..... ❍
1 time last week..... ❍
2 or 3 times last week..... ❍
4 or 5 times last week..... ❍
6 or 7 times last week..... ❍

In the last 7 days, *after lunch and before supper*, how often were you very active (for example: playing sports, exercise classes, strenuous occupational activity, strenuous household or child rearing tasks)? (Check one only.)

None..... ❍
1 time last week ..... ❍
2 or 3 times last week ..... ❍
4 or 5 times last week..... ❍
6 or 7 times last week..... ❍

In the last 7 days, *during the evening*, how often were you very active (for example: playing sports, exercise classes, strenuous occupational activity, strenuous household or child rearing tasks)? (Check one only.)

None ..... ❍
1 time last week ..... ❍
2 or 3 times last week ..... ❍
4 or 5 last week..... ❍
6 or 7 times last week ..... ❍

On the last weekend, how often were you very active (for example: playing sports, exercise classes, strenuous occupational activity, strenuous household or child rearing tasks)? (Check one only.)

None ..... ❍
1 time..... ❍
2 — 3 times..... ❍
4 — 5 times..... ❍
6 or more times..... ❍

6. Which *one* of the following describes you best for the **last 7 days**? Read *all five* statements before deciding on the *one* answer that describes you.

All or most of my free time was spent doing things that involve little physical effort ❍

I sometimes (1 — 2 times last week) did physical things in my free time (e.g. played sports, went running, swimming, bike riding, did aerobics) ❍

I often (3 — 4 times last week) did physical things in my free time ❍

I quite often (5 — 6 times last week) did physical things in my free time ❍

I very often (7 or more times last week) did physical things in my free time. ❍

8. Mark how often you did physical activity (for example: playing sports, exercise classes, strenuous occupational activity).

	None	Little bit	Medium	Often	Very often
Monday	❍	❍	❍	❍	❍
Tuesday	❍	❍	❍	❍	❍
Wednesday	❍	❍	❍	❍	❍
Thursday	❍	❍	❍	❍	❍
Friday	❍	❍	❍	❍	❍
Saturday	❍	❍	❍	❍	❍
Sunday	❍	❍	❍	❍	❍

Were you sick last week, or did anything prevent you from doing your normal physical activities? (Check one.)

Yes ❍
No ❍

If Yes, what prevented you? _____

APPENDIX L: 24 HOUR DIETARY RECALL

University of Saskatchewan
24 Hour Recall Questionnaire

Please list every food and drink you had yesterday

Time	Food Items	Type & Preparation	Amount	Brand Name or Where Bought
Morning				
Mid-morning				
Noon Meal				
Midday				
Evening Meal				
Before Bed				

Was this intake usual? Circle one: Yes / No If no, explain why not:

_____

Any supplements/natural health products? Circle one: Yes / No If yes, list names:

_____

APPENDIX M: CDC AUTHORIZATION TO USE

RE: CDC-INFO: Inquiry [ref:_00DU0YCBU._500t09IKTG:ref]

DELETE REPLY REPLY ALL FORWARD ...

Mark as unread

CDC INFO <cdcinfo@cdc.gov>
Tue 2018-02-27 10:05 AM

To: Barbour-Tuck, Erin;

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Number of charts/graphs/tables/figures	3
The requesting person/organization	University of Saskatchewan
Title or numeric reference of the portion(s)	Chapter 3, figure 3.6, Chapter 5, figure 5.2; Chapter 5 figure 5.3
Title of the article or chapter the portion is from	Somatic Growth;Body composition
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