MODIFIABLE CARDIOVASCULAR RISK FACTORS AND CAROTID INTIMA-MEDIA THICKNESS IN CHILDREN AND YOUTH WITH OBESITY

EVALUATING THE RELATIONSHIPS BETWEEN CARDIOVASCULAR RISK FACTORS AND CAROTID INTIMA-MEDIA THICKNESS OVER TIME IN CHILDREN AND YOUTH WITH OBESITY ENROLLED IN A WEIGHT MANAGEMENT PROGRAM

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TITLE: Evaluating the relationships between cardiovascular risk factors and carotid intima-media thickness over time in children and youth with obesity enrolled in a weight management program

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LAY ABSTRACT

Approximately one third of Canadian children and youth have been classified as having overweight or obesity, and these individuals have an increased risk of developing cardiovascular disease and atherosclerosis, the narrowing of arteries, in adulthood. The measurement of intima and media layer thickness in the carotid artery wall (cIMT) is a dependable marker of atherosclerosis. However, relationships between cardiovascular risk factors and change in cIMT, over time, are not well studied in children and youth with obesity. This study evaluates relationships between change in cIMT, over time, and risk factors such as body composition, cholesterol, blood pressure and blood glucose in this population. Ultrasound scans were conducted to measure cIMT, and fasting blood samples were collected to detect cardiovascular risk factor levels. The findings of this study inform us on how cIMT progresses in children and youth with obesity and identify the factors that predict change in cIMT over time.

ABSTRACT

INTRODUCTION: The high prevalence of obesity in Canadian children and youth predicts an increased burden of cardiometabolic disease across the life course. Carotid intima-media thickness (cIMT) is a surrogate marker of ATH and detects subclinical arterial wall abnormalities. However, relationships between modifiable cardiovascular risk factors (CVRFs) and cIMT progression in children and youth with obesity, remain understudied.

PURPOSE: The study objective was to characterize cIMT progression and to identify CVRFs associated with baseline cIMT and change in cIMT, over time.

HYPOTHESIS: It is hypothesized that measures of adiposity, BP, glycemia and lipid profile will be related to cIMT progression in children and youth with obesity and that cIMT progression will vary across carotid segments.

METHODS: This longitudinal study included 125 children and youth with obesity (5-17y), enrolled in a Canadian Pediatric Weight Management Registry sub-study. B-mode ultrasonography was utilized to assess cIMT at baseline and 1-year follow-up. Measures of adiposity, BP, glycemia and lipid profile were acquired from clinical chart review. Potential relationships between CVRFs and cIMT progression were evaluated using univariable and multivariable regression.

RESULTS: Carotid IMT (mm) changed significantly ($p<0.001$) at the carotid bulb, common carotid artery (CCA) and internal carotid artery (ICA), from baseline to 1-year, and cIMT progressed more rapidly than reported in children with diabetes/FH. Furthermore, cIMT progression was greatest at the carotid bulb, followed by the CCA and

ICA. Baseline cIMT was positively related to SBP, TC/HDL-C, FPG and negatively related to HDL-C (corrected for age, sex, height). Change in cIMT at 1-year was positively related to BMI, non-HDL-C, TC/HDL-C and negatively related to HDL-C (corrected for age, sex, height, baseline cIMT).

CONCLUSIONS: In children and youth with obesity, IMT progression was greater at the carotid bulb than at the CCA and ICA. Measures of adiposity, BP, glycemia and lipid profile were related to baseline cIMT and cIMT progression.

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LIST OF ABBREVIATIONS

2-hr PG: two-hour plasma glucose

ATH: atherosclerosis

BF%: body fat percentage

BIA: bioelectric impedance analysis

BMI: body mass index

CCA: common carotid artery

cIMT: carotid intima-media thickness

CVD: cardiovascular disease

CVRF: cardiovascular risk factor

FH: familial hypercholesterolemia

FPG: fasting plasma glucose

FW: far wall of carotid artery

HbA1c: glycated hemoglobin

HDL-C: high-density lipoprotein cholesterol

HTN: hypertension

ICA: internal carotid artery

IDL-C: intermediate-density lipoprotein cholesterol

IFG: impaired fasting glucose

IGT: impaired glucose tolerance

LDL-C: low-density lipoprotein cholesterol

LVM: left ventricular mass

Non-HDL-C: non-high-density lipoprotein cholesterol

NW: near wall of carotid artery

OGTT: oral glucose tolerance test

OR: odds ratio

RR: relative risk

SDS: standard deviation scores

SMC: smooth muscle cell

T1DM: type one diabetes mellitus

T2DM: type two diabetes mellitus

TC: total cholesterol

TC/HDL-C: total cholesterol-to-HDL cholesterol ratio

TG: triglycerides

VLDL-C: very-low density lipoprotein cholesterol

WC: waist circumference

WHtR: waist circumference to height ratio

WHO: World Health Organization

CHAPTER 1. LITERATURE REVIEW

Relevance of Obesity

The rise in prevalence of childhood obesity is a critical public health issue worldwide (NCD-RisC, 2016) with approximately 42 million children classified as having overweight or obesity in 2013, a number projected to reach 70 million children by 2025 if present obesity rates persist (WHO, 2015). In Canada, obesity rates in children and adolescents have tripled within the past few decades (PHAC 2013; Shields, 2005). In recent years, data from the Canadian Community Health Survey (2004-2005) and Canadian Health Measures Survey (2009-2011, 2012-2013) has suggested that obesity prevalence rates have reached a plateau in Canadian children between the ages of 3 to 19 (Rodd and Sharma, 2016). However, although estimates of prevalence have demonstrated a stabilization during the period of 2004-2013 (Bancej et al., 2015), studies suggest that more data is required to determine if the plateau observed is trending towards a decline (Roberts et al., 2012; Bancej et al., 2015). Nevertheless, estimates of the prevalence of severe obesity remain high in children and adults (Ogden et al., 2014; Roberts et al., 2012; Ogden et al., 2012; Skinner et al., 2014; Twells et al., 2014). Adding to this concern is the high risk of childhood obesity persisting into adulthood, as reported by Freedman and colleagues (2001), where 77% of children with obesity were shown to have obesity as adults. If current trends continue, it is postulated that up to 70% of Canadian adults over 40 years of age will have either overweight or obesity by 2040 (Le Petit et al., 2005). Individuals with obesity are at increased risk of developing severe conditions, including: cardiovascular disease (Zalesin et al., 2008), type 2 diabetes mellitus (Smith et al., 2007), cancer (Danaei et al., 2005) and

depression (Morrison et al., 2014). Consequently, the annual direct healthcare costs of obesity and associated comorbidities are approximated to be $7.1 billion (Twells et al., 2014), with the estimated national economic burden, attributable to excess weight, amounting to $18.7 billion (Krueger et al., 2015). The significant morbidity and increased risk of mortality associated with obesity, introduce numerous challenges for the management and treatment of obesity (American College of Cardiology, 2014).

Implications of Childhood Obesity

Obesity is often viewed solely as the product of a persistent imbalance between caloric intake and caloric expenditure. However, environmental factors, behavioural factors (Delamater et al., 2013), genetics and socioeconomic status (Allison et al., 1999) can all contribute to the development of obesity. The potential ramifications of childhood obesity are extensive and may include psychosocial conditions such as diminished self-esteem, negative self-image, high-risk behaviours, depression and a decline in quality of life (Keating et al., 2011; Williams et al, 2011; Gopinath et al., 2013). Children and youth with obesity may exhibit one or more metabolic comorbidities, including: dyslipidemia (Berenson et al., 1998), elevated blood pressure (Daniels et al., 2005) and impaired glucose tolerance (IGT) (Invitti et al., 2003). In a Centers for Disease Control and Prevention (CDC)/ National Health and Nutrition Examination Survey (NHANES) (1999-2006) study, of children and youth ages 12-19y (n=3,125) (May et al., 2010), 42.9% of those with obesity had an abnormal lipid value, in comparison to 14.2% and 22.3% of those with normal weight and overweight, respectively. The prevalence of prehypertension and

hypertension in youth (ages 11-17y) with overweight or obesity (n=6,790) is estimated to be between 23-30% (McNiece et al., 2007); prevalence increases with elevations in body mass index (BMI) and abdominal adiposity (Din-Dzietham et al., 2007). Impaired glucose tolerance is highly prevalent (25%) in youth with obesity (ages 11-18y), from a multi-ethnic cohort (Sinha et al., 2002). The elevated prevalence of obesity related comorbidities in children and youth results in a heightened risk for development of cardiometabolic disorders in adulthood (Pulgaron et al., 2013).

Current Treatment of Childhood Obesity

In Canada, the predominant approach presently applied to address and treat obesity in the pediatric population, involves weight management programs focused on family-oriented behaviour modification (Lau et al., 2007). Most of these weight management programs are situated in a hospital environment and differ in program length and follow-up frequency (Newton et al, 2007). Ball and colleagues (2011) reported that the family-centered approach has been adopted by a majority of weight management programs in Canada and these programs include a multidisciplinary team of health care professionals that assist children and youth with obesity in making improvements to several aspects of their lifestyle. Behaviour modification, including dietary and lifestyle modifications, involves counselling from registered dieticians and exercise health professionals (Whitlock et al., 2010; Ball et al., 2011). Janicke and colleagues (2014) reported a moderate decline in BMI z-scores (-0.47 BMI SDS) of children and youth with obesity enrolled in such programs. However, the present guidelines in place for identifying the pediatric patients with obesity, that

require pharmacotherapy in addition to behavioural modification, for addressing cardiovascular disease (CVD) risk factors, are lacking (Whitlock et al., 2010). Thus, further investigation in high-risk pediatric populations is required to facilitate appropriate treatment of childhood obesity with related comorbidities.

Ramifications of Childhood Obesity in Adulthood

Childhood obesity and associated conditions lead to an elevated risk of morbidity and mortality in adulthood, due to an increased risk of developing CVD, hypertension and type 2 diabetes mellitus (T2DM) (Freedman et al., 2001; Juhola et al., 2011; Tirosh et al., 2011). Several studies have demonstrated the substantial influence of elevated childhood BMI on adult cardiometabolic health (Raj et al., 2010; Owen et al., 2009; Haji et al., 2006; Lawlore et al., 2010). In a Norwegian study, conducted by Bjorge and colleagues (2008), 227,000 individuals were followed from adolescence (ages 14-19y) to death. Males and females in the highest BMI category ($\geq 85^{th}$ percentile) in adolescence were 2.9 times (RR=2.9, 95% CI: 2.3-3.6) and 3.7 times (RR=3.7, 95% CI: 2.3-5.7), respectively, more likely to die due to ischemic heart disease in adulthood, compared to the reference BMI category (25^{th}-74^{th} percentile) (Bjorge et al., 2008). An Israeli study (n=37,674) reported a 12.0% (HR: 1.12, 95% CI: 1.07-1.18) increase in the risk of coronary heart disease and a 9.8% (HR: 1.10, 95% CI: 1.08-1.12) increased risk of diabetes, for each unit increase in adolescent BMI (kg/m^2) (Tirosh et al., 2011). Furthermore, a longitudinal cohort study by Morrison and colleagues (2007) demonstrated that the presence of metabolic syndrome in adolescents predicts a 14.7-fold greater risk of a CV event by age 50 (OR: 14.7, $p<0.0001$). Findings

from the aforementioned studies demonstrate that increased adiposity in childhood and adolescence is associated with the presence of various cardiometabolic risk factors and consequently, atherosclerotic CVD processes may be intensified in children with obesity. Thus, it is crucial to appropriately address childhood obesity to prevent CV health decline in the pediatric population with obesity, and subsequent mortality from CVD in adulthood.

Defining Cardiovascular Risk Factors in Children and Youth

Measures of Adiposity in Children and Youth

BMI is a widely accepted measure of adiposity in the pediatric population and is derived from the values of height and weight for an individual (Lau et al., 2007). In order to identify children and youth with overweight and obesity, BMI percentile distributions relative to age and sex, from the World Health Organization (WHO) growth charts for Canada, are recommended for the calculation of BMI z-score (de Onis et al., 2007). BMI measurements in the pediatric population have demonstrated associations with other measures of adiposity (Deurenberg et al., 1991; Roche et al., 1981) as well as with several cardiovascular risk factors (CVRFs) that may be present in children and adolescents (Chu et al., 1998). Although BMI is the recommended measure of adiposity, for the classification of overweight and obesity in the pediatric population, waist measures are better indicators of abdominal adiposity (Pouliot et al., 1994; Rankinen et al., 1999). Specifically, waist circumference and the waist circumference to height ratio (WHtR), calculated by waist circumference (in cm) divided by height (in cm), are suggested as measures of central adiposity and have been shown to predict the status of CVRFs in children and youth, to a

better degree than BMI on its own (Khoury et al., 2013). Children and youth with a higher WHtR displayed increased odds of having an abnormal lipid profile and elevated blood pressure (Khoury et al., 2013). Khoury and colleagues (2012) studied children between the ages of 14-15 years and reported a higher prevalence of CVRFs in children with a WHtR of ≥ 0.6 (Khoury et al., 2012), where 25% of the children had high levels of non-HDL-C and 17% displayed stage 1 or stage 2 hypertension. Finally, it is important to note that WHtR agrees with waist circumference (WC) in terms of the associations demonstrated with CVRFs, in both the normal weight pediatric population as well as the population with overweight or obesity (Lau et al., 2007; Khoury et al., 2013). Thus, waist circumference and WHtR may be used in conjunction with other measures of adiposity, to evaluate overall health status (Expert Panel., 2011; Khoury et al., 2013; Khoury et al., 2012).

A limitation of BMI is that it does not account for whether an increased body mass corresponds to elevations in fat mass, muscle mass or bone mass. Bioelectric impedance analysis (BIA), however, can differentiate between lean mass and fat mass and can estimate body fat percentage (Jaffrin et al., 2008; Talma et al., 2013; Kyle et al., 2015). Importantly, BF % has been shown to be associated with CVRFs in children and adolescents (Expert Panel, 2011). At elevated levels of BF %, specifically exceeding 20% fat in boys and 30% fat in girls, ages 6-18y, there is an increased prevalence of CVRFs (Going et al., 2011). Thus, BF % is suggested as an additional measure of adiposity along with BMI (Expert Panel, 2011), as it quantifies adipose tissue and improves overweight/obese classification of muscular/wide-framed children and youth (McCarthy et al., 2006).

Blood Pressure in Children and Youth with Obesity

High blood pressure (BP) is recognized as a significant risk factor for the development of cardiovascular disease in the pediatric population (Hao et al., 2017). In children and adolescents, the ranges of normal blood pressure differ in relation to age, height and sex (Lau et al., 2007). Thus, hypertension (HTN) is defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is greater than or equal to the 95th percentile for the age, height and sex of the child/adolescent (Lau et al., 2007)**.** In children and youth with obesity, the principal type of HTN observed is elevated SBP (Raitakari et al., 2003). The prevalence of elevated BP observed in clinic populations (in children and youth with obesity) ranges from 25-32% for high SBP and 4-17% for high DBP (Lau et al., 2007). Sorof and colleagues (2003) reported a relative risk of 3.26 for hypertension in children with obesity. Hao and colleagues (2016) found that BP trajectories from childhood to young adulthood demonstrated significant associations with atherosclerosis (ATH) risk in young adulthood. Similar findings were reported in numerous studies which found that higher BP values (≥95th percentile) in children and adolescents could predict an increased risk for ATH in adulthood (Hao et al., 2017; Berenson et al., 2002).

Dyslipidemia in Children and Youth with Obesity

The high prevalence of obesity in the pediatric population has contributed to an increased proportion of children and youth with dyslipidemia (Cook et al., 2003; Berenson et al., 1998; McGill et al., 2000a; McGill et al., 2000b). The pattern of dyslipidemia most commonly observed in children and youth with obesity involves the overproduction of

very-low-density lipoprotein cholesterol (VLDL-C), and presents as elevated total cholesterol (TC), triglycerides (TG) and LDL-C along with increased circulating small, dense LDL-C particles (Kwiterovich et al., 2008) and decreased high-density lipoprotein cholesterol (HDL-C) levels (Cortner et al., 1990; Boyd et al., 2005; Koenigsberg et al., 2006). This pattern of combined dyslipidemia, is present in 20 to 30 percent of children and youth with obesity (Gidding et al., 1995; Wattigney et al., 1991; Freedman et al., 2007; Sinaiko et al., 1999). In the NHANES data, elevated triglycerides (≥1.5 mmol/L) were present in 23.4% of all youth (12-19y); 33.5% of those with a BMI in the 85th to <95th BMI percentile and 51.8% of those with a BMI >95th percentile. Abnormally low HDL-C (<1.0 mmol/L) levels were reported in 23.3% of all youth (12-19y), 32.3% with BMI 85th to <95th BMI percentile, and 50% for youth with a BMI >95th percentile (Cook et al., 2003).

In addition to the aforementioned measures of lipid profile, levels of non-high-density lipoprotein cholesterol (Non-HDL-C) and total cholesterol-to-HDL ratio are also elevated in the dyslipidemic profile and abnormalities in these measures are also predictive of T2DM and CVD in adulthood (Morrison et al., 2007; Morrison et al., 2008). Non-HDL-C is a measure of all the cholesterol content present in the following atherogenic lipoprotein particles: very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL-C), low density lipoprotein (LDL-C) and lipoprotein[a] (Expert Panel, 2011). Despite the status of LDL-C as the most atherogenic lipoprotein, studies have demonstrated that lipoproteins such as VLDL, that are rich in triglyceride (TG) content, also demonstrate an association with the development of CVD (Hokanson et al., 1996).

VLDL remnants and IDL-C have an increased cholesterol content in comparison to VLDL and are also considered to be atherogenic (Havel et al., 1994). When calculating LDL-C using the Friedewald equation: LDL-C (mmol/L) = (TC)-(HDL-C) -(TG)/2.2 (Havel et al., 1994), the atherogenic VLDL remnants are not accounted for, which ignores their effects on CVD risk (Havel et al., 1994). In the Bogalusa study (N=1,163) (Srinivasan et al., 2002) non-HDL-C independently predicted CVD better than LDL-C (Cui et al., 2001) in adults. From a longitudinal aspect, for children evaluated between the ages of 4-5 years and then followed-up 27 years later, the odds ratios (ORs) of having dyslipidemia as an adult were greater when based upon childhood measures of non-HDL-C (OR=4.49) in comparison to LDL-C (OR=3.46) (Expert Panel, 2011). Childhood levels of TC/HDL-C were predictive of coronary artery calcification and abnormal lipid profiles in adulthood (Juonala et al., 2008). Thus, non-HDL-C and TC/HDL-C, in children and youth, were shown to be associated with the development of subclinical ATH (Expert Panel, 2011) and appeared to be better predictors of dyslipidemia and CVD in adulthood than TC, LDL-C and HDL-C alone (Srinivasan et al., 2006).

Dyslipidemia in childhood and adolescence has been reported to be associated with the progression of atherosclerotic lesions (McMahan et al., 2005; McGill et al., 2000). In an autopsy study of 204 participants (mean age: 18y), the percent surface involvement of the coronary arteries with fatty streaks and fibrous plaques, was correlated with childhood levels of total cholesterol ($r=0.67$, $p<0.05$), LDL-C ($r=0.67$, $p<0.05$) and VLDL-C ($r=0.41$,

$p<0.05$) (Berenson et al., 1998), suggesting a significant association between childhood dyslipidemia and atherosclerosis.

Dysglycemia in Children and Youth with Obesity

A diagnosis of prediabetes in the pediatric population allows for the identification of children and adolescents with an increased risk of developing type 2 diabetes mellitus (T2DM) as well as CVD (Lau et al., 2007; Styne et al., 2017). Prediabetes may be characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and/or elevated glycated hemoglobin (HbA1c) (Harper et al., 2013). Youth with overweight or obesity had a 2.6-fold higher prevalence of IFG and IGT in comparison to youth with a normal weight (Li et al., 2009) and up to 21% of children and youth with obesity develop IGT, suggesting that dysglycemia is common in the pediatric population with obesity (Morrison et al., 2012).

Importantly, prediabetes has been reported to be associated with an elevated risk of CVD, in several studies (DeFronzo et al., 2011). A 2016 systemic review of 53 prospective cohort studies (n=1,611,339) in adults (Huang et al., 2016), showed associations between prediabetes and the risk of CV events, coronary heart disease and stroke. Specifically, individuals with IFG had an overall 13% increased risk of CV events in comparison to those with normal fasting glucose (RR: 1.13, 95% CI: 1.05 to 1.21); individuals with IGT had a 30% increased risk of CV events than those with normal glucose tolerance (RR: 1.30, 95% CI: 1.19 to 1.42); and individuals with an elevated HbA1c had an overall 21%

increased risk of CV events compared to those with normal glycated hemoglobin (RR: 1.21, 95% CI: 1.01 to 1.44) (Huang et al., 2016). These findings highlight the importance of prevention, screening and treatment of dysglycemia, earlier on, in children and youth with obesity.

Routine screening for T2DM is suggested for children and adolescents within a high-risk population, such as those with obesity. The guidelines released by the Canadian Diabetes Association (CDA) as well as those from the American Diabetes Association (ADA), suggest that routine testing be completed for T2DM from the age of 10 years (Expert Panel, 2011). The CDA and ADA recommend that children and adolescents are screened with fasting plasma glucose (FPG), as it has demonstrated high sensitivity for detecting diabetes in the adult population (Forouhi et al., 2006). The classification criteria for impaired fasting glucose used by the ADA (2010) is between 5.6-6.9 mmol/L whereas the CDA (2018) (Punthakee et al., 2018) defines IFG as between 6.1-6.9 mmol/L. Although the use of HbA1c on its own is not recommended by the CDA for the diagnosis of diabetes in children and adolescents, due to its discordance with oral glucose tolerance tests (OGTT) and FPG tests, long-term data on HbA1c elevation in adults has suggested that the measure is a better predictor of CV events than FPG itself (Joshu et al., 2012). The prediabetes criteria based on HbA1c levels, are defined by the ADA (2010) as 5.7-6.4% and by the CDA (2018) (Punthakee et al., 2018) as 6.0-6.4%. It is also important to note the limitations that pertain to the use of FPG as a measure of dysglycemia. In a study of children and adolescents with obesity, 68% of prediabetes diagnoses were missed when relying solely on IFG (Morrison

et al., 2012). On the other hand, OGTTs were used by < 36% of clinicians, due to the high variability between tests and the lack of validation of the OGTT in the pediatric population (Haemer et al., 2014, Canadian Diabetes Association, 2013). Despite the limitations of the OGTT, it is reported to display a higher sensitivity in the screening for dysglycemia in children and youth with obesity (Morrison et al., 2012) as well as a stronger association with cardiovascular health outcomes in adults, in comparison to FPG (Huang et al., 2016). Impaired glucose tolerance, assessed via an OGTT, is defined as glucose levels between 7.8-11.0 mmol/L (ADA, 2010; CDA, 2018).

Significance of Cardiovascular Disease

Over the past decade, early detection methods and management of CV risk factors have led to a reduction in the number of newly diagnosed cases of CVD in Canada, from 221,800 in 2000-2001 down to 158,000 newly diagnosed adults in 2012-2013 (PHAC, 2013). However, despite the decline in new cases of CVD, approximately 2.4 million Canadian adults are living with diagnosed ischemic (or coronary) heart disease (PHAC, 2013). CVD is the second most prevalent cause of death in Canadians, with approximately 29% of all deaths resulting from it (Statistics Canada, 2011; PHAC, 2009). Not surprisingly, the financial costs associated with heart disease exceed $21.2 billion per year, making CVD the costliest disease in Canada (Tarride et al., 2009). The aforementioned statistics are disturbing, given that, 8 out of 10 first heart attacks are preventable through application of lifestyle changes, including routine physical activity and a healthier diet (PHAC, 2009). However, currently, 2 out of 3 adolescents (12-19 years) and 9 out of 10 adults (20+ years)

are living with at least one risk factor for CVD (PHAC, 2009). Although there is a decline in CVD risk factors like smoking and cholesterol, Canada is seeing an overwhelming prevalence of overweight and obesity, as well as T2DM, suggesting an increased risk for the development of ATH and CVD (Dai et al., 2009).

Atherosclerosis Progression

Atherosclerosis involves the development of structural abnormalities in the arterial wall, which include damage to the endothelial layer as well as arterial wall thickening, that commences in the early stages of life (Ross et al., 1993). Leukocyte adhesion and buildup, at the endothelial cell layer of an artery, marks the onset of the atherosclerosis process (Majesky, 2007). Following adhesion, leukocytes and LDL migrate into the sub-endothelial area and the monocytes differentiate into macrophages, instigating a pro-inflammatory state which results in consecutive immune responses, ultimately leading to the formation of an intermediate fatty streak lesion (Bland et al., 1986; Majesky, 2007). During lesion maturation to an atheroma, as smooth muscle cells (SMCs) migrate towards the intima layer and multiply (Majesky, 2007), the media layer increases in thickness. After a duration of time, the increased thickening of the arterial wall can begin to expand outwards into the lumen, thus narrowing its diameter and posing as an impediment to blood flow (Bland et al., 1986) (see **Figure 1**).

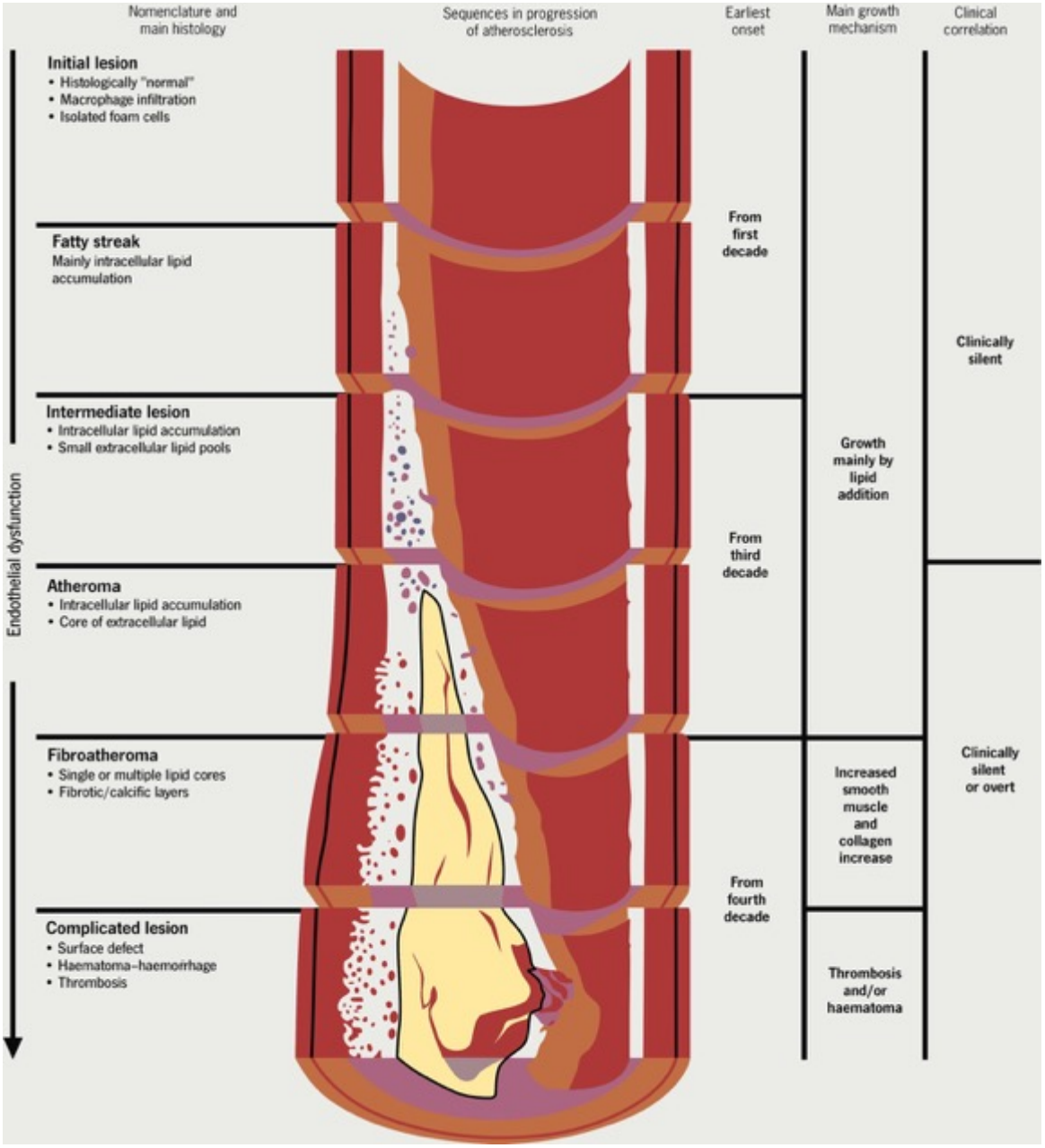


Figure 1. Progression of Atherosclerosis. Atherosclerosis involves the development of structural abnormalities in the arterial wall, which can occur from the first decade of life. These changes are often clinically silent and involve insults to the endothelial layer as well as increased thickness of the arterial wall. Moving into the third decade of life, these structural abnormalities can progress to lesions in the arterial wall and finally, atheroma formation. This may progress to a complicated lesion, leading to a blockage in arterial blood flow. This image has been adapted from the British Journal of Cardiology (2017).

Atherosclerosis in Children and Youth

Although atherosclerosis usually presents clinically in adulthood, the process begins in the early phases of life, during childhood or adolescence. Several pathology studies have reported detecting subclinical atherosclerosis as early as infancy or even the fetal stage (Matturri et al., 2003; Stary et al., 2000). Matturri and colleagues (2003) reported subclinical alterations in the intima layer of coronary arteries, in autopsies of human fetuses of smoking mothers. Stary and colleagues (2000) conducted autopsy studies and found lipid accumulation in the aortas of human fetuses. Foam cell accumulation is present in approximately 70% of adolescents and this progresses to a preatheroma or atheroma stage in 15% of youth between 16 and 19 years of age (Stary et al., 2000). The increased risk of premature atherosclerosis progression in children and youth with obesity may result in elevated CVD risk in adulthood, if not managed appropriately.

Non-Invasive Measurement of Vascular Changes

Atherosclerosis progresses gradually, beginning in childhood, and manifests itself clinically at the time of a cardiovascular event (Peters et al., 2012). The arterial wall is the site of atherosclerosis development and although it progresses silently, subclinical ATH may be estimated via several methods of non-invasive imaging (Mukherjee et al., 2002; Widlansky et al., 2003; London et al., 2002). The arterial wall is comprised of the intima, media and adventitia layers, with the intima being adjacent to the lumen of the artery (Landmesser et al., 2004). Specifically, the intima layer, consists of a single layer of endothelial cells and participates in the maintenance of vessel tone (Ross et al., 1993). The

intimal surface is susceptible to insults by action of several risk factors and this damage may trigger endothelial dysfunction (Slyper et al., 2004). Endothelial dysfunction may result in: morphological changes, which involve arterial wall thickening; mechanical changes, which involve arterial stiffness; and physiological changes, which present as a reduced ability to respond to shear stress (Groner et al., 2006). Ultrasound is a reproducible, safe and reliable choice for imaging of the aforementioned changes related to ATH (Peters et al., 2013), where measures that may be used, include: intima-media thickness (IMT), to assess arterial wall thickening; pulse wave velocity, to assess arterial stiffness; and flow-mediated dilation, to assess shear-stress response (Groner et al., 2006). Carotid IMT (cIMT) is a widely-accepted surrogate marker of subclinical atherosclerosis (Peters et al., 2013) and current evidence, on the utility of cIMT for the study for CVD risk, is presented in the succeeding sections.

Carotid Intima-Media Thickness in Adults

Increase in carotid intima-media thickness (cIMT) can indicate subclinical arterial wall structural abnormalities in pediatric and adult populations (Menezes et al., 2016). Carotid IMT is a validated measure for evaluating CVD risk in adults (Stein et al., 2008; Peters et al., 2013). In the Carotid Atherosclerosis Progression Study (CAPS), cIMT predicted cardiovascular events in adults without known cardiovascular disease (ages 19-90, n=5,056), where participants in the highest quartile of cIMT (≥0.98 mm) had a 1.85-fold increased risk of a myocardial infarction or stroke (Lorenz et al., 2006). The Atherosclerosis Risk in Communities Study (ARIC) reported a 6.7-fold increased risk of a

myocardial infarction and 2.9-fold increased risk of death by a CV event, in adults (ages 45-64, n=12,841) within the highest tertile of cIMT (Chambless et al., 1997). In the Bogalusa Heart Study, the following risk factors were significant determinants of cIMT in adults (ages 25-40y, n=1,203): SBP predicted common carotid artery (CCA) IMT (r^2=13.9%, p<0.002) and composite cIMT (inclusive of the CCA, carotid bulb and internal carotid artery (ICA) segments) (r^2=12.3%, p<0.002); TC/HDL-C predicted CCA IMT (r^2=3.8%, p<0.002) and composite cIMT (r^2=5.4%, p<0.002); and waist circumference predicted CCA cIMT (r^2=0.6%, p<0.002) (Tzou et al., 2007). Consistent with the findings of the Bogalusa Heart Study, the Muscatine Offspring Study reported that the significant correlates of composite cIMT, after adjustment for age, sex and height, in adults (ages 18-34, n=635) ,were: DBP (r=0.18, p<0.01), total cholesterol (r=0.20, p<0.01), and BMI (r=0.21, p<0.001) and 45.4% of cIMT variance was explained by age, sex, height, DBP, total cholesterol and BMI (Dawson et al., 2009).

Carotid Intima-Media Thickness in Children and Youth

Although cIMT is not routinely used as a clinical measure in children with obesity, it is an accepted non-invasive measurement of subclinical atherosclerosis in observational studies evaluating the risk factors associated with atherosclerosis (Menezes et al., 2016). Carotid IMT has been used as a prognostic tool in children and youth with chronic conditions, which expose them to a higher risk for development of atherosclerotic CVD in the future (Aggoun et al., 2000; Järvisalo et al., 2001; Sorof et al., 2003; Iannuzzi et al., 2006). Järvisalo and colleagues (2001) measured cIMT (mean age: 11 years, n=88) in children

with familial hypercholesterolemia (FH) (n=16/88) and children with type 1 diabetes mellitus (T1DM) (n=44/88), to determine the risk of ATH in children with chronic conditions, in comparison to healthy controls (n=28/88). Both children with FH and children with T1DM had significantly higher ($p<0.001$) cIMT values than the healthy controls (Järvisalo et al., 2001). Importantly, the risk factors reported to be significantly associated with cIMT, in children with FH, included: age, male sex, LDL-C (far wall (FW): CCA, carotid bulb, ICA) (Wiegman et al., 2015) and TC/HDL-C (FW CCA) (Khalifah et al., 2014). LDL-C ($r^2=16.0\%$, $p<0.001$) was also significant associated with cIMT (FW: CCA, carotid bulb, ICA) in children with T1DM (Wiegman et al., 2004).

In addition, several studies have reported a higher cIMT in children with obesity, in comparison to normal weight control groups (Friedemann et al., 2012 and Casariu et al., 2011). Park and colleagues (2015) conducted a review of 19 cross-sectional studies in adolescents, where 13 out of 19 studies reported a significant positive association between several measures of adiposity (waist circumference, body fat %, BMI z-scores) and cIMT. Six out of these thirteen studies demonstrated an increased cIMT in adolescents with overweight or obesity in comparison to normal weight adolescents (Park et al., 2015). Lamotte and colleagues (2011) conducted a review of 26 cross-sectional studies in children and adolescents with obesity and 22 out of 26 studies reported a greater cIMT in children and adolescents with obesity, in comparison to the control group of normal weight children. Previous studies have linked an elevated cIMT in children and youth with obesity, to the

presence of modifiable CV risk factors, including: elevated blood pressure (Elkiran et al., 2013), dysglycemia (Beauloye et al., 2007) and lipid profile (de Giorgis et al., 2014).

Predictors of cIMT in Children and Youth with Obesity

Most studies evaluating potential predictors of cIMT in children and youth with an elevated BMI, included individuals classified as having normal weight, overweight or obesity, whereas, only a handful of studies have focused solely on children and youth with obesity (Toledo-Corral et al., 2011). Given that cIMT physiologically increases over time, studies have suggested that age and height are significant predictors of cIMT in children and youth with obesity (Toledo-Corral et al., 2011). Specifically, Ciccone and colleagues (2016) reported that age explains 9.5% of variation in cIMT (FW CCA) (r^2=0.095, p=0.045), whereas other studies have reported that age accounts for nearly 17% of variation in cIMT (Park et al., 2015).

Children and youth with obesity display elevated adipose tissue content and thus, assessment of measures of adiposity, including: **BMI, waist circumference and body fat %,** are considered important in evaluating the CVD risk in this population (Goran et al., 1995). Melo and colleagues (2016) investigated the ability of BMI and waist circumference to predict cIMT (FW CCA) in children (n=349, ages 11-12) with normal weight (n=231) and overweight/obesity (n=118). An elevated BMI was related to a 2.56-fold increased risk of a greater cIMT (≥85th percentile) (FW CCA) (OR: 2.56, CI: 1.09 to 6.03, p<0.05), in comparison to those with a BMI within the normal weight range (Melo et al., 2016).

Furthermore, an elevated waist circumference was associated with a 3.24-fold increased risk of an elevated cIMT (≥85th percentile) (FW CCA) (OR: 3.24, CI: 1.59 to 6.58, $p<0.05$), in children and youth with obesity (Melo et al., 2016). Ryder and colleagues (2016) assessed youth with overweight or obesity (n=252, mean age: 15.1y) and found that body fat % was a significant determinant of cIMT (FW CCA) ($r^2=0.048$, $p<0.001$). Schiel and colleagues (2007) found that BMI z-score explained approximately 26% of variation in cIMT (FW CCA) ($r^2=0.263$, $p<0.001$) in children and youth with overweight or obesity (n=29, mean age: 13.6y), whereas Reinehr and colleagues (2006) reported that BMI was able to explain 5% of the variation in cIMT (FW CCA) ($r^2=0.05$, $p=0.013$) in children with obesity (n=96). These dissimilar findings may be attributable to differences in the sample sizes and age ranges of study participants. Nevertheless, Casariu and colleagues (2011) reported that BMI ($r=0.49$, $p<0.05$) and WC ($r=0.59$, $p<0.05$) were significantly associated with cIMT (FW CCA) in children and youth with obesity (n=50, age range: 6-18 y).

High **blood pressure (BP)** is also reported to be associated with increased cIMT, in several cross-sectional studies in children and youth with obesity (Pall et al., 2003; Urbina et al., 2011). Urbina and colleagues (2011) studied the effects of hypertension (HTN) on cIMT in youth and found that when participants were grouped into normotensive (n=531), pre-HTN (n=65) and HTN (n=127) categories, cIMT was increased in the pre-HTN group and significantly ($p<0.05$) higher in youth with HTN compared to normotensive participants. Importantly, multivariable regression analyses conducted by Urbina and colleagues (2011) demonstrated that BP was a significant ($r^2=0.022$, $p<0.0001$) independent predictor of

cIMT (FW: CCA, carotid bulb, ICA) in children and youth with obesity (n=234, age range: 10-23y). SBP was reported to explain a maximum of 21% of variation in cIMT (12-segment) in children and youth with obesity (n=136, age range: 10-24) (Urbina et al., 2009). Thus, BP is an important CV risk factor associated with cIMT in pediatric populations, however, the relationship between BP and cIMT progression, over time, has not been well explored in children and youth with obesity.

Another important CVRF associated with elevated cIMT, in the pediatric population with obesity, is dysglycemia. Reinehr and colleagues (2006) reported that **fasting plasma glucose** was a significant predictor of cIMT (FW CCA) (r^2=0.05, $p<0.05$) in children with obesity (n=96, age range: 9-13y), independent of age, sex, BMI, LDL-C, HDL-C, SBP and DBP. Additionally, in children with obesity (n=250, ages 10.7-11.4y), impaired fasting glucose (defined as FPG≥5.6 mmol/L) was associated with a 7.7-fold increased risk of an elevated cIMT (NW and FW CCA) (OR:7.77, $p<0.01$) in comparison to the normal weight controls (n=150) (Pacifico et al., 2010). Furthermore, Reinehr and colleagues (2013) reported that **impaired glucose tolerance** (IGT) was a significant ($p<0.05$) predictor of an increased cIMT (NW and FW CCA) in children and youth with overweight or obesity (n=254, age range: 7-16y), independent of age, sex and pubertal stage. Finally, Kotb and colleagues (2012) studied children with overweight and obesity (n=27, age range: 12-19) and reported that glycemic control (**HbA1c**) was significantly associated (r=0.6, $p<0.001$) with an increased cIMT (FW CCA). It is important to note, however, that relationships

between the measures of glycemia and cIMT progression in the pediatric population with obesity, without the presence of diabetes, have not been fully addressed.

The measures of (fasting) lipid profile in children and youth with obesity, are associated with cIMT (Sinaiko et al., 1999; Gidding et al., 2006). Each increase of 0.025 mmol/L in **LDL-C** was associated with a 3% increased risk of elevated cIMT (≥0.005 mm/y) (CCA FW) (OR:1.03, CI: 1.002-1.006, p=0.003) in Latino children and youth with overweight (Toledo-Corral et al., 2011). **TC/HDL-C** and **non-HDL cholesterol** have been reported to be associated with an elevated cIMT by several studies (Juonala et al., 2008; Li et al., 2003). However, the associations between measures of lipid profile and cIMT progression, have not been well assessed in the literature pertaining to children and youth with obesity. Thus, given that relationships between CVRFs and cIMT progression have not been well studied in the pediatric population with obesity (without the presence of genetic dyslipidemias and diabetes), it is necessary to evaluate the predictors of cIMT progression in this population.

Longitudinal cIMT Studies

Few studies have evaluated cIMT in children and youth with obesity, utilizing a longitudinal study design. Dalla Pozza and colleagues (2011) conducted a longitudinal study, of cIMT over 4 years, in children and adolescents (n=70) with type 1 diabetes mellitus (T1DM). In this study, cIMT (FW CCA) progressed 0.009 mm over the course of 4 years (0.0023 mm annually) and the cIMT z-scores (based on sex- and height- dependent normative values from literature) increased significantly over 4 years (0.58 ± 0.75, p <

0.001) along with BMI z-scores which also rose significantly (0.41 ± 0.81, $p < 0.01$) (Dalla Pozza et al., 2011). HbA1c (%) and SBP z-score at baseline were also predictors of change in cIMT (Dalla Pozza et al., 2011). Wiegman and colleagues (2004) studied children with familial hypercholesterolemia and reported an increase of 0.005 mm (0.0025 mm annually) in cIMT (12-segment), over the span of 2 years; in multivariable analyses, neither sex nor age influenced these results. A study by Toledo-Corral and colleagues (2011) investigated cIMT progression in 72 Latino adolescents with overweight, over the course of two years; 38/72 adolescents demonstrated an elevated cIMT (FW CCA), with a mean increase of 0.017± 0.003mm (0.0085 mm annually) over two years. Juonala and colleagues (2010) also studied cIMT progression, over 6 years in young adults (n=1,809), to determine the childhood risk factors associated with changes in cIMT and reported that childhood HDL/LDL cholesterol ratio was significantly positively associated with changes in cIMT (FW CCA) (-0.005 (CI: -0.009 to -0.001) mm, p=0.01). Children that demonstrated an increase in HDL/LDL cholesterol ratio and an improvement in obesity status between childhood and adulthood, displayed a slower rate of cIMT progression. These findings highlight the importance of introducing interventions that target lipids and obesity in childhood, so that ATH progression later in life may be slowed.

Although several studies have suggested an association between CV risk factors and cIMT in children with and youth with obesity (as reported in **Predictors of cIMT in Children and Youth with Obesity**), the majority are cross-sectional in nature and do not explore the progression of cIMT in the pediatric population with obesity, over time. Thus, longitudinal

studies evaluating change in cIMT over time, in children and youth with obesity, are required to identify those at greatest risk for ATH development.

Methodology of Carotid Intima-Media Thickness Measurement in Children

An increasing number of ultrasound protocol studies do offer evidence for an appropriate approach to designing and analyzing a cIMT study (Dogan et al., 2010; Dogan et al., 2011; Wikstrand et al., 2007). Current guidelines in adults and children (Mannheim Carotid IMT and Plaque Consensus) (Touboul et al., 2012; Urbina et al., 2009), suggest that imaging of the carotid artery should be conducted with the participant lying in a supine position; the neck of the participant should be extended, and the head rotated 45 degrees, towards the opposite direction of the side being scanned; scans should be initiated with a transverse scan of the carotid artery, allowing for the identification of critical landmarks in the vessel. Secondly, it is suggested that a circumferential longitudinal scan should be conducted to distinguish the pre-defined carotid segments, by holding the transducer perpendicular to the vessel (Peters et al., 2012; Dogan et al., 2011; Touboul et al., 2012; Urbina et al., 2009). The three segments of the carotid artery that should be examined are the: common carotid artery (CCA), internal carotid artery (ICA) and carotid bulb, measuring 10 mm of each section (see **Appendix Figure 2**). Thus, a total of 12 segments should be used to calculate mean cIMT, as the 3 pre-defined arterial sections should be measured for the near and far walls of both the left and right carotid arteries. The arterial segments measured should be delineated in relation to a replicable anatomical marker in the artery, called the carotid flow divider (Urbina et al., 2009; Morrison et al., 2010). Video recordings of a minimum 5

second duration should be obtained for offline analysis and a minimum of 3 measurements should be conducted per segment to determine cIMT (Morrison et al., 2010).

Arterial Segment Selection for cIMT Measurement

The measure of carotid intima-media thickness in pediatric studies is, however, heterogeneous in the carotid segments chosen, the carotid walls (near or far) and the reading methods utilized (Peters et al., 2012). One must consider this heterogeneity when reviewing the literature with the primary outcome measure as cIMT.

Several approaches have diverged from the "gold standard" described previously. While certain studies limit their scanning protocols to the far wall of the CCA alone (2-segment approach) (Stein et al., 2008), more comprehensive studies include the near and far wall of the carotid bulb, CCA and ICA measurements in their protocols (12-segment approach) (Iglesias del Sol et al., 2002). The predominant arguments presented for the selection of an ultrasound protocol limited to the CCA are based upon the high reproducibility and completeness of CCA cIMT data, in comparison to the cIMT data obtained from the ICA and carotid bulb. Indeed, reproducibility data produced by earlier cIMT studies demonstrated a reproducibility of ≥ 0.85 for the CCA and <0.75 for the carotid bulb and ICA (in adults) (Mack et al., 1993; Persson et al., 1992). Furthermore, the Rotterdam study (in adults), presented completeness rates of 97% for the CCA, 83% for the carotid bulb and 56% for the ICA (Iglesias del Sol et al., 2002).

However, in recent studies, substantial improvements in reproducibility and completeness rates for cIMT measurements of the three arterial segments are shown (Dogan et al., 2010). Measurement of the CCA, carotid bulb and ICA for both the far and near walls had an intraclass correlation coefficient (ICC) of 0.924 in adults (Dogan et al., 2011). Thus, the two cIMT measurements had highly similar reproducibility, attributable to improvements in cIMT measurement protocols (Dogan et al., 2010, Dogan et al., 2011), as well as progress in ultrasound technology, that allows for increased spatial and density resolution (Touboul et al., 2012). In terms of data completeness, Peters and colleagues (2012), reported that completeness rates for cIMT measurements inclusive of the CCA, ICA and carotid bulb were as high as 84% in adults with elevated CVD risk and as high as 94% in comparatively healthy adults. Difficulties that occur in obtaining ICA measurements are due to frequent branching of this segment at an angle (Nambi et al., 2012). In the Atherosclerosis Risk in Communities (ARIC) study, 51.4% of the ICA segments could not be imaged in comparison to just 9% of the CCA and carotid bulb segments (Nambi et al., 2012). Thus, ICA measurements for cIMT may be less reliable than the CCA and carotid bulb (Nambi et al., 2012). Reproducibility and completeness data for cIMT inclusive of the CCA, ICA and carotid bulb in children have not been well reported. Overall, concerns regarding decreased reproducibility and low data completeness for other carotid segments, should not form the sole basis for limiting cIMT measurement to the CCA; the importance of evaluating IMT at all carotid segments, especially at the carotid bulb, is highlighted by the literature presented below.

Dogan and colleagues (2011) evaluated the findings of fifteen lipid-modification trials in adults, that presented data on both CCA cIMT and mean cIMT inclusive of the CCA, carotid bulb and ICA, before and after treatment (Dogan et al., 2011). Their review of the placebo groups of these randomized controlled trials (RCTs) demonstrated that cIMT progression differed, over time, between the CCA, carotid bulb and ICA (Dogan et al., 2011, Espeland et al., 2003). Specifically, in 6 out of 8 placebo-controlled trials, absolute cIMT progression was greater in the carotid bulb in comparison to progression in the CCA cIMT and this difference was of statistical significance in 4 out of 6 trials. (Dogan et al., 2011). Therefore, as stated in the Mannheim cIMT and Plaque Consensus, cIMT progresses in a non-uniform manner across carotid arterial segments (Rosvall et al., 2015).

Due to the lack of knowledge surrounding cIMT progression and its predictors in children and youth, especially in the pediatric population with obesity (excluding those with genetic dyslipidemias and diabetes), studies conducted in adults have been the main points of reference when considering arterial segment selection. Tzou and colleagues (2007) assessed cIMT at the CCA, carotid bulb and ICA for 1203 young adults (mean age: 36y) participating in the Bogalusa Heart Study. Carotid bulb IMT was highest at baseline and also progressed most rapidly with age, in comparison to the CCA and ICA. Nguyen and colleagues (2011) assessed cIMT progression rates in young adults (n=842, age range: 24-43y) over an average of 2.4 years and observed that progression rates were significantly ($p<0.0001$) greater at the carotid bulb, followed by the CCA and ICA segments. These findings suggest that carotid bulb assessment may yield a greater sensitivity in detecting

subclinical ATH in young adults (Tzou et al., 2007, Nguyen et al., 2011; Urbina et al., 2002).

Consistent with the aforementioned findings, different correlates (CVRFs) are reported for different carotid segments, in adults (Urbina et al., 2002; Dogan et al., 2011). Urbina and colleagues (2002) assessed the relationships between CVRFs and cIMT at different carotid segments in young adults (n=518, mean age: 32 y) and reported that HDL-C and LDL-C were more closely related (adjusted for age, sex and race) to carotid bulb IMT than other segments: HDL-C: Bulb ($r= -0.18$, $p<0.001$), CCA ($r= -0.10$, $p<0.05$), ICA ($r= -0.01$, $p>0.05$); LDL-C: Bulb ($r=0.18$, $p<0.001$), CCA ($r=0.15$, $p<0.001$), ICA ($r=0.13$, $p<0.01$). LDL-C explained 1.06% of variance in carotid bulb IMT ($r^2=0.0106$, $p<0.05$), whereas LDL-C explained 0.66% variance in CCA IMT ($r^2=0.0066$, $p<0.05$), in young adults (n=3,023, mean age: 45y) participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study (Polak et al., 2010). These segment-specific differences in the associations between CVRFs and carotid IMT progression may be connected to different clinical outcomes (Dogan et al., 2011; Rosvall et al., 2015), however, remain understudied in the pediatric population with obesity.

Evaluation of near and far wall cIMT

The evaluation of cIMT using B-mode ultrasonography involves measuring cIMT on the far wall (FW) and/or near wall (NW) of carotid arterial segments (Morrison et al., 2010; Dogan et al., 2011). In vitro experiments have demonstrated that far wall cIMT is a reliable

measure of the true wall thickness of arterial segments, whereas near wall cIMT is a less accurate measure for the estimation of arterial wall thickness (Wikstrand et al., 2007; Liu et al., 2008; Pignoli et al., 1986). However, other studies have reported high reproducibility for near wall cIMT as well as nearly equal completeness rates for the near and far wall cIMT measurements (Dogan et al., 2010; Wildman et al., 2004; Peters et al., 2012; Furberg et al., 1994). The Muscatine study (in adults) presented the following completeness rates for the near and far wall cIMT: CCA NW = 98.9%, CCA FW =99.7%; carotid bulb NW = 92.7%, carotid bulb FW= 99.7%; ICA NW = 74.0%, ICA FW =88.0% (Davis et al., 2001). Hence, data completeness did not differ greatly between near wall and far wall cIMT measurements. Additionally, cIMT measurements inclusive of the near wall were utilized in the Asymptomatic Carotid Artery Progression Study (ACAPS) (in adults), with a high reproducibility of r=0.79 (Furberg et al., 1994). Dogan and colleagues (2011) reported that the combination of near and far wall cIMT was a better predictor of treatment effects on cIMT in adult clinical trials. Thus, although near wall cIMT alone is not an appropriate measure of arterial wall thickness, the combined near and far wall cIMT measurements show reduced random error, improved precision and a stronger association with cardiovascular risk than far wall cIMT alone (Poredos et al., 2004; Touboul et al., 2002).

Reading method and measurement of cIMT

Ultrasound images for cIMT measurement are analyzed using either manual edge detection or semi-automated edge detection programs. Semi-automated edge detection programs display decreased variability in cIMT measurement in comparison to manual edge

detection, as variability between readers may be avoided (Polak et al., 2011; Dalla Pozza et al., 2015). It is important to note, however, that a single reader whose reading style remains consistent over time is considered nearly equivalent to a semi-automated edge detection program, in terms of variability in cIMT measurement (Polak et al., 2011). While there is a chance of inaccurate tracing in manual edge detection, its use has been validated by several adult population studies in literature (Lonn et al., 2001; Riley et al., 1992). It is also recognized that semi-automated edge detection is more suitable for cIMT measurement restricted to the CCA and manual edge detection is more suitable in studies where the carotid bulb and ICA are measured in addition to the CCA (Bots et al., 2007; Kastelein et al., 2007).

Normative cIMT values in children and adolescents

Although considerable information is available regarding cIMT in the adult population, there is a paucity in the literature when it comes to longitudinal normative cIMT values in children and adolescents (Böhm et al., 2009). Cross-sectional normative values for children and adolescents were proposed by Doyon and colleagues (2013). Mean cIMT values were obtained from 1,055 healthy weight children and youth between 6-17 years of age from Germany, Sweden, Turkey and Poland (Doyon et al., 2013). The intra-class correlation between manual caliper and semi-automated measurement methods used in the study was reported to be r=0.83, whereas, the coefficient of variation reported in the reproducibility study for these methods (n=74) was 9.9% (Doyon et al., 2013). The inter-observer coefficient of variation was reported to be 7.3%, for two sonographers that independently

measured cIMT in 55 participant data sets (Doyon et al., 2013). This dataset allows for the calculation of cIMT-for-age and cIMT-for-height z-scores. However, a major drawback of these values is that only the far wall of the CCA (Doyon et al., 2013) was measured. Thus, if cIMT measurements are restricted to the far wall of the CCA, the effects of CVRFs on changes in arterial wall structure may not be detected (Dogan et al., 2010; Peters et al., 2012). Finally, as arterial wall thickness is not uniform across the carotid segments, restricting cIMT measurement to the far wall of the CCA is not advisable as it may result in a less representative measurement of any thickening occurring in the carotid artery (Touboul et al., 2012; Wunsch et al., 2006).

Summary. Considering the high prevalence of childhood obesity and the increased risk of CVD development in children and youth with an elevated BMI, it is important to understand their risk of ATH development by utilizing validated and non-invasive measures, so that appropriate prevention and treatment strategies may be implemented, if required. Several cross-sectional studies have evaluated the associations between CV risk factors and cIMT in the pediatric population and reported age, sex, SBP, measures of adiposity, measures of glycemia and lipid profile as significant correlates of cIMT. However, the relationships between CV risk factors and cIMT progression, over time, have not been well evaluated in the pediatric population with obesity (without the presence of genetic dyslipidemias and diabetes). The segment-specific differences in the associations between CVRFs and carotid IMT progression remain understudied in children and youth with obesity. Overall, the gap in knowledge surrounding cIMT progression, over time, in children and youth with obesity and the under-investigated area of differences in

associations between cIMT and CVRFs across carotid segments, make it difficult to understand what treatment strategies may be most efficacious in addressing ATH progression in this population. Thus, this project aimed to characterize cIMT progression in children and youth with obesity and to investigate the modifiable CV risk factors that may predict this change.

CHAPTER 2. PROJECT OBJECTIVES, RATIONALE AND HYPOTHESES

Project Objectives

Given the increased risk of future cardiovascular events, in children and youth with an elevated BMI (Morrison et al., 2007), and the high prevalence of childhood obesity (PHAC., 2012), it is imperative to investigate the modifiable CV risk factors that influence ATH progression in children and youth with obesity. Evaluation of the annualized rate of carotid IMT progression would allow for the recognition of any segment-specific differences in the degree of cIMT progression, in children and youth with obesity. Finally, identifying the CV risk factors that predict the progression of vascular structural changes, may assist clinicians in recognizing the treatment strategies most effective in slowing the progression of arterial thickening associated with ATH in this population.

Objective 1:

The central objective of this project was to evaluate the relationships between modifiable cardiovascular risk factors (BMI, WC, body fat %, SBP, DBP, TC, TG, HDL-C, LDL-C, TC/HDL-C, non-HDL-C, FPG, 2-hr PG, HbA1c) (CVRFs) and carotid arterial wall thickness, over time, in children and youth (ages 5-17y) with obesity. For this project, carotid intima-media thickness (cIMT) was used as a surrogate measure of subclinical arterial wall abnormalities and was selected as the outcome of interest. In order to explore the relationships between obesity, subclinical ATH and CVD risk in this pediatric population, the following research questions were assessed:

Research Questions:

1. What baseline CVRFs are correlates of cIMT in children and youth with obesity (ages 5-17y)?
    a) What baseline CVRFs are correlates of cIMT at baseline, while correcting for age, sex and height?
    b) What cardiovascular risk factors at baseline are independent predictors of cIMT in children and youth with obesity, 1 year after commencement of a weight management program, in multivariable models including significant variables of interest, after adjustment for age, sex, height and baseline cIMT as covariates?

Objective 2:

In order to characterize cIMT progression in children and youth with obesity, the second objective of this project was directed at determining the annualized rate of cIMT progression and comparing IMT progression rates across carotid segments. The following research questions were assessed to address this secondary objective:

Research Questions:

2. Is there a change in cIMT for children and youth with obesity, enrolled in a weight management program, 1 year after the program commences? 2 years? What is the annualized rate of change in cIMT?
3. Does cIMT progression vary across carotid segments in children and youth with obesity?

Exploratory Objective:

Changes in cardiovascular risk factor levels may affect cIMT progression rates and thus, the exploratory objective of this project revolved around evaluating the effects of changes in CVRF levels from baseline to 1-year follow-up on cIMT progression over 1-year, while controlling for age, sex, baseline cIMT and baseline CVRF value. The following research question addressed this exploratory objective:

Research Question:

4. What ***changes*** in cardiovascular risk factors are associated with cIMT progression over the course of 1 year, whilst controlling for age, sex, baseline cIMT and baseline CVRF value?

Study Rationale

The primary objective of this project was developed in order to examine the cardiovascular risk factors that may influence cIMT progression in children and youth with obesity. Currently, the literature concerning cIMT in the pediatric population, primarily consists of cross-sectional pediatric studies, which evaluate and compare cIMT measurements made at a single time point, between groups with an elevated BMI and normal-weight control groups (Toledo-Corral et al., 2011). The relationships between CV risk factors and cIMT progression, in children and youth with obesity, remain understudied. Thus, it is important to evaluate the CV risk factors that predict cIMT progression in this population, in order to expand the literature pertaining to longitudinal cIMT studies in the pediatric population with obesity and thereby, to identify children at greatest risk for ATH progression.

Segment-specific differences in cIMT progression have been reported by studies in adults and may be connected to different clinical outcomes but remain understudied in children and youth with obesity (Dogan et al., 2011; Rosvall et al., 2015). Thus, the second objective of this project is to evaluate the changes in cIMT across carotid segments and determine whether segment-specific differences are displayed in this population.

Study Hypotheses

It is hypothesized that measures of adiposity, blood pressure, glycemia and lipid profile will be related to the progression of cIMT over 1 year, and that these CV risk factors will be significant predictors of cIMT in children and youth with obesity, as suggested in previous cross-sectional studies (Casariu et al., 2011; Beauloye et al., 2007), but not well explored in longitudinal studies. It is also hypothesized that mean carotid IMT (mm) will increase annually, at all assessed carotid segments and progression will be greater at the carotid bulb in comparison to other carotid segments. Due to the limited number of studies assessing IMT progression across carotid segments in the pediatric population, our hypothesis that cIMT will vary across carotid segments, is based on previous reports in studies of young adults (Tzou et al., 2007; Urbina et al., 2002). Finally, based on observations from adult studies, it is hypothesized that correlates and predictors of cIMT will vary across carotid segments, in children and youth with obesity (Urbina et al., 2003; Tzou et al., 2007).

CHAPTER 3. METHODOLOGY

Canadian Pediatric Weight Management Registry (CANPWR Study)

The Canadian Pediatric Weight Management Registry (CANPWR) is a multi-center study involving a prospective cohort of children and youth between the ages of 2-17 years, with a BMI greater than or equal to the 85th percentile at the time of entry to a weight management program. This study aims to evaluate the factors that influence the progression of health indicators in children and youth in weight management programs across Canada and to elucidate the determinants of change in anthropometrics and obesity related conditions (Morrison et al., 2014). CANPWR has 10 participating clinic sites across Canada that include 5 sites in Ontario, 2 sites in Quebec, 1 site in British Columbia and 2 sites in Alberta. A sub-study of the CANPWR main study at McMaster was introduced in 2014, to look at ATH in children with obesity. The primary outcome measure of this sub-study is carotid intima-media thickness (cIMT). Children and youth in the CANPWR main study and sub-study are followed over a 3-year period, with follow-ups at: 6 months, 12 months, 24 months and 36 months from the baseline visit (see **Appendix Figure 1**); sub-study participants have cIMT measured at baseline and annually, up to 3 years.

Study Design and Population

The study for this MSc thesis was a longitudinal observational study of children and youth with overweight/obesity, ages 5-17 years, and newly enrolled in the Growing Healthy Weight Management Program at the Children's Exercise and Nutrition Centre (CENC) situated at McMaster's Children's Hospital. Children and youth provided assent and their

parents/guardians consented the CANPWR Main study and cIMT sub-study at the time of enrollment into the CENC. As part of the CANPWR protocol, eligible participants were first asked about their interest in learning about the CANPWR study through a consent-to-contact procedure with an impartial health professional, prior to any communication with the patient. Participants were allotted an identification number when enrolled, which served to keep their identity confidential. All participant information was kept in a secure location and maintained confidential; any participant identifiable information was secured in a locked cabinet, separate from study data. Exclusion criteria applied to children and youth under the age of 5 years or those with clinically diagnosed familial hypercholesterolemia and/or diabetes, at time of entry into the weight management program. The primary method of data collection for project data, was a review of participant clinical charts and CANPWR study/cIMT sub-study baseline and follow-up questionnaires (see **Appendix Table 1**). Baseline cIMT was measured within 4 weeks of the date of consent and enrolment in CANPWR. One-year follow-up cIMT was measured within a 1 year ± 6-month window (in reference to the baseline date).

Primary Outcome Measures

The primary outcome measure of this project is carotid intima-media thickness (cIMT), specifically:

1. Carotid bulb far wall IMT (mm): calculated with the far wall of the carotid bulb of the left and right carotid arteries.
2. Mean carotid bulb IMT (mm): calculated with the near and far wall of the carotid bulb of the left and right carotid arteries.

The secondary outcome measures include:

1. CCA far wall IMT (2-segment cIMT) (mm): calculated with the far wall of the CCA for the left and right carotid arteries.
2. Mean CCA IMT (mm): calculated with the near and far wall of the CCA for the left and right carotid arteries.
3. ICA far wall IMT (mm): calculated with the far wall of the ICA of the left and right carotid arteries.
4. Mean ICA IMT (mm): calculated with the near and far wall of the ICA for the left and right carotid arteries.
5. 12-segment mean cIMT: calculated with the near and far wall of the carotid bulb, CCA and ICA for the left and right carotid arteries (only calculated for participants with measurements available for all segments outlined here).

Carotid Intima Media Thickness: Ultrasound and Measurement Protocol

Quantitative B-mode ultrasonography was utilized to measure cIMT on both the left and right carotid arteries and scans were conducted using 7.5-13 MHz linear array transducers (GE VIVID 7 imaging system) with Doppler potential by a senior sonographer with extensive training. Scans were initiated with a transverse scan of the carotid artery, which allowed for the identification of critical landmarks in the vessel. Then, a circumferential longitudinal scan was conducted to distinguish the 3 pre-defined carotid arterial segments, so that images of these sections may be captured for analyses (Peters et al., 2012; Dogan et al., 2011; Touboul et al., 2012; Urbina et al., 2009). The 3 segments of the carotid artery are the: common carotid artery (CCA), internal carotid artery (ICA) and carotid bulb, each section being 10 mm in length. The arterial segments measured, were delineated in relation to a replicable anatomical marker in the artery, called the carotid flow divider (Urbina et al., 2009; Morrison et al., 2010). The ICA is located proximally at 1 cm from the flow divider; the carotid bulb is located at the tip of the flow divider and extends distally by 1 cm; the common carotid artery is located 1 cm distal from the flow divider and extends distally for 1 cm (Morrison et al., 2010; Dogan et al., 2010) (see **Appendix Figure 2**).

At least 3 video recordings of a minimum 5 second duration or the approximate length of a cardiac cycle, were obtained. A minimum of 3 measurements were taken for each segment and the average mean cIMT was then calculated. The cIMT ultrasound scans were conducted with electrocardiography gating, which involved capturing images of the arterial segments at the point where the electrocardiogram (ECG) displayed the tip of the R-wave.

Manual edge detection was utilized to obtain measurements of cIMT and cross hairs were placed at intervals of 0.5 mm on each segment of the carotid artery (10 mm in length)

Primary Exposures of Interest

The exposures of interest examined for their relationship with cIMT included: measures of adiposity, blood pressure, lipid profile and glycemia.

The extent of adiposity was determined based on: body mass index (BMI) (kg/m^2), BMI z-score (age and sex specific), waist circumference (cm) (WC), waist circumference to height ratio and body fat percentage (%). Height (cm) and weight (kg) were obtained using the Harpenden Stadiometer (London, UK) and an Inbody Body Composition Analyzer scale (California, USA), respectively, and were used to calculate **BMI** (kg/m^2) (Melo et al., 2016). **BMI z-score** (Schiel et al., 2007) was then calculated from age- and sex-specific WHO (2006) growth charts for Canada (de Onis et al., 2007). **Waist circumference (cm)** (Casariu et al., 2011) was measured using a measuring tape (with light clothing on), mid-way between the lower rib and iliac crest (Fernández et al., 2004). **Waist circumference to height ratio** (Khoury et al., 2013) was determined by dividing waist circumference (cm) by height (cm). An Inbody Body Composition Analyzer scale (California, USA) was utilized to determine **body fat %** (Ryder et al., 2016), through bioelectrical impedance analysis (BIA), using impedance values of a minor electrical current, as it moves through the water in the body. In order to estimate BF %, the BIA technique assumes that approximately 73% of fat-free mass is comprised of body water and thus, is a good

electrical conductor, whereas fat mass is a poor conductor given its minimal water content (de Castro et al., 2017; Lee et al., 2008; Armando et al., 2009).

Systolic blood pressure (SBP) and **diastolic blood pressure (DBP)** (Urbina et al., 2011; Urbina et al., 2009) were measured using the automated Oscillometric BPTru device (British Columbia, Canada), by taking 6 consecutive measurements over a 10-minute time period (at rest), on the day of the cIMT ultrasound scan. Blood pressure values were classified as abnormal if SBP or DBP was greater than or equal to the 95th percentile for age, sex and height (Falkner et al., 2004).

Participants fasted overnight (no food or beverage except for water; minimum 8-hour fast) for blood draws, to obtain fasting laboratory measures. The traditional measures of lipid profile, including: **total cholesterol (TC)** (Gidding et al., 2006)**, triglycerides (TG)** (Expert Panel, 2011)**, low-density lipoprotein cholesterol (LDL-C)** (Toledo-Corral et al., 2011) and **high-density lipoprotein cholesterol (HDL-C)** (Expert Panel, 2011), were obtained from clinical chart review at baseline and 1-year follow-up. TC, TG and HDL-C were all measured using Roche analyzer and LDL-C was determined using the Friedewald formula (Morrison et al., 2010). **Non-HDL-cholesterol** and **TC/HDL ratio** (Juonala et al., 2008; Li et al., 2003) were derived from traditional measures of lipid profile, to allow for a more comprehensive measure of atherogenic lipoprotein particles. Non-HDL-C is calculated by subtracting the value of HDL-C from total cholesterol (TC), once they are measured in the fasting plasma sample of an individual (Expert Panel, 2011). TC/HDL-C

is obtained by dividing total cholesterol by HDL-C. Lipid values were deemed abnormal if they met the criteria outlined by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in children and adolescents (2011) (Expert Panel, 2011).

Measures of glycemia examined, included: **fasting plasma glucose (FPG)** (Reinehr et al., 2006; Pacifico et al., 2010)**, 2-hour plasma glucose (2-hr PG)** (Reinehr et al., 2013) and **glycated hemoglobin (HbA1c)** (Kotb et al., 2012). 2-hr PG was determined after the administration of a 75g oral glucose tolerance test (OGTT). FPG and 2-hr PG were measured using Roche analyzer (Morrison et al., 2010). Values of measures of glycemia were deemed abnormal if they met the criteria outlined by the American Diabetes Association (ADA) 2010 guidelines (ADA, 2010).

Covariates

Participant **age**, **sex** and **height** (for baseline and 1-year follow-up analyses) and **baseline cIMT** (for 1-year follow-up analyses only) were included as covariates, to allow for adjustment for potential confounding effects in the multivariable linear regression analyses. Previous studies have shown age, sex and height to be independent predictors of cIMT in the pediatric population with obesity (Alpsoy et al., 2013; Urbina et al., 2009).

Statistical Analyses

Data collected for the CANPWR Main Study and cIMT sub-study was entered into iDataFax, a web-based application stored at the Population Health Research Institute (Hamilton, Ontario). Continuous variables are reported as mean ± standard deviations and categorical variables are reported as percentages. Descriptive statistics were reported for baseline and 1-year follow-up. Variables were tested for normality, using the Kolmogorov-Smirnov test. Residuals were normally distributed, as assessed by visual inspection of a normal probability plot. Linearity was established by visual inspection of scatterplots. To determine changes in participant CVRFs and cIMT measures over the course of 1 year; paired samples t-tests were conducted to analyze the differences between participant characteristics at baseline versus at 1-year follow-up. One-sample t-tests were conducted to determine if the differences in cIMT progression, between different cIMT measures, were significantly different from zero.

In order to evaluate the relationships between modifiable CVRFs at baseline and cIMT at baseline and 1-year follow-up, in children and youth with obesity, univariable linear regression analyses were conducted. Variables that demonstrated clinical significance ($p<0.1$) from the univariable linear regression analyses were included in the multivariable linear regression analyses. Partial correlation analyses were also conducted, to evaluate the relationships between modifiable CVRFs at baseline and cIMT at baseline and 1-year follow-up, while correcting for age, sex and height (at baseline) and age, sex, height (baseline values) and baseline cIMT (at 1-year follow-up). The multivariable regression

models included significant variables of interest, along with covariates, for the purpose of identifying independent predictors (baseline exposures) of cIMT ($p<0.05$) measured at baseline and one-year follow-up. The exposures of interest included: measures of adiposity (BMI, body fat %, WC), SBP and DBP, measures of glycemia (FPG, 2-hr PG, HbA1c (%)) and measures of lipid profile (TC, TG, HDL-C, LDL-C, non-HDL-C, TC/HDL-C). The covariates were: age, sex, height (for baseline and 1-year follow-up analyses) and baseline cIMT (for 1-year follow-up analyses only). Multicollinearity was assessed using the variance inflation factor (VIF), which assesses the extent to which the variance of an estimated regression coefficient increases if variables are correlated (Vatcheva et al., 2016). Any variables with a VIF>10 were removed from the multivariable linear regression model (Vatcheva et al., 2016). SPSS Statistics 23 (Armonk, NY, USA) and GraphPad Prism 7 (La Jolla, California, USA) were utilized to perform all analyses and a significance level of $p=0.05$ was used.

In order to address the exploratory objective (see **Review of Project Objectives**), changes in measures of: adiposity, blood pressure, lipid profile and glycemia, between baseline and 1-year follow-up, were assessed for their associations with cIMT progression over the course of 1 year. The changes in aforementioned CVRFs, from baseline to 1-year follow-up, were organized into 3 tertiles and were defined as follows: middle tertile (1/3 of all participants: closest to no change at follow-up), lower tertile (1/3 of all participants: closest to decreased value at follow-up) or upper tertile (1/3 of all participants: closest to elevated value at follow-up) (Rosvall et al., 2015). The 'similar' category, or middle tertile, was

used as the reference point for risk factor change. Linear regression models were utilized to assess associations between changes in CVRFs and cIMT progression (over 1-year), while adjusting for age, sex, baseline cIMT and baseline CVRF value.

Statistical Power Analyses

The primary research question aimed to determine the predictors of cIMT in children and youth with obesity, at baseline and one year after commencing a weight management program. A multivariable model consisting of 8 variables for baseline cIMT and 9 variables for cIMT over 1-year (including exposures and covariates) was utilized to predict the required follow-up for this project, on the basis of power estimates (see **Appendix, page 90**). The covariates included age, sex, height (for baseline and 1-year follow-up analyses) and baseline cIMT (for 1-year follow up analyses). The candidate variables included: BMI, body fat %, WC, SBP, DBP, FPG, 2-hr PG, HbA1c, TC, TG, HDL-C, LDL-C, non-HDL-C and TC/HDL-C, where the selection of specific variables for multivariable regression analyses would be based on the results of correlation analyses (variables with a significance of $p<0.1$) and the evidence supporting each variable. For baseline cIMT analyses, a sample size of 95 participants was calculated, by Quazi Ibrahim (CANPWR statistical analyst), as sufficient to explain a minimum of 15% of total cIMT variation. This calculation was based on a multivariable model (8 variables) with 80% power ($\beta=0.80$), while accounting for 15% missing values, at 95% confidence ($\alpha=0.05$). For 1-year follow-up cIMT analyses, a sample size of 110 participants was calculated as sufficient to explain a minimum of 15% total cIMT variation. This calculation was based on a multivariable model (9 variables) with

80% power (β=0.80), while accounting for 15% missing values, at 95% confidence (α=0.05) (see **Appendix, page 90**).

CHAPTER 4: RESULTS

CANPWR Study and cIMT Sub-Study Recruitment flow.

From the outset of the Canadian Pediatric Weight Management Registry (CANPWR) study recruitment in December 2013, to the completion of study recruitment in October 2017, 420 participants were recruited at McMaster Children's Hospital out of the total of 1335 participants recruited across Canada. Recruitment for the CANPWR cIMT sub-study commenced in October 2014 and 210 participants were enrolled into the cIMT sub-study by recruitment completion. Thereby, 68% of eligible participants enrolled in the CANPWR Main study from October 2014 onwards, were enrolled into the cIMT sub-study (see **Figure 2**). In terms of the longitudinal aspect of the cIMT sub-study, 1-year follow-ups commenced in October 2015 and 2-year follow-ups began in November 2016. The number of visits that were completed, missed or in-window for 1-year and 2-year follow-ups are outlined in **Figure 2**.

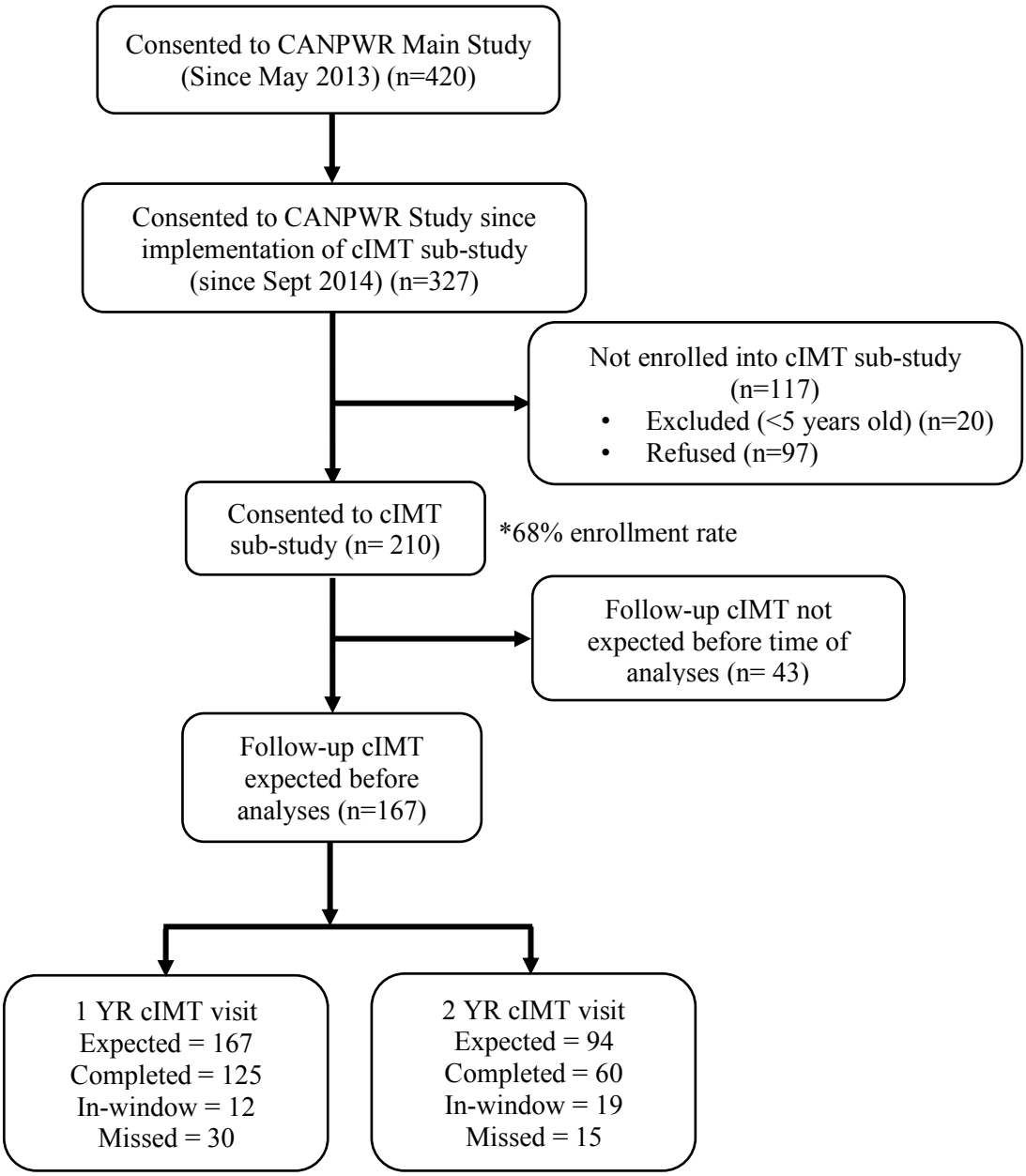


Figure 2. CANPWR Study and cIMT Sub-Study Recruitment and Follow-Up Flow Chart at Time of Analyses. From the outset of CANPWR recruitment in December 2013, 420 participants were consented into the CANPWR Main study. Since the start of sub-study recruitment in October 2014, 307 participants out of the 327 participants enrolled in the CANPWR Main study were eligible for participation in the cIMT sub-study. Out of these 307 participants, 210 participants were consented into the cIMT sub-study, resulting in a 68% recruitment rate.

Participant Characteristics

Participant Demographics

A total of 125 participants (of 167 expected) have completed at least 1 year of follow-up (see **Figure 2)**. Baseline descriptives were evaluated for the attendees (n=125) and non-attendees (n=42) for 1-year follow-up cIMT scans (see **Appendix Table 2**). Mean values of participant characteristics were not significantly different between attendee versus non-attendee baseline data. Carotid IMT was available for 125 participants at baseline and 1-year follow-up (see **Table 2)** and 60 participants at 2-year follow-up (see **Appendix Table 3**). Participant characteristics are presented in **Table 1: Participant Characteristics at Baseline and 1-year Follow-up**. The 125 (43.2% male) participants with baseline and 1-year cIMT measures were ages 12.6 ± 2.90y at baseline and 13.6 ± 2.92y at 1-year follow-up and 80.0% (n=100) were Caucasian. The mean BMI z-score for participants was 3.3 ± 1.01 at baseline and 3.4 ± 1.21 at 1-year follow-up. As per the WHO 2006 cut-offs (de Onis et al., 2007), 5.7% (n=7) of participants were classified with overweight, 34.7% (n=43) of participants were classified with obesity and 59.6% (n=74) were classified with severe obesity for their specific age and sex, at baseline. At 1-year follow-up, 6.7% (n=8) of participants were classified with overweight, 35.0% (n=42) were classified with obesity and 58.3% (n=70) were classified with severe obesity for their specific age and sex.

Changes in Participant Cardiovascular Risk Factors from Baseline to 1-Year Follow-Up

Participant cardiovascular risk factors, at both baseline and 1-year follow-up, are summarized in **Table 1.** Participant BMI increased by 1.51 kg/m^2 from baseline to 1-year follow-up (32.70±6.28 vs. 34.40±7.94, p<0.001), however BMI z-score did not change significantly (3.33±1.01 vs. 3.36±1.21, p=0.763). Waist circumference increased by 6.61 cm from baseline to 1-year follow-up (96.10±15.25 vs. 102.71±16.14cm, p=0.006), however waist circumference-to-height ratio did not change significantly (0.62±0.07 vs. 0.63±0.09, p=0.436), as waist circumference and BMI increase with age. Body fat %, also, did not change from baseline to 1-year follow-up (43.62±7.16 vs. 42.88±7.95%, p=0.664). SBP increased by 1.15 mmHg (1.05% increase) from baseline to 1-year follow up (110.09±11.64 vs. 111.24±11.11, p<0.001), but there were no significant changes in DBP, SBP percentile for age-sex-height and DBP percentile for age-sex-height. TC levels decreased by 0.15 mmol/L (4.20±0.63 vs. 4.05±0.72, p=0.003) and HDL-C decreased by 0.06 mmol/L (1.14±0.21 vs. 1.08±0.21, p<0.001) from baseline to 1-year follow-up, however non-HDL-C and TC/HDL-C ratio did not change significantly. TG values and LDL-C values did not change significantly from baseline to 1-year follow-up. HbA1c increased by 0.05% from baseline to 1-year follow-up (5.26±0.35 vs. 5.31±0.45, p<0.05), however FPG and 2-hr PG did not change significantly. In summary, the CVRFs that changed significantly from baseline to 1-year follow-up, included: BMI, WC, SBP, HbA1c (all increased over 1 year), TC and HDL-C (both decreased over 1 year), whereas, BMI z-score, WHtR, BF %, DBP, SBP/DBP percentiles for age-sex-height, TG, LDL-C,

TC/HDL-C, non-HDL-C, FPG and 2-hr PG did not change significantly, over 1 year (see **Table 1**).

Prevalence of Abnormalities in CVRFs

The prevalence of abnormalities in CVRFs, at baseline and 1-year follow-up, are depicted in **Figure 3** (only participants that were assessed at both baseline and 1-year follow-up were included in these analyses, to maintain comparability). Abnormal values of at least one laboratory measure were identified for 55.2% (n=69) of participants at baseline and 42.4% (n=53) of participants at 1-year follow-up. Abnormal TG and HDL-C levels were observed for approximately 20% of participants assessed at both baseline and 1-year follow-up, as expected in a population with overweight/obesity. Abnormal TGs (≥1.5 mmol/L) were observed in 20.0% (n=25) of study participants at baseline and at 1-year follow-up. Abnormal HDL-C levels (<1.0 mmol/L) were reported in 16.0% (n=20) and 17.6% (n=22) of participants at baseline and 1-year follow-up, respectively. Abnormally elevated levels of non-HDL-C (≥3.8 mmol/L) were reported for 8.0% (n=10) of participants at baseline and 8.8% (n=11) of participants at 1-year follow-up. Abnormal TC/HDL-C ratio (≥5.0) values were observed in 4.0% (n=5) and 6.4% (n=8) participants at baseline and 1-year follow-up, respectively.

Importantly, there were significant decreases in the prevalence of abnormal levels of glycemia and blood pressure, from baseline to 1-year follow-up (*$p<0.05$ by McNemar's test). Abnormal measures of glycemia (IFG (≥5.6 mmol/L), IGT (≥7.8 mmol/L), elevated

HbA1c levels (≥ 5.7%)) were reported in 10.4% (n=13) and 5.6% (n=7) of participants at baseline and 1-year follow-up, respectively. From the 13 participants with abnormal measures of glycemia at baseline, 2 participants were being treated to address their prediabetes; this may have contributed, partially, to the decrease in prevalence of abnormalities in measures of glycemia. Abnormal SBP and DBP (≥95th percentile for age, sex and height) were observed in 11.2% (n=14) of participants at baseline and 4.0% (n=5) of participants at 1-year follow-up. From the 14 participants with abnormal measures of blood pressure at baseline, 1 participant was on anti-hypertensive medications to address their elevated blood pressure; this may have contributed, partially, to the decrease in prevalence of abnormal blood pressure. It is also important to consider the proportion of missing data: 1.6% and 3.2% missing for BP at baseline and 1-year, respectively; 9.6% and 30.4% missing for measures of lipid profile and glycemia at baseline and 1-year, respectively. Furthermore, data were missing more often at follow-up, for participants with a baseline CVRF value within a normal range, as opposed to those with an abnormal CVRF value at baseline.

Table 1: Participant Characteristics at Baseline and 1-Year Follow-up

Variable		Baseline				1-YR F/UP				
	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max	Change from BL to 1-YR F/UP	p-value
Participant Demographics										
Age(y)	125	12.61 (2.90)	12.58	5.42, 17.92	125	13.56 (2.92)	13.50	6.42, 18.92	0.95	**<0.001**
Sex: Male (%)	125	54 (43.20%)	-	-	125	54 (43.20%)	-	-	-	-
Race: Caucasian (%)	125	100 (80.00%)	-	-	125	100 (80.00%)	-	-	-	-
Weight (kg)	124	81.90 (26.14)	78.70	34.30, 152.50	120	91.17 (28.48)	86.20	32.80, 169.30	9.27	**<0.001**
Height (m)	124	156.33 (14.77)	158.20	120.30, 193.00	120	161.42 (13.60)	162.50	127.70, 195.00	5.09	**<0.001**
BMI (kg/m^2)	124	32.70 (6.28)	31.93	20.97, 52.38	120	34.40 (7.94)	33.14	17.97, 61.69	1.70	**<0.001**
BMI z-score	124	3.33 (1.01)	3.32	1.49, 9.00	120	3.36 (1.21)	3.15	0.84, 9.24	0.03	0.763
Waist circumference (cm)	81	96.10 (15.25)	94.20	59.50, 131.00	51	102.71 (16.14)	102.50	74.00, 133.50	6.61	**0.006**
Waist circumference to Height Ratio	81	0.62 (0.07)	0.62	0.41, 0.83	51	0.63 (0.09)	0.64	0.42, 0.79	0.01	0.436
Body Fat (%)	107	43.62 (7.16)	43.80	23.60, 56.70	98	42.88 (7.95)	43.90	15.60, 56.50	-0.74	0.664

Participant Cardiovascular Risk Factors	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max	Change from BL to 1-YR F/UP	p-value
Systolic BP (mmHg)	123	110.09 (11.64)	109.00	83.00, 145.00	121	111.24 (11.11)	110.80	80.50, 144.00	1.15	**<0.001**
Diastolic BP (mmHg)	123	69.23 (9.31)	68.20	51.20, 104.33	121	69.09 (8.86)	68.60	48.60, 96.25	-0.14	0.089
SBP Percentile	122	52 (27)	51	4, 100	116	52 (27)	51	1, 100	0.00	0.749
DBP Percentile	122	64 (23)	67	13, 100	116	62 (22)	0.64	6, 100	-2	0.328
TC (mmol/L)	113	4.20 (0.63)	4.09	2.87, 5.78	87	4.05 (0.72)	4.03	2.71, 6.32	-0.15	**0.003**
HDL Cholesterol (mmol/L)	113	1.14 (0.21)	1.13	0.78, 1.64	87	1.08 (0.21)	1.07	0.61, 1.68	-0.06	**<0.001**
LDL Cholesterol (mmol/L)	113	2.50 (0.59)	2.48	1.23, 4.30	87	2.41 (0.64)	2.42	1.01, 4.52	-0.09	0.162
Triglycerides (mmol/L)	113	1.31 (0.68)	1.13	0.40, 5.09	88	1.30 (0.53)	1.22	0.45, 2.87	-0.01	0.077
Non-HDL-C (mmol/L)	113	3.06 (0.64)	2.96	1.85, 4.80	87	2.99 (0.71)	3.00	1.61, 5.58	-0.07	0.064
TC/HDL Ratio	113	3.77 (0.81)	3.72	2.13, 5.97	87	3.90 (0.99)	3.65	2.14, 8.54	0.13	0.377
Fasting Plasma Glucose (mmol/L)	113	4.77 (0.47)	4.70	4.00, 6.90	87	4.84 (0.83)	4.80	2.90, 11.40	0.07	0.299
2-hr Plasma Glucose (mmol/L)	59	5.92 (1.27)	5.70	2.60, 10.90	16	5.83 (1.75)	5.3	3.30, 9.00	-0.09	0.481
HbA1c (%)	102	5.26 (0.35)	5.25	4.60, 6.50	78	5.31 (0.45)	5.30	4.70, 8.50	0.05	**0.033**

All measures are reported as mean (standard deviation) unless otherwise stated. P values in boldface indicate significance ($p<0.05$).

Table 2: Participant Carotid IMT at Baseline and 1-Year Follow-up

Variable		Baseline			1-YR F/UP					
Participant cIMT Measures	**N**	**Mean (SD)**	**Median**	**Min, Max**	**N**	**Mean (SD)**	**Median**	**Min, Max**	**Change from BL to 1-YR F/UP**	**p-value**
Mean Far Wall Bulb cIMT (mm)	125	0.429 (0.039)	0.425	0.333, 0.585	123	0.448 (0.045)	0.441	0.368, 0.658	0.019	**<0.001**
Mean Near Wall Bulb cIMT (mm)	122	0.441 (0.044)	0.438	0.349, 0.563	120	0.464 (0.046)	0.457	0.374, 0.586	0.023	**<0.001**
Average Mean Bulb cIMT (mm)	122	0.435 (0.037)	0.433	0.349, 0.542	120	0.456 (0.039)	0.453	0.372, 0.570	0.021	**<0.001**
Mean Far Wall CCA cIMT (mm)	125	0.388 (0.033)	0.385	0.325, 0.490	124	0.398 (0.035)	0.396	0.327, 0.503	0.010	**<0.001**
Mean Near Wall CCA cIMT (mm)	125	0.408 (0.043)	0.398	0.337, 0.521	124	0.419 (0.047)	0.412	0.326, 0.556	0.011	**<0.001**
Average Mean CCA cIMT (mm)	125	0.398 (0.032)	0.390	0.338, 0.482	124	0.409 (0.035)	0.402	0.338, 0.507	0.011	**<0.001**
Mean Far Wall ICA cIMT (mm)	87	0.358 (0.033)	0.347	0.311, 0.508	83	0.362 (0.033)	0.352	0.324, 0.481	0.004	0.114
Mean Near Wall ICA cIMT (mm)	69	0.354 (0.031)	0.344	0.314, 0.496	63	0.362 (0.041)	0.348	0.310, 0.504	0.008	0.065
Average Mean ICA cIMT (mm)	69	0.356 (0.028)	0.350	0.315, 0.455	63	0.362 (0.033)	0.353	0.323, 0.467	0.006	**0.019**
Mean cIMT, 12-segments (mm)	69	0.400 (0.029)	0.397	0.359, 0.493	63	0.413 (0.034)	0.411	0.364, 0.505	0.013	**<0.001**
Mean cIMT, 2-segments (mm)	125	0.389 (0.033)	0.385	0.325, 0.490	124	0.398 (0.035)	0.396	0.327, 0.503	0.009	**<0.001**

Measures reported as mean (standard deviation) unless otherwise stated. P values in boldface indicate significance ($p<0.05$).

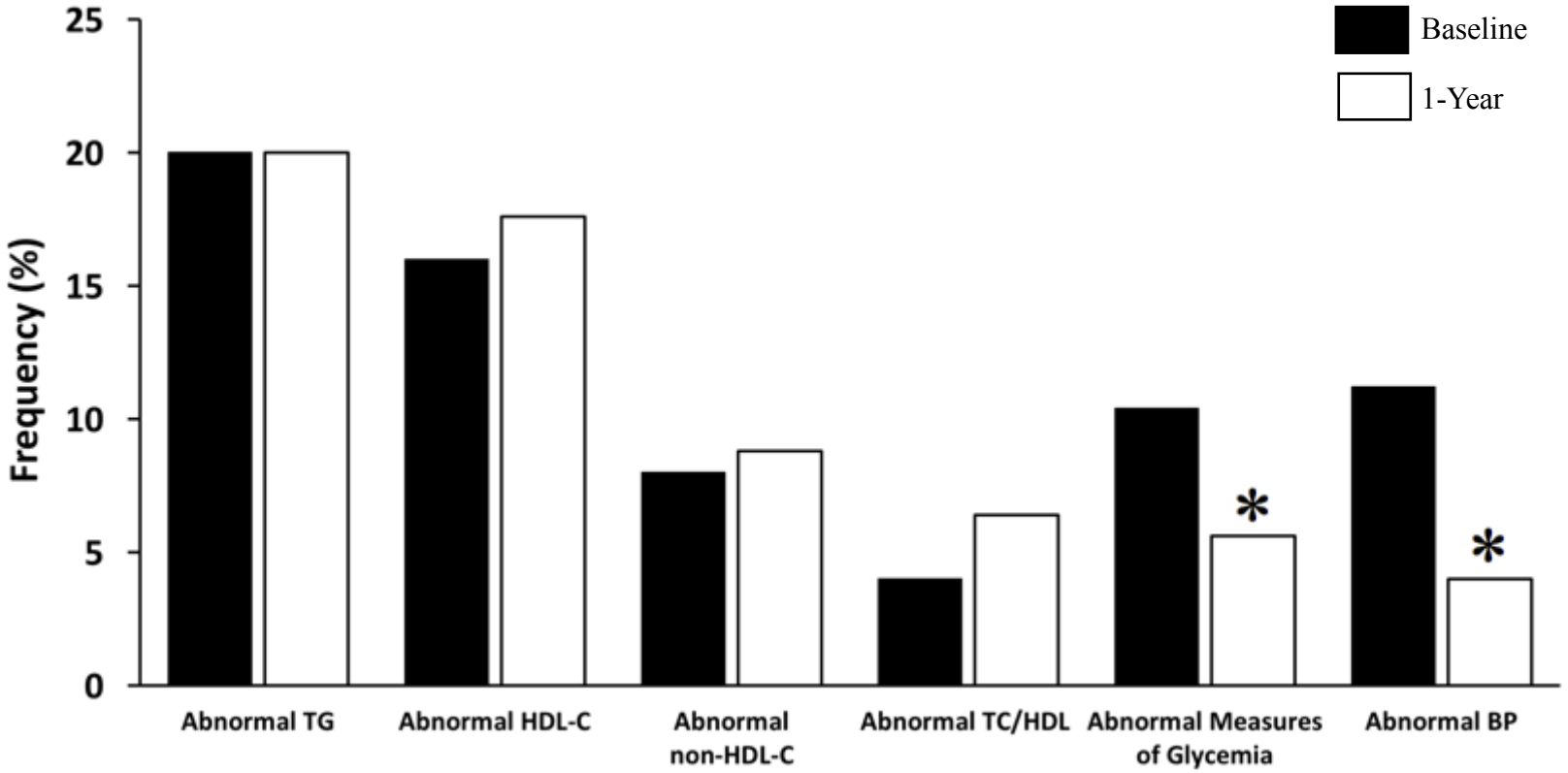


Figure 3. Prevalence of Abnormalities in CVRFs at Baseline and 1-year Follow-up. Assessment of abnormalities in cardiovascular risk factors was conducted on the basis of relevant pediatric guidelines (Falkner et al., 2004; Expert Panel, 2011; ADA, 2010). Criteria for abnormal values were: TG ≥1.5 mmol/L; HDL-C <1.0 mmol/L; Non-HDL ≥3.8 mmol/L; TC/HDL-C ratio ≥5.0; FPG ≥5.6 mmol/L; 2hrPG ≥7.8mmol/L; HbA1c ≥5.7%; SBP and DBP ≥95th percentile for age, sex and height. *p<0.05 by McNemar's test.

Carotid Intima-Media Thickness Measurements

Carotid intima-media thickness (cIMT) was measured at baseline for the 167 participants that were expected for 1-year follow-up, including both follow-up attendees and non-attendees (see **Appendix Table 2**). Mean baseline cIMT measurements were not significantly different between attendees and non-attendees at 1 year. The primary outcome of interest was carotid bulb IMT. Far wall carotid bulb IMT was available for 125 participants at baseline and 123 participants at 1-year follow-up (see **Table 2)**. Carotid bulb IMT inclusive of the near and far walls (mean carotid bulb IMT) was available for 122 participants at baseline and 120 participants at 1-year follow-up. Thus, near wall IMT was missing for 2.4% and 4.0% of participants at baseline and 1-year follow-up, respectively. Far wall common carotid artery (CCA) IMT (2-segment cIMT) and CCA cIMT inclusive of near and far walls (mean CCA IMT) was available for 125 and 124 participants at baseline and 1-year follow-up, respectively (near wall IMT missing for 0.8%). Internal carotid artery (ICA) far wall IMT was available for 87 participants at baseline and 83 participants at 1-year follow-up. ICA cIMT inclusive of near and far walls (mean ICA IMT) was available only for 69 and 63 participants at baseline and 1-year follow-up, respectively (near wall IMT missing for 20.7% of participants with ICA IMT available). Overall, data was missing for up to: 4% of carotid bulb IMT measures, 0.8% of CCA IMT measures and 50.4% of ICA IMT measures. Mean 12-segment cIMT (mm) was calculated for 69 participants at baseline and 63 participants at 1-year follow-up, restricted by the number of participants that had ICA cIMT measurements available.

Carotid bulb far wall IMT and mean carotid bulb IMT (near and far walls) increased significantly ($p<0.001$) by 0.019 mm (CI: 0.014, 0.024; $t(122) = 7.603$, $p<0.001$) and 0.021 mm (CI: 0.017, 0.026; $t(119) = 10.381$, $p<0.001$), respectively, from baseline to 1-year follow-up. CCA far wall IMT (2-segment) and mean CCA IMT, inclusive of near and far walls, also increased significantly by 0.010 mm (CI: 0.005, 0.013; $t(123) = 4.739$, $p<0.001$) and 0.011 mm (CI: 0.007, 0.013; $t(123) = 6.611$, $p<0.001$), respectively, from baseline to 1-year follow-up. ICA far wall IMT showed no significant increase from baseline to 1-year follow-up, whereas mean ICA IMT, inclusive of near and far walls, increased significantly by 0.006 mm (CI: 0.001, 0.011; $t(62)= 2.399$, $p=0.019$) from baseline to 1-year follow-up. Carotid IMT calculated with the 12-segment approach, increased significantly from baseline to 1-year follow-up, by 0.013 mm (CI: 0.008, 0.015; $t(62)= 6.969$, $p<0.001$) (see **Table 2**). Progression of cIMT from baseline to 2-year follow-up is presented in **Appendix Table 3**, for the 60 participants that completed 2-year cIMT scans at time of analyses. Annualized cIMT progression rates (mm/year) at 1-year are displayed in **Figure 4**. Carotid IMT progression for 1-year and 2-year follow-up are displayed and compared in **Appendix Figure 3**.

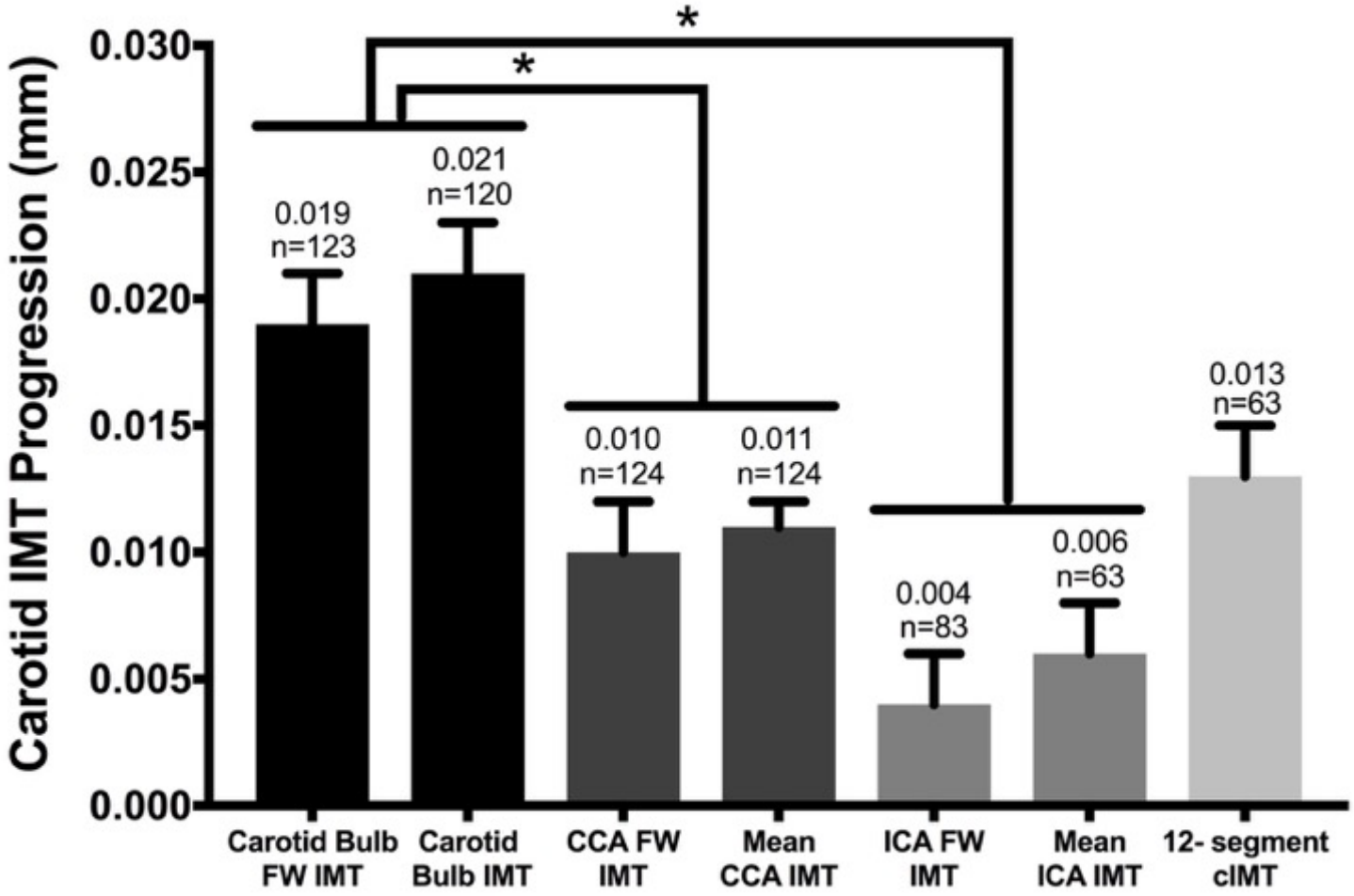


Figure 4. Carotid IMT progression from baseline to 1-year follow-up. Carotid IMT progression (mm) for cIMT measures from baseline to 1-year follow-up are presented, with cIMT progression being significantly greater at the carotid bulb, in comparison to the CCA and ICA (*$p<0.001$).

Correlation Analyses: Cardiovascular Risk Factors and cIMT

Potential correlates of cIMT measures at baseline and 1-year follow-up were evaluated using univariable linear regression analyses (see Appendix **Figures 4-5** and **Appendix Tables 4-5**). Variables were normally distributed, as assessed by the Kolmogorov-Smirnov test. Residuals were normally distributed, as assessed by visual inspection of a normal probability plot. Linearity was established by visual inspection of scatterplots (see **Appendix Figures 6-13**). As expected, age, sex and height were shown to be consistently associated with measures of cIMT at both baseline and 1-year follow-up. Thus, partial correlation analyses were conducted to evaluate whether there is a statistically significant linear relationship between baseline CVRFs and cIMT measures at baseline and 1-year follow-up, after accounting for baseline age, sex, height (for baseline and 1-year cIMT) and baseline cIMT value (for 1-year cIMT only) (see **Tables 3-4**).

Measures of Adiposity and cIMT

Measures of adiposity evaluated for their association with cIMT measures at baseline and 1-year follow-up, included: BMI, WC and body fat % (see **Appendix Table 6);** the distributions of these relationships are presented in **Appendix Figures 11-13.** After correlations were adjusted for age, sex, and height, there was a moderate partial correlation between baseline BMI and mean ICA IMT only (r=0.249, p=0.046) and WC was not significantly related to any cIMT measures at baseline (see **Table 3**). Interestingly, body fat % was not associated with any measure of cIMT, at baseline or 1-year follow-up. After correlations were adjusted for age, sex, height and baseline cIMT, there was a moderate, positive partial correlation between baseline BMI and change in mean CCA IMT over 1

year (r=0.218, p=0.017) whereas WC was not significantly linearly related to any cIMT measures at 1-year follow-up, (see **Figure 6)** (see **Table 4**). Overall, BMI was positively correlated with 1-year cIMT, after adjustment for covariates, whereas, there were no significant relationships observed with WC and body fat %.

Measures of Blood Pressure and cIMT

After controlling for age, sex and height, baseline SBP was moderately, positively correlated with baseline 12-segment cIMT (r=0.287, p=0.021) and ICA IMT (r=0.230, p=0.045) (see **Table 3)**, whereas, DBP was not associated with any measures of cIMT. Thus, although SBP may be related to cIMT, this may not be the case for DBP.

Measures of Glycemia and cIMT

Measures of glycemia evaluated for their association with cIMT at baseline and 1-year follow-up, included: FPG, 2-hr PG and HbA1c (see **Appendix Table 6**); the distributions of these relationships are presented in **Appendix Figure 6**. There was a significant positive correlation between baseline FPG and carotid bulb far wall IMT (primary outcome measure) (r=0.200, p=0.037) (see **Figure 5**) (see **Table 3**), after adjustment for age, sex and height. Thereby, FPG may be an important correlate of cIMT in children and youth with obesity, as one would expect, given that age, sex and height do not change normal fasting glucose. Values of baseline 2-hr PG and HbA1c were not significantly associated with any measure of cIMT at baseline or 1-year follow-up (see **Tables 3-4**).

Measures of Lipid Profile and cIMT

Measures of lipid profile assessed for their association with cIMT measures at baseline and 1-year follow-up, included: HDL-C, TC/HDL-C and non-HDL-C (see **Appendix Table 6**); the distributions of these relationships are presented in **Appendix Figures 7-8.** TC, TG and LDL-C were not evaluated, to avoid redundancy, as markers of atherogenic lipoprotein particles were chosen for assessment (TC/HDL-C and non-HDL-C), on the basis of evidence presented in literature (Expert Panel, 2011). Upon adjustment for age, sex and height, baseline HDL-C was a significant negative correlate of some of the baseline measures of cIMT: carotid bulb far wall IMT (r=-0.203, p=0.034) and CCA far wall IMT (r=-0.238, p=0.013) (See **Figure 5**) (see **Table 3**). Baseline HDL-C was also significantly negatively correlated with mean CCA IMT at 1-year (r=-0.214, p=0.027), after adjusting for age, sex, height and baseline cIMT (see **Figure 6**) (see **Table 4**). There was a statistically significant, positive correlation between baseline TC/HDL-C and CCA far wall IMT (r=0.185, p=0.044) and mean CCA IMT (r=0.198 p=0.039), after adjustment for age, sex and height (see **Figure 5**) (see **Table 3**). Baseline non-HDL-C was significantly associated with change in carotid bulb far wall IMT over 1-year (r=0.231, p=0.017), while controlling for baseline age, sex, height and baseline cIMT (see **Figure 6**) (see **Table 4**). Thus, amongst children and youth with obesity, values of HDL-C, TC/HDL-C and non-HDL-C were related to various measures of cIMT.

	12-segment cIMT (n=69)		Carotid Bulb FW IMT (n=125)		Mean Carotid Bulb IMT (n=122)		CCA FW IMT (2-segment) (n=125)		Mean CCA IMT (n=125)		ICA FW IMT (n=87)		Mean ICA IMT (n=69)	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
BMI (n=124)	0.208	0.097	0.034	0.713	0.013	0.886	-0.071	0.437	-0.037	0.687	0.045	0.688	0.249	0.050
WC (n=81)	-0.014	0.929	-0.008	0.942	-0.074	0.529	0.004	0.937	-0.082	0.429	-0.035	0.797	0.044	0.779
BF% (n=107)	0.158	0.233	-0.023	0.814	-0.062	0.538	-0.141	0.152	-0.080	0.421	0.039	0.741	0.156	0.237
HDL-C (n=113)	-0.148	0.255	-0.203	**0.034**	-0.245	**0.011**	-0.238	**0.013**	-0.166	0.084	-0.085	0.459	-0.067	0.607
Non-HDL-C (n=113)	-0.020	0.880	0.338	0.093	0.052	0.597	0.095	0.326	0.143	0.138	-0.026	0.824	-0.077	0.556
TC/HDL-C (n=113)	0.040	0.758	0.168	0.080	0.174	0.074	0.185	**0.044**	0.198	**0.039**	-0.011	0.922	-0.060	0.645
SBP (n=123)	0.287	**0.021**	0.047	0.610	0.104	0.265	-0.004	0.969	0.070	0.447	0.048	0.663	0.230	**0.045**
DBP (n=123)	0.218	0.081	0.124	0.179	0.168	0.072	0.002	0.983	-0.016	0.865	-0.026	0.816	0.036	0.778
FPG (n=113)	0.230	0.077	0.200	**0.037**	0.117	0.229	0.137	0.157	0.165	0.056	0.137	0.236	0.180	0.168

Table 3. Partial correlation coefficient table for baseline cIMT measures. Partial correlations between baseline participant characteristics and measures of cIMT at baseline, adjusted for age, sex and height. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose. P values in boldface indicate significance ($p<0.05$).

	12-segment cIMT (n=63)		Carotid Bulb FW IMT (n=123)		Mean Carotid Bulb IMT (n=120)		CCA FW IMT (2-segment) (n=124)		Mean CCA IMT (n=124)		ICA FW IMT (n=83)		Mean ICA IMT (n=63)	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
BMI (n=124)	0.007	0.958	0.050	0.591	0.080	0.396	-0.013	0.892	0.218	**0.017**	0.059	0.606	-0.072	0.591
WC (n=81)	0.036	0.828	0.096	0.413	0.045	0.710	0.089	0.444	0.212	0.067	-0.078	0.581	-0.087	0.598
BF% (n=107)	0.016	0.910	0.093	0.356	0.060	0.554	0.015	0.881	0.127	0.203	0.010	0.931	-0.059	0.675
HDL-C (n=113)	-0.238	0.083	-0.021	0.828	0.008	0.935	-0.187	0.054	-0.214	**0.027**	-0.183	0.122	-0.238	0.084
Non-HDL-C (n=113)	0.132	0.343	0.231	**0.017**	0.120	0.223	0.187	0.054	0.051	0.604	0.100	0.398	0.150	0.279
TC/HDL-C (n=113)	0.282	**0.039**	0.184	0.059	0.087	0.378	0.241	**0.012**	0.165	0.090	0.182	0.123	0.280	**0.040**
SBP (n=123)	0.102	0.444	0.094	0.317	0.030	0.751	-0.071	0.470	0.043	0.643	0.033	0.771	0.072	0.592
DBP (n=123)	0.045	0.735	0.060	0.523	-0.098	0.301	0.048	0.606	0.034	0.716	-0.152	0.184	0.092	0.491
FPG (n=113)	-0.031	0.827	0.003	0.979	0.069	0.486	0.055	0.573	0.151	0.121	-0.026	0.830	0.066	0.641

Table 4. Partial correlation coefficient table for cIMT measures at 1-year follow-up. Partial correlations between baseline participant characteristics and measures of cIMT at 1-year follow-up, adjusted for age, sex, height and baseline cIMT. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose. P values in boldface indicate significance ($p<0.05$).

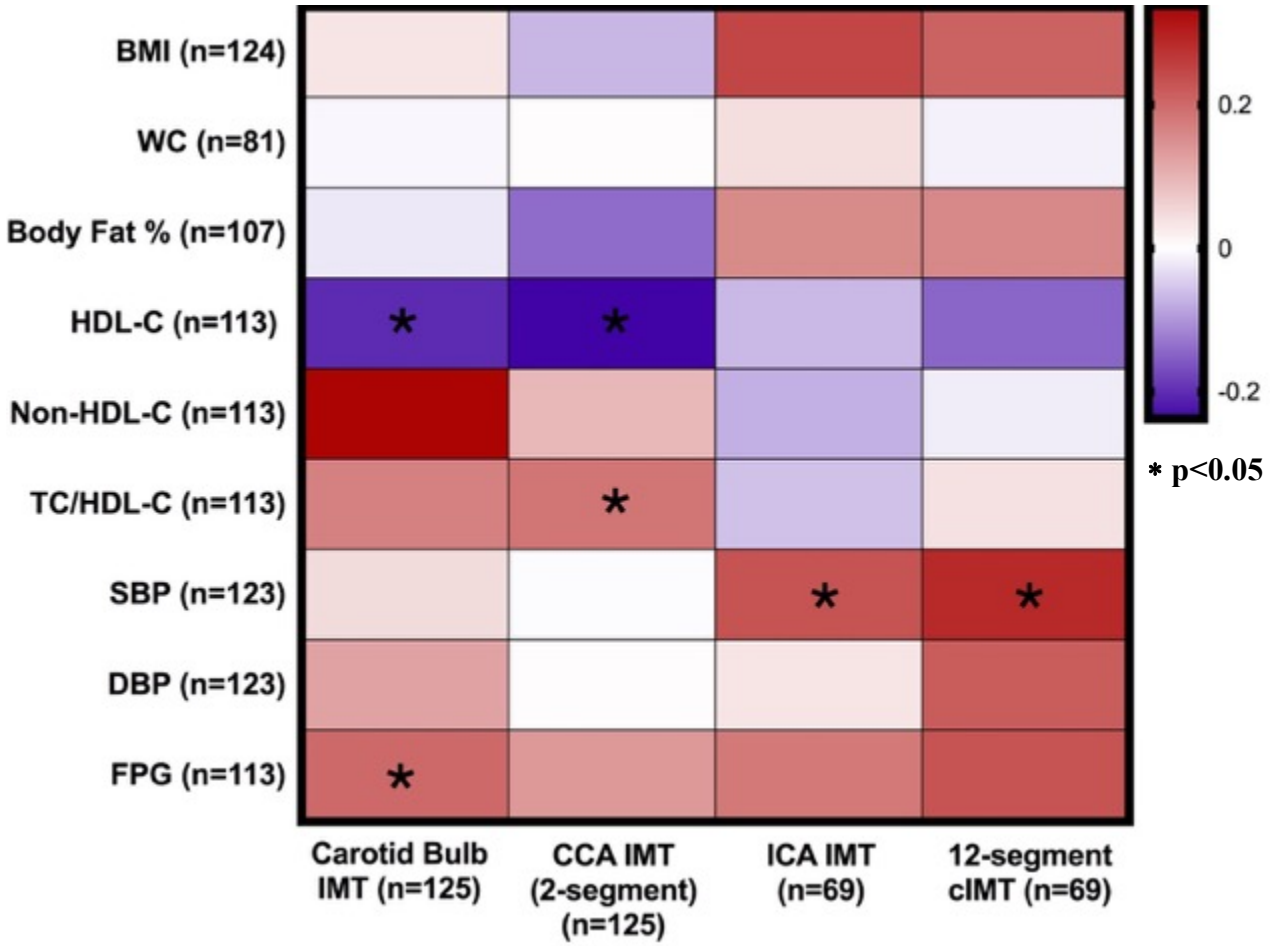


Figure 5. Partial correlation coefficient heat map for baseline cIMT measures. Heat map of the partial correlations between baseline participant characteristics and measures of cIMT at baseline, adjusted for age, sex and height. *P < .05. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

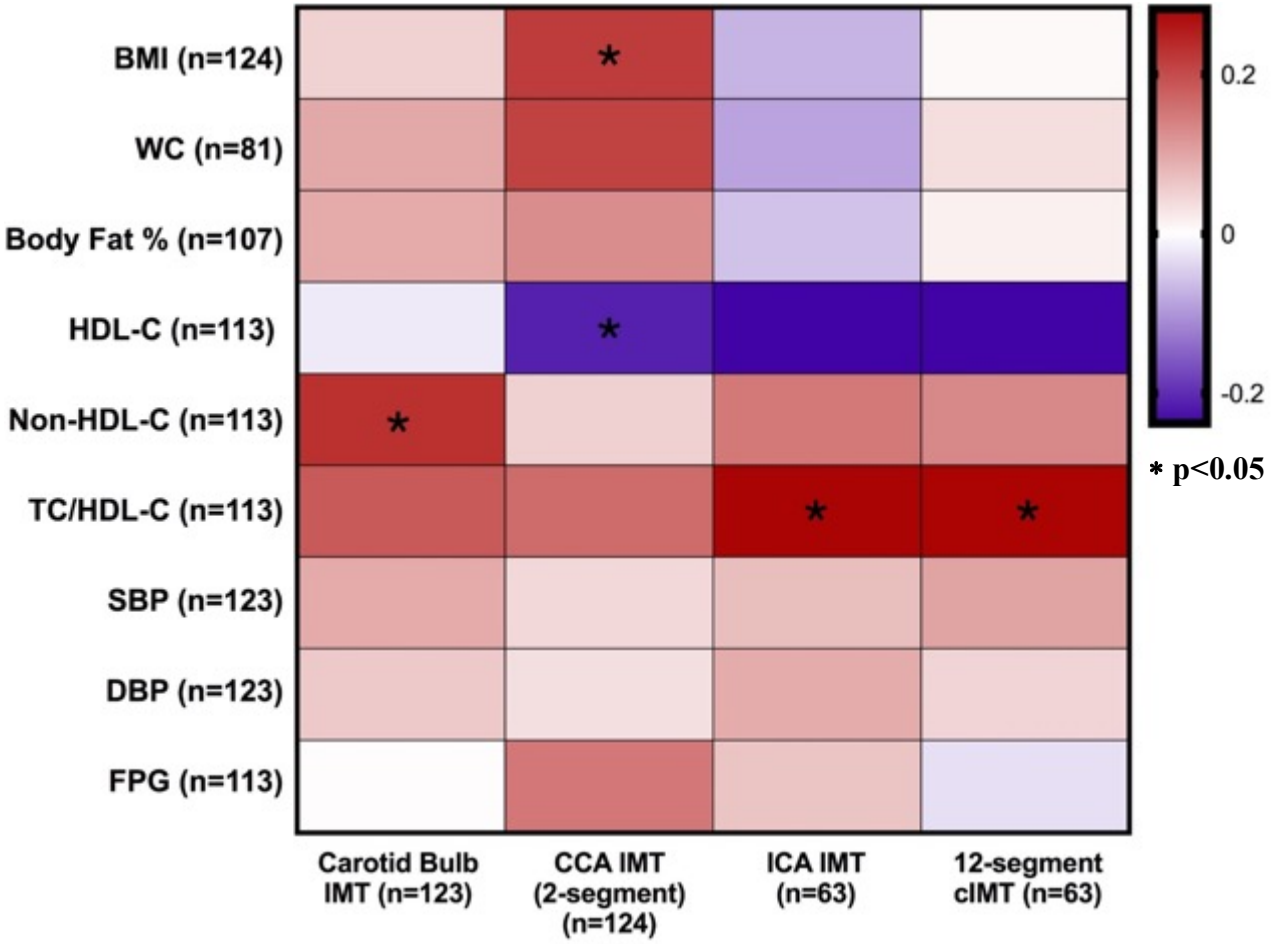


Figure 6. Partial correlation coefficient heat map for 1-year cIMT measures. Heat map of the partial correlations between baseline participant characteristics and measures of cIMT at 1-year follow-up, adjusted for age, sex, height and baseline cIMT. *P < .05. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

Multivariable Regression Analyses for cIMT at Baseline and cIMT over 1-year

Multivariable linear regression analyses were then utilized to evaluate independent relationships between baseline CVRFs and measures of cIMT at baseline and 1-year follow-up (corrected for baseline cIMT) (see **Appendix Tables 7-8**). Variables that were clinically significant ($p<0.1$) from partial correlation analyses (see **Tables 3-4**), for one or more cIMT measures, were included in all multivariable linear regression models, in order to maintain comparability of correlates between cIMT measures. For all multivariable linear regression models, the assumption of normality was met, as assessed by Q-Q plots. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was no evidence of multicollinearity, as assessed by VIF values less than 10 and tolerance values greater than 0.1. At baseline and 1-year follow-up, the variables included in the final multivariable linear regression models, were: age, sex, height, baseline cIMT (for 1-year follow-up only), BMI, non-HDL-C, SBP, DBP and FPG (see **Appendix Tables 7-8**), selected on the basis of significance ($p<0.1$) in partial correlation analyses. Non-HDL-C was selected over TC/HDL-C, given the large number of studies that support its use, over other markers of atherogenic lipoprotein particles (Ridker et al., 2005; Sniderman et al., 2006; Moriyama et al., 2016).

The multivariable regression models for cIMT measures, at 1-year follow-up (corrected for baseline cIMT), explained a total variance: 87.62% for mean 12-segment cIMT (mm), 71.57% for carotid bulb far wall IMT, 73.46% for mean carotid bulb IMT, 70.15% for CCA

far wall IMT (2-segment cIMT), 81.57% for mean CCA IMT, 58.20% for ICA far wall IMT, and 66.11% for mean ICA IMT (see **Appendix Table 8)**.

Male sex was independently associated with CCA IMT (far wall: p=0.017, near and far wall: p=0.032), and far wall ICA IMT (p=0.025) at 1-year follow-up (adjusted for baseline cIMT). Multivariable regression analyses revealed that age and height were not independently associated with any measures of cIMT at 1-year follow-up (p>0.05) (see **Appendix Table 8)**. Baseline BMI was independently related to mean CCA IMT (p=0.032) at 1-year follow-up (adjusted for baseline mean CCA cIMT). For every 1 kg/m^2 increase in BMI at baseline, there was an increase in mean CCA IMT, of 0.0007 mm (see **Table 5**). Baseline non-HDL cholesterol was independently related with carotid bulb far wall IMT (p=0.045) at 1-year follow-up (adjusted for baseline far wall carotid bulb IMT). For every 1 mmol/L increase in non-HDL-C, there was an increase in far wall carotid bulb IMT, of 0.0081 mm (see **Table 5**). Baseline SBP, DBP and FPG were not independently related to any measure of cIMT at 1-year follow-up (p>0.05) (see **Appendix Table 8)**.

Overall, at **baseline**: age and FPG were independent predictors of carotid bulb IMT; and SBP was an independent predictor of CCA IMT. At 1**-year follow-up**: male sex was an independent predictor of CCA IMT and ICA IMT; baseline BMI was an independent predictor of CCA IMT and baseline non-HDL-C was an independent predictor of the primary outcome measure, carotid bulb IMT. These findings suggest that BMI and non-HDL-C should be focused on, when addressing cIMT progression (see **Table 5**).

Table 5. Significant Independent Predictors of Baseline cIMT and cIMT over 1-year (corrected for baseline cIMT)

Independent Predictor	Baseline cIMT*	Regression Coefficient	1-Year cIMT**	Regression Coefficient
Age	Carotid Bulb (far wall)	0.0045 (0.0020)	-	-
Male Sex	-	-	CCA (far wall)	0.0105 (0.0044)
			CCA (near and far wall)	0.0071 (0.0034)
BMI	-	-	CCA (near and far wall)	0.0007 (0.0003)
SBP	CCA (near and far wall)	0.0009 (0.0004)	-	-
Non-HDL-C	-	-	Carotid Bulb (far wall)	0.0081 (0.0040)
FPG	Carotid Bulb (far wall)	0.0207 (0.0076)	-	-

*In a multivariable model, adjusted for covariates, including: age, sex and height
**In a multivariable model, adjusted for covariates, including: age, sex, height and baseline cIMT

Exploratory Analyses: Changes in CVRFs and cIMT Progression over 1 year

Changes in CVRFs from baseline to 1-year follow-up were assessed for patterns of association with cIMT progression. From all CVRFs assessed, a clear pattern of association was present between cIMT progression and changes in: body fat %, TC/HDL-C, FPG and SBP. Participants with similar risk factor levels after 1-year were used as the reference group in analyses of CVRF change.

Participants with a higher BF % change (upper tertile: > +1.2%) at follow-up had a higher carotid bulb and higher CCA IMT progression than those having similar BF % (middle tertile: -2.2 to +1.2% change) at follow-up. There was no difference observed in the carotid bulb or CCA IMT progression, for participants with the greatest decrease in BF % (lower tertile: < -2.2% change), in comparison to those with a similar (middle tertile: -2.2 to +1.2% change) BF % after 1 year (see **Figure 7**). Changes in BF % were not associated with cIMT progression rates for any other measures of cIMT. Analyses were conducted while adjusting for age, sex, baseline cIMT and baseline BF %.

Participants with a decreased value of TC/HDL-C (lower tertile: <-0.09 change) at follow-up had a lower CCA IMT progression rate, than those with a similar TC/HDL-C (middle tertile: -0.09 to +0.13 change) at follow-up. Participants with an increased TC/HDL-C > +0.13 over 1 year (upper tertile), had a higher carotid bulb IMT progression rate in comparison to those with a similar TC/HDL-C (see **Figure 7**). Changes in TC/HDL-C were

not associated with cIMT progression rates for any other measures of cIMT. Analyses were conducted while adjusting for age, sex, baseline cIMT and baseline TC/HDL-C.

Participants with a higher FPG (upper tertile: > +0.2 mmol/L) at follow-up had a higher carotid bulb IMT progression than those with a similar FPG (middle tertile: -0.1 to +0.2 mmol/L change) at follow-up. Participants with a decreased value of FPG (lower tertile: <-0.1 mmol/L change) at follow-up had a lower CCA IMT progression rate, than those with a similar FPG (middle tertile: -0.1 to +0.2 mmol/L change) at follow-up (see **Figure 8**). Changes in FPG were not associated with cIMT progression rates for any other measures of cIMT. Analyses were conducted while adjusting for age, sex, baseline cIMT and baseline FPG.

Participants with a decreased value of SBP (lower tertile: < -3.8 mmHg) at follow-up had a lower CCA IMT progression rate, than those with a similar SBP (middle tertile: -3.8 to +5.0 mmHg change) at follow-up. There was no observed difference in carotid bulb IMT progression between those with a higher (upper tertile > 5.0 mmHg)/lower (lower tertile: < -3.8 mmHg) SBP and those with a similar SBP (middle tertile: -3.8 to +5.0 mmHg change) at F/UP (see **Figure 8**). Changes in SBP were not associated with cIMT progression rates for any other measures of cIMT. Analyses were conducted while adjusting for age, sex, baseline cIMT and baseline SBP.

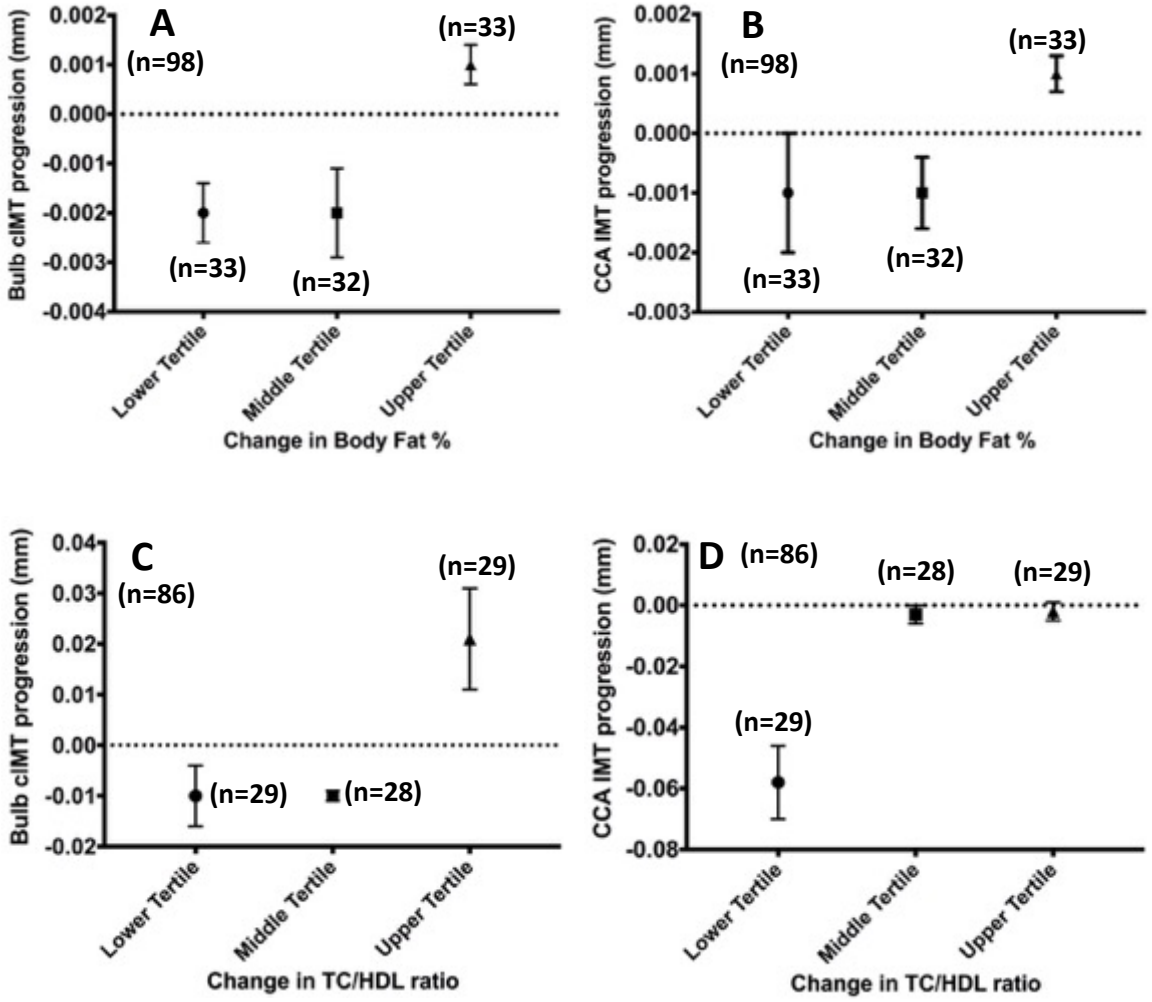


Figure 7. Change in CVRFs and cIMT progression rates at 1-year follow-up. Higher body fat % at 1-year F/UP (upper tertile: > +1.2%) was associated with a **(A)** higher carotid bulb IMT progression rate and **(B)** higher CCA IMT progression rate, in comparison to those with a similar BF% at F/UP (middle tertile: -2.2 to +1.2% change). Higher TC/HDL at 1-year F/UP (upper tertile: > +0.13 change) was associated with a **(C)** higher carotid bulb IMT progression rate and a lower TC/HDL at 1-year F/UP (lower tertile: < -0.09) was associated with a **(D)** lower CCA progression rate, in comparison to those with a similar TC/HDL ratio at F/UP (middle tertile: -0.09 to +0.13 change).

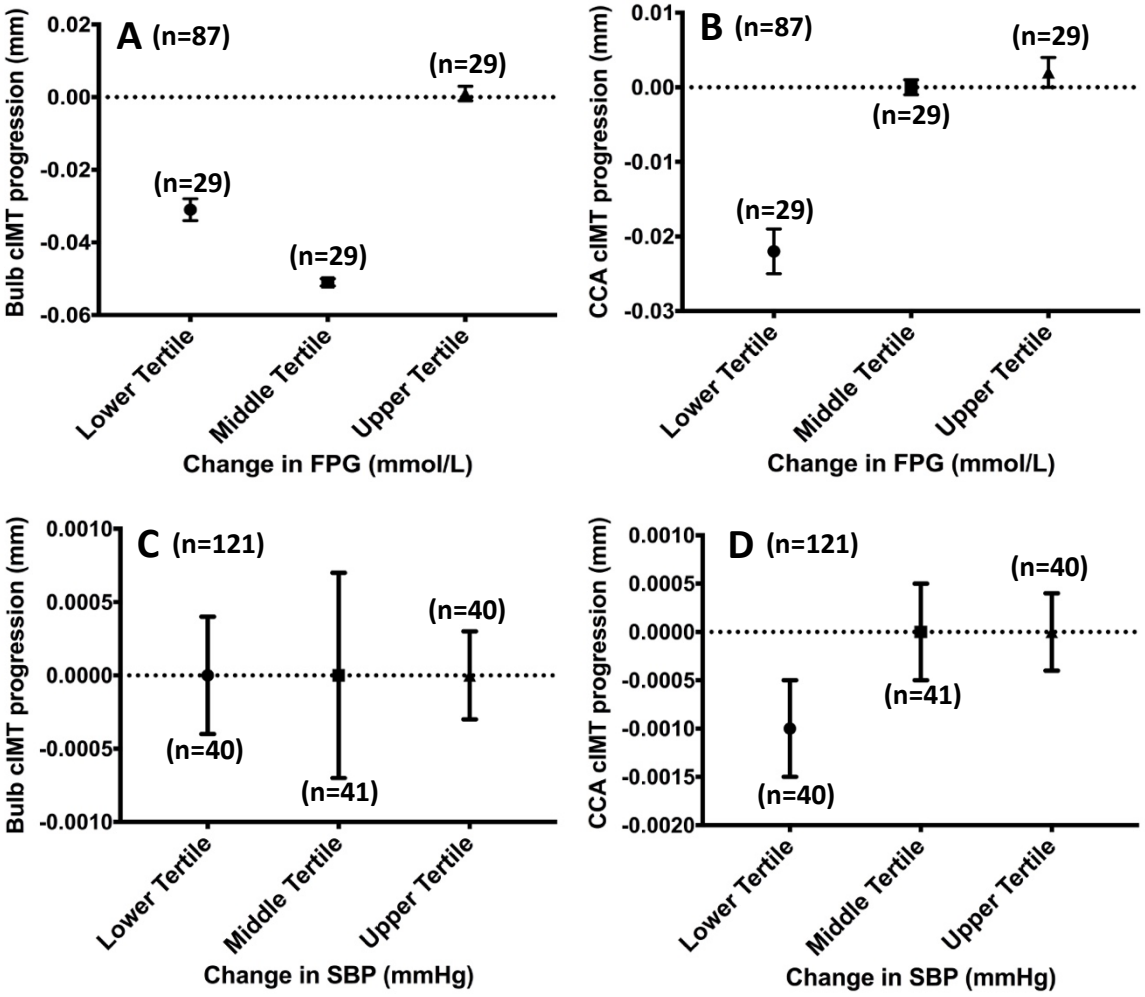


Figure 8. Change in CVRFs and cIMT progression rates at 1-year follow-up. Higher FPG at 1-year F/UP (upper tertile: > +0.2 mmol/L) was associated with a **(A)** higher carotid bulb IMT progression rate and a lower FPG at 1-year F/UP (lower tertile: < -0.1 mmol/L) was associated with a **(B)** lower CCA progression rate, in comparison to those with a similar FPG at F/UP (middle tertile: -0.1 to +0.2 mmol/L change). Lower SBP at 1-year F/UP (lower tertile: < -3.8 mmHg) was associated with a **(D)** lower CCA IMT progression rate, however, there was no observed difference in carotid bulb IMT progression between those with a higher (upper tertile > 5.0 mmHg)/lower (lower tertile: < -3.8 mmHg) SBP and those with a similar SBP (middle tertile: -3.8 to +5.0 mmHg change) at F/UP **(C)**.

CHAPTER 5: DISCUSSION

The primary objective of this project was to evaluate the relationships between CVRFs and cIMT progression as well as to compare correlates of cIMT across carotid segments, in children and youth with obesity. The secondary objective of this project was to characterize the progression of cIMT at different carotid segments in this population and is discussed, prior to the primary objective, below.

At baseline, mean cIMT (mm) was significantly greater at the carotid bulb in comparison to IMT measured at the CCA and ICA ($p<0.001$). Thus, we show that children and youth with obesity (without the presence of genetic dyslipidemias and diabetes), do display a greater extent of arterial wall thickening in the carotid bulb, in comparison to CCA and the ICA. This finding supports our study hypothesis and reports from studies conducted in young adults with and without an increased risk of CVD (Tzou et al., 2007; Urbina et al., 2002; Polak et al., 2010). We were able to measure carotid bulb IMT (primary outcome measure) and CCA IMT (including 2-segment) with high completeness. However, measurements of the ICA (and thereby, 12-segment cIMT) were missing for approximately half of all participants. We found that progression of cIMT (mm) from baseline to 1-year follow-up was site-specific and change in cIMT over 1 year was greater at the carotid bulb than change in cIMT at the CCA and ICA, for measurements including far wall only. Our findings support our hypothesis and also agree with findings in several adult studies where cIMT was reported to progress in a non-uniform manner across carotid segments and the

highest rate of progression was observed at the carotid bulb, followed by the CCA and ICA (Nguyen et al., 2011; Espeland et al., 2003; Mackinnon et al., 2004; Koskinen et al., 2009).

The annualized progression rates from baseline to 1-year follow-up (n=125) were relatively similar to progression rates observed from baseline to 2-year follow-up (n=60). Carotid IMT progression rates at 1-year follow-up, ranged between: 0.015-0.026 mm/y at the carotid bulb; 0.006-0.013 mm/y at the CCA; 0.001-0.011 mm/y at the ICA; and, 0.008-0.015 mm/y for 12-segment cIMT. The mean far wall CCA IMT (2-segment cIMT) progression for children and adolescents with obesity, in this study (0.010 mm/year), was greater in comparison to studies in children and youth with T1DM (0.0023 mm/year) (Dalla Pozza et al., 2011) and was similar to that observed in children with OW/OB (0.0085 mm/year) (Toledo-Corral et al., 2011). The mean cIMT progression in this study, using the 12-segment approach (0.013 mm/year) was considerably greater in comparison to the 12-segment cIMT progression reported in children with FH (0.0025 mm/year) (Wiegman et al., 2004). Annualized cIMT progression rates at 2-year follow-up, ranged between: 0.012-0.019 mm/y at the carotid bulb; 0.003-0.010 mm/y at the CCA; 0.001-0.007 mm/y at the ICA; and, 0.006-0.011 mm/y for 12-segment cIMT. In contrast, progression of cIMT (measured at the carotid bulb, CCA and ICA) with age in unaffected, healthy siblings (n=64, ages 6-17y) (control group) of children with familial hypercholesterolemia was reported to be <0.001mm/year (Kusters et al., 2014). Toledo-Corral and colleagues (2011) defined advanced cIMT progression as 0.005 mm/year (2-segment) for overweight Latino youth, on the basis on adult cut-offs, whereas studies in children with FH and T1DM,

reported cIMT progression rates of 0.0025 mm/year (12-segment) (Wiegman et al., 2004) and 0.0023 mm/year (2-segment) (Dalla Pozza et al., 2011), respectively. Although these studies utilized 2-segment cIMT and 12-segment cIMT, the reported progression rates were still lower than those reported for the corresponding cIMT measures in our study (2-segment cIMT: 0.006-0.013 mm/y; 12-segment: 0.008-0.015 mm/y). Thus, the annualized cIMT progression rates observed in this study, suggest a greater degree of cIMT progression in our study population of children and youth with obesity, and change in cIMT across carotid segments appears to surpass advanced progression cut-offs based on adult thresholds (≥0.005 mm/y) (Toledo-Corral et al., 2011).

Correlates of Baseline cIMT Across Carotid Segments

As previously discussed, different correlates (CVRFs) have been reported for different carotid segments, in several studies in adults (Urbina et al., 2002) and thus, segment-specific correlates of cIMT were assessed. Overall, our analyses showed that carotid bulb IMT was associated with a higher number of CVRFs than the CCA and ICA (for cIMT inclusive of the far wall only, as well as, cIMT inclusive of the near and far walls) and that there are segment-specific differences in the correlates of cIMT, which supports our hypothesis and agrees with the findings of studies conducted in young adults (Tzou et al., 2007; Urbina et al., 2002). However, many of the CVRFs change with age and sex and cIMT is also related to height; therefore, further sections will discuss the correlates of baseline cIMT, after adjustment for age, sex and height and the correlates of cIMT progression over 1 year, after adjustment for age, sex, height and baseline cIMT.

Measures of Adiposity and Carotid-Intima Media Thickness

The relationships between measures of adiposity and baseline cIMT, as well as cIMT progression over 1 year, were evaluated. We found that, when assessing cIMT progression, BMI was a significant (p=0.017) correlate of mean CCA IMT (near and far wall), after adjustment for age, sex, height and baseline cIMT, however not 2-segment cIMT (CCA far wall). This relationship remained significant (p=0.032) in multivariable analyses (see **Appendix Table 11**), suggesting that this measure of adiposity is independently related to cIMT progression in children and youth with obesity. This finding is consistent with our study hypothesis and also agrees with the observations of a study conducted in young adults (n=459, mean age: 32y), where BMI was only significantly related to CCA IMT progression (r=0.16, p<0.001) but was not associated with carotid bulb or ICA IMT progression, after adjustment for age, sex and race (Mackinnon et al., 2004). Thus, these findings suggest that BMI is associated with cIMT progression in children and youth with obesity and may be utilized as a predictor of CV risk in this population (Park et al., 2015).

Baseline body fat % was not significantly related to any baseline cIMT measures, after adjustment for age, sex and height. In exploratory analyses, however, participants with a higher body fat % at follow-up, had a higher carotid bulb and higher CCA IMT progression in comparison to those with a similar body fat % after 1 year, indicating that *changes* in extent of adiposity may predict cIMT progression better than extent of adiposity at baseline (see **Figure 7**).

Waist circumference was not associated with any measures of baseline cIMT after adjustment for age, sex and height. Waist circumference was also not associated with cIMT progression, for any of the carotid segments assessed, similar to reports by Melo and colleagues (2016), where the risk for increased cIMT was not any greater in children (age range: 11-12y) who exhibited high central adiposity (measured by waist circumference) than children with higher total adiposity (measured by BMI). As suggested by Chowdhury and colleagues (2014), an elevated cIMT in children with obesity may be related to a greater degree of somatic growth, that accompanies increased adiposity in this population, and is not necessarily solely related to the increase in central adiposity, as observed in our study. This may be attributable to the fact that all participants in this study had obesity (no comparisons to individuals with normal weight), and thus, the *severity* of obesity may be an important predictor.

Blood Pressure and Carotid-Intima Media Thickness

In multivariable analyses, SBP was independently related to only baseline CCA IMT ($p=0.034$) (inclusive of near and far walls). Similar findings were reported in an older population of children and youth with obesity (n=234, age range: 10-24), where SBP was an independent predictor of baseline cIMT at the CCA (Urbina et al., 2011).

However, when the relationships between SBP and change in cIMT over one year were assessed, baseline SBP was not significantly associated with progression of cIMT. Our findings were not consistent with a longitudinal study conducted in adults (n=3383, mean

age: 52y), where baseline SBP was a significant independent predictor of cIMT progression at all carotid segments ($p<0.05$) (Mackinnon et al., 2004). This disparity may be explained by the lower prevalence of abnormal SBP in our study at baseline (11.2%), in comparison to the greater prevalence of abnormal SBP seen in the young adults (23.9%) studied by Mackinnon and colleagues (2004). Mackinnon and colleagues (2004) studied change in cIMT over the course of approximately 3 years, and thus, the relationship between baseline SBP and cIMT progression was assessed over a longer duration of time than the 1-year time period utilized for this study. Thereby, the lower prevalence of abnormal SBP, combined with the shorter duration of cIMT progression assessed in our analyses, may have hindered our ability to observe a relationship between baseline SBP and cIMT progression.

Measures of Lipid Profile and Carotid-Intima Media Thickness

The relationships between measures of lipid profile and baseline cIMT, as well as cIMT progression, were evaluated. In partial correlation analyses (adjusted for age, sex and height), we found that HDL-C was significantly, negatively, related to both carotid bulb IMT (far wall: $p=0.034$; near and far wall: $p=0.011$) and far wall CCA IMT ($p=0.013$) at baseline. This finding is consistent with our hypothesis and is similar to that of Urbina and colleagues (2002), that conducted partial correlations (adjusted for age, sex and race) in young adults and reported HDL-C as significantly and negatively related to CCA IMT ($p<0.05$) and carotid bulb IMT ($p<0.001$). We also found that baseline HDL-C was negatively ($p<0.05$) related to change in CCA cIMT over 1-year (analyses adjusted for age, sex, height and baseline cIMT). This finding supports the study hypothesis and agrees the

observations of a study conducted by Nguyen and colleagues (2011), in young adults (n=842, mean age: 24-43), where HDL-C was negatively related to ($p<0.05$) CCA IMT progression, but not carotid bulb or ICA IMT progression. Overall, our findings suggest that lower values of baseline HDL-C may be predictive of greater cIMT progression, over time, in children and youth with obesity.

In our partial correlation analyses, baseline non-HDL cholesterol (Non-HDL-C) was found to be significantly ($p=0.017$) related to change in carotid bulb IMT over 1-year (analyses adjusted for age, sex, height and baseline cIMT), however, not with CCA or ICA IMT. Furthermore, when we conducted multivariable analyses for change in cIMT, over 1-year, non-HDL-C was found to be an independent predictor of carotid bulb IMT progression ($p=0.045$). These findings supported the study hypothesis and agreed with the reports of several studies in adolescents and young adults (Cui et al., 2001; Srinivasan et al., 2006), where non-HDL-C was found to be a dependable predictor of levels of atherogenic lipoprotein particles, especially in participants with elevated TG levels (Moriyama et al., 2016). We also observed that, although baseline non-HDL-C was related to carotid bulb IMT progression over one year, it was not a significant predictor of cIMT at baseline. These findings mirror those of a longitudinal study in adults (n=1,195; age range: 35-64y), where Huang and colleagues (2012) suggested that, given the progressive nature of ATH development, it takes time for elevated lipids at baseline to demonstrate an effect on cIMT, and indeed, in their analyses, baseline values of non-HDL-C were more strongly associated with cIMT measured 9 years later ($p<0.001$).

Additionally, we found that this measure of atherogenic lipoprotein particles was an independent predictor of only carotid bulb IMT progression in our study, which agrees with the observations made by Urbina and colleagues (2002), where stronger correlations were reported between carotid bulb IMT and measures of lipid profile, in comparison to the CCA and ICA. The increased sensitivity for detecting relationships between elevated atherogenic lipoproteins (captured by non-HDL-C measurement) and cIMT progression, at the carotid bulb, is proposed to be partly attributable to the hemodynamics at the carotid bulb (Timóteo et al., 2012). Briefly, low mean sheer stress and the fluctuations in wall shear stress direction, may result in the increased deposition of cholesterol particles from the plasma, at the endothelial monolayer (Ku et al., 1985). Thus, based on our findings and reports from previous studies in adults, assessment of the carotid bulb is important when evaluating the relationships between measures of atherogenic lipid profile and cIMT progression (Dogan et al., 2011); thereby, relationships between cIMT and non-HDL-C may be missed when assessing cIMT using solely the 2-segment (far wall CCA) approach. As per our findings, elevated baseline non-HDL-C may be a good predictor of cIMT progression (especially in the carotid bulb), over time, in children and youth with obesity.

In exploratory analyses, participants with an increased TC/HDL-C at follow-up had a higher carotid bulb IMT progression rate, in comparison to those with a similar value of TC/HDL-C. Participants with a decreased value of TC/HDL-C at follow-up had a lower CCA IMT progression rate in comparison to those with a similar TC/HDL-C after 1 year. In comparison to TC/HDL-C, literature (Ray et al., 2009) suggests that non-HDL-C may be more closely correlated with apolipoprotein B (apoB) measurement (measure of the

number of proatherogenic particles); this finding supported the selection of non-HDL-C for multivariable analyses, along with the lack of an association between the primary outcome measure and baseline TC/HDL-C values. However, although baseline TC/HDL-C was not significantly related to change in the primary outcome measure of cIMT, over 1-year, exploratory analyses suggest that *changes* in TC/HDL-C may be more predictive of changes in IMT progression rates, rather than baseline values of this CVRF (see **Figure 7**).

Measures of Glycemia and Carotid-Intima Media Thickness

We also evaluated relationships between measures of glycemia and baseline cIMT, as well as cIMT progression. In univariable regression analyses, fasting plasma glucose (FPG) was the only measure of glycemia related to cIMT for the participants in this study. FPG was significantly ($p<0.05$) related to baseline CCA IMT and carotid bulb IMT at baseline, however, was not associated with baseline ICA IMT ($p>0.05$). FPG remained significantly related to baseline carotid bulb IMT ($p<0.05$) and neared significance ($p=0.056$) for baseline CCA IMT, after adjustment for: age, sex and height; this is one variable that is not predicted to change with age or maturation, or to differ by sex. Finally, FPG was found to be an independent predictor of carotid bulb IMT ($p<0.05$), in multivariable analyses. In agreement with our findings, FPG was also reported as an independent predictor of cIMT, by Reinehr and colleagues (2006), that found that baseline FPG could explain 5% of the variance in cIMT ($p<0.05$) in children with obesity (n=96, age range: 9-13y).

However, baseline FPG was not significantly related to cIMT progression, over one year, for any of the cIMT segments evaluated in our study. Our findings were consistent with those of Mackinnon and colleagues (2004) (n=3,384) as well as Nguyen and colleagues (2011) (n=842), that also found no significant associations between fasting plasma glucose and cIMT progression in adults. However, it is important to note, that similar to our study, where we reported a low prevalence of abnormal FPG (3.2%) values, Mackinnon and colleagues (2004) also reported a low prevalence of elevated FPG (2.4%). Thus, the absence of any significant relationships between baseline FPG and cIMT progression may have been due to the low number of participants with elevated FPG at baseline, in this study.

The measures of 2-hr plasma glucose (2-hr PG) and glycated hemoglobin (HbA1c) were not significantly related to any measure of cIMT ($p>0.05$). Our findings did not agree with those of Reinehr and colleagues (2006), that reported elevated 2-hr PG (IGT) as a significant predictor of elevated cIMT, in children and youth with obesity (n=461). However, the number of participants missing 2-hr PG values (test not conducted) were quite high in our study, with about 53% missingness (further discussed in **Limitations**); thereby, the prevalence of abnormal glucose tolerance in this study was only 3.2%. The lack of significant associations between baseline HbA1c and cIMT, in our study, was not consistent with the findings of Kotb and colleagues (2012), where HbA1c was found to be significantly associated with a greater cIMT in children with overweight and obesity. Similar to the 2-hr PG values, the prevalence of abnormal HbA1c was low in our study,

with only 6.4% of participants showing elevated HbA1c at baseline. Thus, the absence of any significant associations between 2-hr PG or HbA1c, and cIMT, may be attributed to the low prevalence of abnormalities of these measures in this study population as well as the lower number of participants that had 2-hr PG values available, for these analyses.

Limitations

As data utilized in this project were obtained from the case report forms (CRFs) of the CANPWR main study and its cIMT sub-study, a large proportion of data was collected by chart review of clinical patient charts, located in the Children's Exercise and Nutrition Centre at McMaster Children's Hospital. Thus, one limitation of this study was that data collection for certain variables was limited to the information and reports available in patient clinical charts. Missingness of values of cardiovascular risk factors were assessed and for measures of adiposity, waist circumference was missing for 35.2% of the participants, whereas body fat % was missing for 14.4% of participants, which may suggest that these were not as regularly assessed, in clinic, as BMI. Missing values were an issue, especially when assessing 2-hr PG values from oral glucose tolerance tests (OGTTs), as 52.8% of participants did not have 2-hr PG values (at baseline) available for analyses, thus hindering the assessment of relationships between baseline 2-hr PG and cIMT. The high missingness of 2-hr PG values may be due to the criteria for the evaluation of OGTTs, as they are not usually recommended for children under the age of 10 and children/youth need to meet additional criteria (such as family history of diabetes), to be eligible for an OGTT. Furthermore, 18.4% of participants were missing HbA1c values and 9.6% were missing

FPG values. Finally, 9.6% of participants did not have fasting lipid profile measures available.

It is also important to consider that study participants were enrolled in a weight management program, so there may be some bias in terms of the referral process to this clinic, and thus, the findings of this study may not be fully applicable to all children and youth with obesity. Given that this study population consisted of participants that were primarily Caucasian (prevalence of 80%), the findings of this study may not be generalizable to other study populations inclusive of more ethnically diverse participants.

Another limitation related to this study was the low prevalence of abnormalities in FPG and SBP values, that may have impeded the detection of any significant relationships that may exist between these CVRFs and cIMT. In addition, the analyses for this project were longitudinal, however the time frame was short (baseline to 1-year follow-up) in comparison to longitudinal cIMT studies in adults (Nguyen et al., 2011; Tzou et al., 2007). Finally, cIMT was measured using manual caliper readings. Although this method has been validated and shown to be reproducible, a semi-automated border detection program (Kotb et al., 2012) may have improved the accuracy of cIMT measurements, as well as allowed for decreased variability in measurements (Urbina et al., 2009). Given the substantial proportion of participants with severe obesity in our study population, an elevated body mass was a contributor to some technical challenges, in terms of performing carotid ultrasound scans. Specifically, greater degrees of fat deposition and deeper vessels

surrounding the neck resulted in lower scan quality, for some participants (Dobs et al., 1999). Ultrasound technicians adhered to appropriate scanning protocols (including proper neck positioning), to ensure that scans obtained were of the best possible quality and any difficulties in scanning were noted on participant case report forms, for future scans.

Future Directions

Given that this thesis was written using the data available for the 125 participants that had completed 1-year follow-up, out of the 210 participants enrolled in the cIMT sub-study, it is important to re-run the analyses conducted for this thesis, once all participants have attended follow-up. Thus, the findings of this study should be re-assessed to determine if they are consistent, after the inclusion of data from more participants. Furthermore, as the cIMT sub-study protocol involves the analysis of cIMT, annually, up to 3-year follow-up, the influence of cardiovascular risk factors on cIMT progression should also be evaluated at 2-year and 3-year follow-up time points, once those follow-ups reach completion. Future steps should also include assessment of the effects of changes in modifiable cardiovascular risk factors (from baseline to follow-up) on cIMT progression at 1-year, 2-year and 3-year follow-up time points, once data has been collected for all participants enrolled in the sub-study, to allow for ample power to run statistical tests for significance. Further analyses may also be conducted to compare associations between CVRFs and cIMT for participants ages>10y versus participants aged≤10y. Finally, future studies could involve the assessment of other non-invasive measures of vascular changes such as pulse wave velocity

and flow-mediated dilation, in order to evaluate changes at the arterial wall, associated with subclinical atherosclerosis, in more detail.

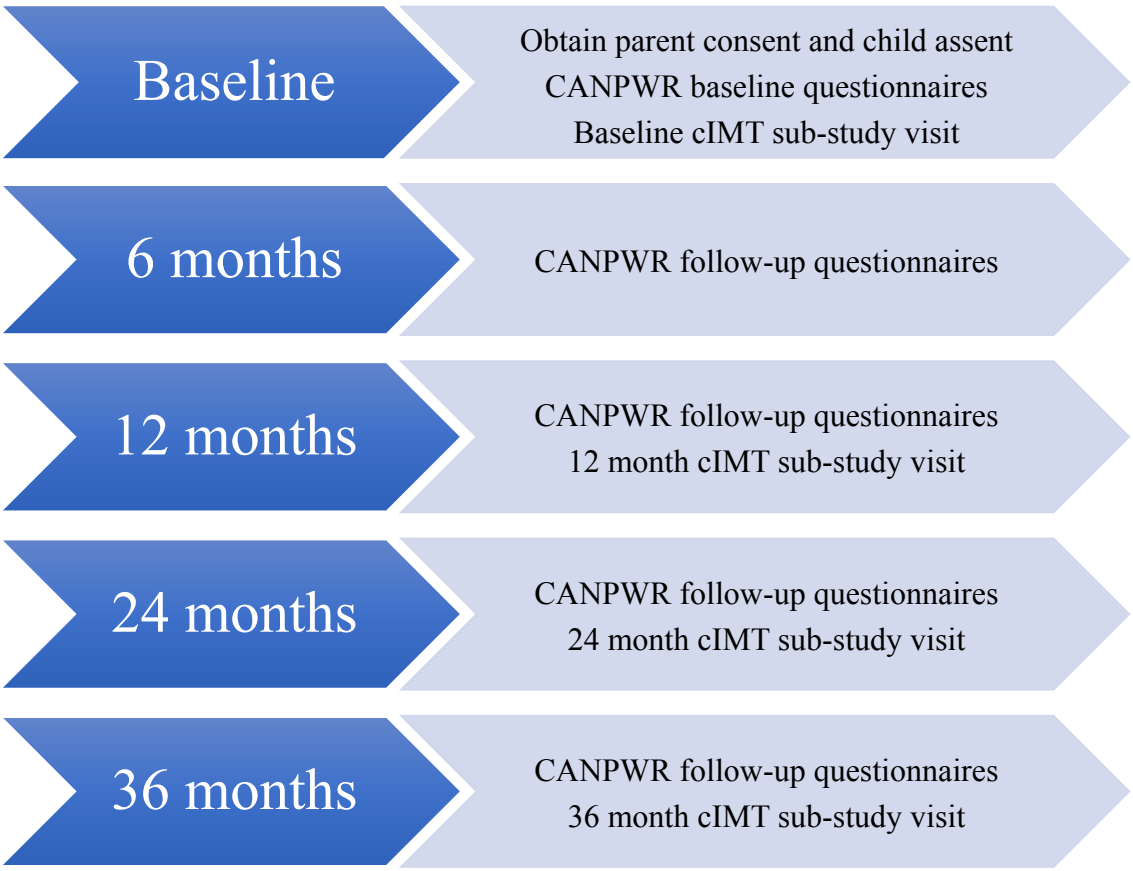
Conclusions

This thesis aimed to evaluate the relationships between modifiable cardiovascular risk factors and cIMT in children and youth with obesity. We demonstrated that the annualized progression of cIMT was non-uniform across carotid segments. Carotid bulb IMT progressed at a greater rate than CCA and ICA IMT, in children and youth with obesity. Furthermore, carotid bulb IMT progression was greater than that of 2-segment and 12-segment cIMT, the two standard measures of cIMT in pediatric and adult literature. The correlates of the primary outcome measure, carotid bulb IMT, at baseline, were: HDL-C and FPG, whereas, the correlate of carotid bulb IMT progression over 1-year, was non-HDL-C. CCA IMT, at baseline, was correlated with HDL-C and TC/HDL-C, whereas, the correlate of CCA IMT progression, was BMI. The correlate of 12-segment cIMT at baseline was SBP, whereas, the correlate of 12-segment cIMT, over 1 year, was TC/HDL-C. This ongoing study will also evaluate the effects of changes in cardiovascular risk factors on cIMT progression, to further improve our understanding of modifiable CVRFs that may be important targets for treatment. Given our findings, carotid bulb IMT may be a more sensitive measure of early ATH than the more frequently used CCA IMT and modification strategies should be focused on improving BMI and non-HDL-C in children and youth with obesity, so that progression of cIMT, associated with ATH development, may be slowed.

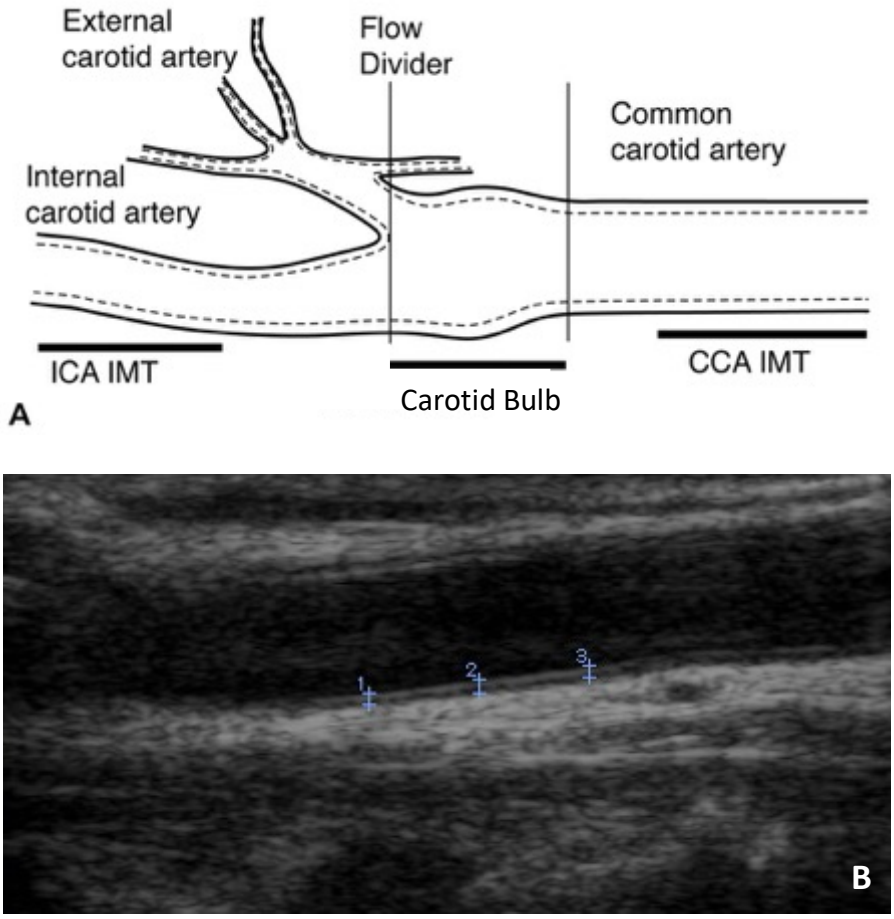
APPENDICES

Measure	Data Collection Procedure
Informed Consent to Study	CANPWR Main and cIMT sub study consent
Participant Demographics	
Age	CANPWR Questionnaires
Gender	CANPWR Questionnaires
Ethnicity	CANPWR Questionnaires
Socioeconomic Status	CANPWR Questionnaires
Participant Anthropometric and Physical Measures	
Height (in cm)	Review of Clinical Chart: Measured by Clinicians at patient clinic visits
Weight (in kg)	Review of Clinical Chart: Measured by Clinicians at patient clinic visits
Waist Circumference (in cm)	Review of Clinical Chart: Measured by Clinicians at patient clinic visits
Blood Pressure (mmHg)	Review of Clinical Chart: Measured by Clinicians at patient clinic visits via BPTru Blood Pressure Machine
Body Mass Index (BMI)	Calculated from height and weight measurements in clinic chart
Body Fat Percentage (%)	Review of Clinical Chart: Measured by Clinicians at patient clinic visits via 4-point Bioelectrical Impedence Analysis
Participant Clinical Measures	
Glycemia- Fasting Blood Glucose, 2-hr PG, HbA1c (%)	Review of Clinic Chart: Routine Clinical Blood work
Lipids- Fasting Lipid Profile	Review of Clinic Chart: Routine Clinical Blood work

Appendix Table 1. Data Collection Method Summary. The primary method of data collection for participant anthropometrics, physical measures and clinical measures was retrospective review of their clinical chart from the Growing Healthy Weight Management Program at the Children's Exercise and Nutrition Centre located at the McMaster Children's Hospital. Furthermore, the patient demographics as mentioned above, were captured using the CANPWR study questionnaires. Participants were allotted an identification number when enrolled, which served to keep their identity confidential. All the collected participant information was kept in a secure location and was maintained confidential; any participant identifying information was secured in a locked cabinet.



Appendix Figure 1: CANPWR Study and cIMT Sub-Study Timeline. The CANPWR main study and cIMT sub-study participants are followed over a 3-year period with follow-ups at 6 months, 12 months, 24 months and 36 months from the baseline visit. Regardless of whether participants are attending the weight management clinic or not, participants enrolled in the CANPWR study are still followed-up for the full duration of 3 years. CANPWR study questionnaires capture patient demographics, family medical history, food and drink frequency data, sleep quality, physical activity frequency and quality-of-life.



Appendix Figure 2: Carotid intima-media thickness measurement using B-mode ultrasonography.
A: The carotid segments at which cIMT should be measured include the ICA, carotid bulb, and CCA for both the near and far walls, delineated with the dotted lines. Measurements should be obtained for both the left and right carotid arteries, yielding a total of 12 measurements. Each anatomical segment should be defined relative to the carotid flow divider. CCA: common carotid artery; ICA: internal carotid artery.
B: Cross hairs should be placed at intervals of 0.05 mm on each segment (10 mm in length) of the carotid artery (in this image, the CCA). The top line of cross hairs should be placed on the lumen-intima boundary whereas the bottom line of cross hairs should be placed on the media-adventitia boundary. A minimum of 3 measurements are recommended for each segment for the calculation of average mean cIMT. Figure 2A has been adapted from Polak et al (2010) and Figure 2B has been adapted from Brandt et al (2013).

Sample Size Calculation

Estimated sample size to examine the association between cIMT and CVRFs among children and youths enrolled in a weight management program

Study design: Longitudinal
Primary outcome measure: Carotid bulb IMT (mm) (primary outcome)
Candidate variables: Age, Sex, Height, Baseline cIMT
Systolic blood pressure, Diastolic blood pressure,
HDL-C, Non-HDL-cholesterol, TC/HDL-C ratio,
BMI, Body fat %, Waist circumference,
Fasting plasma glucose, HbA1c%

Covariates: Age, Sex, Height (for baseline and 1-year cIMT), Baseline cIMT (for 1-year cIMT)

Model: Multiple Linear Regression Analyses

Estimated Sample Sizes

Level of Significance (α %)	Power (%)	No. of variables controlled	No. of variables tested	No. of variables in full model	R^2 for full model (%)[1]	Estimated Sample Size	Missing values (%)[2]	Sample Size[3]
5	80	4	5	9	15	96	15	110
5	80	3	5	8	15	83	15	95

[1]Minimum R^2 value for full model
[2]Missing values: source could be independent variables or dependent variable
[3]Sample size accounting for possible missing values

Appendix Table 2. Participant Characteristics at Baseline: Non-Attendees and Attendees

Variable		**Follow-up Non-Attendees (N=42)**				**Follow-Up Attendees Only (N=125)**			
Participant Demographics	**N**	**Mean (SD)**	**Median**	**Min, Max**	**N**	**Mean (SD)**	**Median**	**Min, Max**	**p-value**
Age(y)	42	13.07 (2.84)	13.33	7.17, 17.50	125	12.61 (2.90)	12.58	5.42, 17.92	0.371
Sex: Male (%)	42	26 (61.90%)	-	-	125	54 (43.20%)	-	-	0.036
Race: Caucasian (%)	42	29 (69.05%)	-	-	125	100 (80.00%)	-	-	0.143
Weight (kg)	42	85.36 (25.96)	82.10	40.70, 152.50	124	81.90 (26.14)	78.70	34.30, 152.50	0.567
Height (m)	42	157.88 (12.76)	159.80	125.70, 184.00	124	156.33 (14.77)	158.20	120.30, 193.00	0.715
BMI (kg/m^2)	42	33.53 (6.83)	32.01	24.33, 52.38	124	32.70 (6.28)	31.93	20.97, 52.38	0.512
BMI z-score	42	3.34 (1.06)	3.05	1.49, 5.99	124	3.33 (1.01)	3.32	1.49, 9.00	0.841
Waist circumference (cm)	25	95.56 (18.07)	92.00	59.50, 125.00	81	96.10 (15.25)	94.20	59.50, 131.00	0.754
Waist circumference to Height Ratio	25	0.61 (0.09)	0.60	0.41, 0.75	81	0.62 (0.07)	0.62	0.41, 0.83	0.577
Body Fat (%)	37	44.26 (6.77)	44.60	26.80, 56.70	107	43.62 (7.16)	43.80	23.60, 56.70	0.573
Participant Cardiovascular Risk Factors	**N**	**Mean (SD)**	**Median**	**Min, Max**	**N**	**Mean (SD)**	**Median**	**Min, Max**	**p-value**
Systolic BP (mmHg)	42	109.96 (10.39)	107.25	94.20, 145.00	123	110.09 (11.64)	109.00	83.00, 145.00	0.893

Diastolic BP (mmHg)	42	68.55 (6.89)	67.40	57.00, 86.75	123	69.23 (9.31)	68.20	51.20, 104.33	0.419
SBP Percentile age-sex-height	42	51 (27)	43	7, 100	122	52 (27)	51	4, 100	0.817
DBP Percentile age-sex-height	42	62 (21)	62	23, 98	122	64 (23)	67	13, 100	0.412
Total Cholesterol (mmol/L)	36	4.18 (0.65)	4.21	2.93, 5.60	113	4.20 (0.63)	4.09	2.87, 5.78	0.377
HDL Cholesterol (mmol/L)	36	1.16 (0.23)	1.18	0.82, 1.57	113	1.14 (0.21)	1.13	0.78, 1.64	0.814
LDL Cholesterol (mmol/L)	36	2.50 (0.51)	2.54	1.50, 3.44	113	2.50 (0.59)	2.48	1.23, 4.30	0.602
Triglycerides (mmol/L)	36	1.20 (0.49)	1.04	0.51, 2.73	113	1.31 (0.68)	1.13	0.40, 5.09	0.110
Non-HDL Cholesterol (mmol/L)	36	3.03 (0.65)	3.00	1.89, 4.58	113	3.06 (0.64)	2.96	1.85, 4.80	0.347
TC/HDL Ratio	36	3.73 (0.86)	3.65	2.46, 5.80	113	3.77 (0.81)	3.72	2.13, 5.97	0.446
Fasting Plasma Glucose (mmol/L)	35	4.82 (0.34)	4.80	4.10, 5.70	113	4.77 (0.47)	4.70	4.00, 6.90	0.555
2-hr Plasma Glucose (mmol/L)	24	5.87 (1.04)	5.75	4.30, 8.10	59	5.92 (1.27)	5.70	2.60, 10.90	0.793
HbA1c (%)	35	5.37 (0.33)	5.30	4.80, 6.30	102	5.26 (0.35)	5.25	4.60, 6.50	0.152
Participant cIMT Measures	**N**	**Mean (SD)**	**Median**	**Min, Max**	**N**	**Mean (SD)**	**Median**	**Min, Max**	**p-value**
Mean Far Wall Bulb cIMT (mm)	42	0.437 (0.042)	0.430	0.370, 0.587	125	0.429 (0.039)	0.425	0.333, 0.585	0.263
Mean Near Wall Bulb cIMT (mm)	41	0.441 (0.039)	0.432	0.379, 0.548	122	0.441 (0.044)	0.438	0.349, 0.563	0.779

Average Mean Bulb cIMT (mm)	41	0.439 (0.036)	0.436	0.374, 0.522	122	0.435 (0.037)	0.433	0.349, 0.542	0.697
Mean Far Wall CCA (2-segment) cIMT (mm)	42	0.386 (0.030)	0.383	0.331, 0.453	125	0.388 (0.033)	0.385	0.325, 0.490	0.569
Mean Near Wall CCA cIMT (mm)	42	0.406 (0.037)	0.397	0.349, 0.492	125	0.408 (0.043)	0.398	0.337, 0.521	0.612
Average Mean CCA cIMT (mm)	42	0.396 (0.027)	0.387	0.345, 0.473	125	0.398 (0.032)	0.390	0.338, 0.482	0.531
Mean Far Wall ICA cIMT (mm)	31	0.347 (0.019)	0.344	0.321, 0.391	87	0.358 (0.033)	0.347	0.311, 0.508	0.056
Mean Near Wall ICA cIMT (mm)	20	0.359 (0.031)	0.349	0.314, 0.445	69	0.354 (0.031)	0.344	0.314, 0.496	0.590
Average Mean ICA cIMT (mm)	20	0.356 (0.023)	0.347	0.320, 0.412	69	0.356 (0.028)	0.350	0.315, 0.455	0.829
Mean cIMT, 12-segments (mm)	20	0.401 (0.021)	0.397	0.367, 0.450	69	0.400 (0.029)	0.397	0.359, 0.493	0.892

All measures are reported as mean (standard deviation) unless otherwise stated.

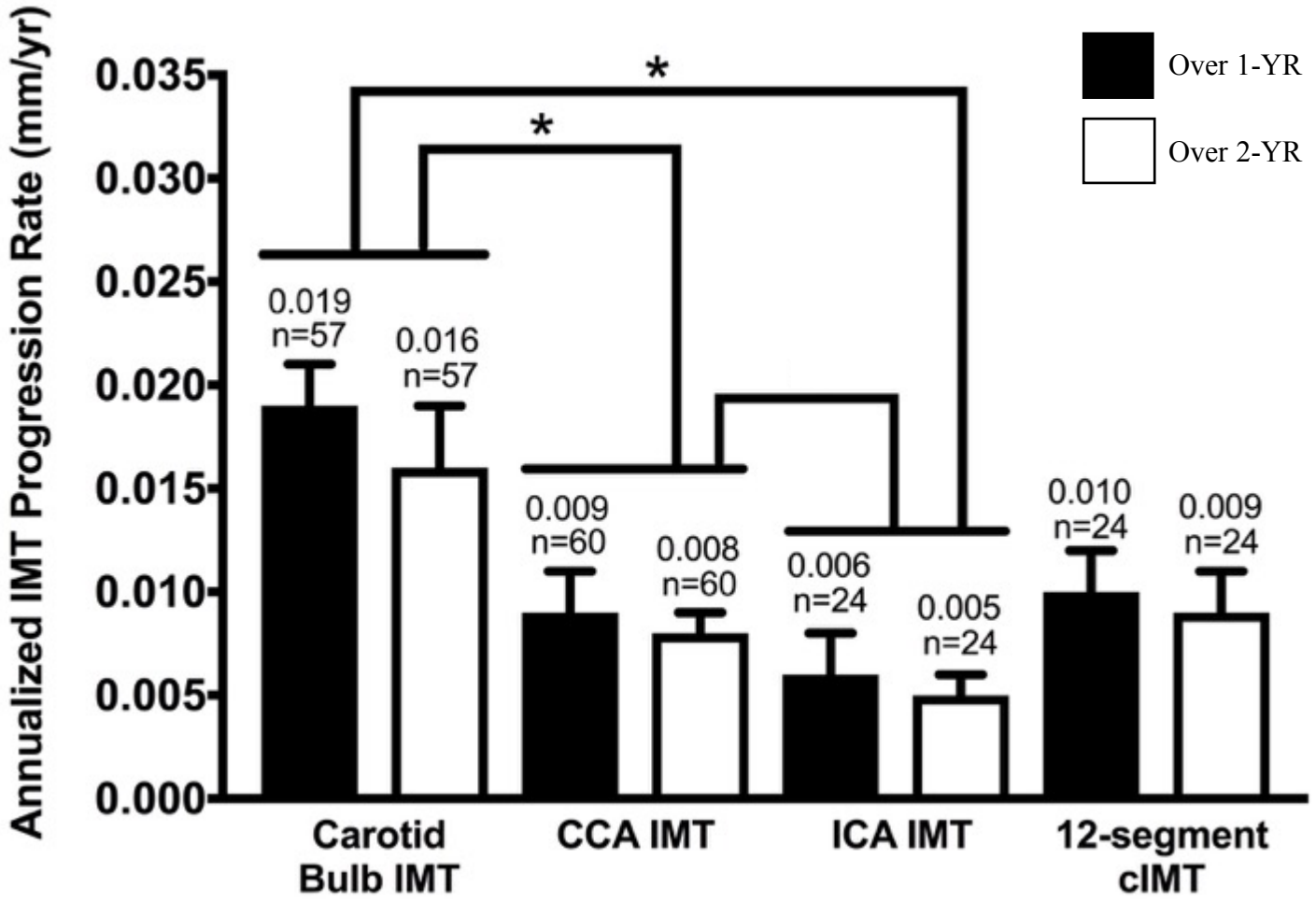
Appendix Table 3. Participant Characteristics at Baseline and 2-year Follow-up.

Variable		**Baseline**				**2-YR F/UP**				
Participant Demographics	**N**	**Mean (SD)**	**Median**	**Min, Max**	**N**	**Mean (SD)**	**Median**	**Min, Max**	**Change from BL to 2-YR F/UP**	**p-value**
Age(y)	125	12.61 (2.90)	12.58	5.42, 17.92	60	15.18 (2.95)	15.00	7.50, 20.17	2.57	**<0.001**
Sex: Male (%)	125	54 (43.20%)	-	-	60	31 (51.67%)	-	-	-	-
Race: Caucasian (%)	125	100 (80.00%)	-	-	60	51 (85.00%)	-	-	-	-
Weight (kg)	124	81.90 (26.14)	78.70	34.30, 152.50	60	98.00 (27.08)	93.25	52.90, 171.80	16.10	**<0.001**
Height (m)	124	156.33 (14.77)	158.20	120.30, 193.00	60	165.53 (14.10)	164.30	116.70, 195.70	9.20	**<0.001**
BMI (kg/m^2)	124	32.70 (6.28)	31.93	20.97, 52.38	60	35.66 (8.91)	34.00	22.53, 77.17	2.96	**0.019**
BMI z-score	124	3.33 (1.01)	3.32	1.49, 9.00	51	3.33 (1.48)	3.03	0.49, 9.13	0.00	0.998
Waist circumference (cm)	81	96.10 (15.25)	94.20	59.50, 131.00	28	106.36 (18.02)	100.75	82.00, 144.50	10.26	**0.038**
WC to Height Ratio	81	0.62 (0.07)	0.62	0.41, 0.83	28	0.64 (0.08)	0.62	0.52, 0.81	0.02	0.366
Body Fat (%)	107	43.62 (7.16)	43.80	23.60, 56.70	55	43.19 (8.20)	44.70	13.10, 57.00	-0.43	0.090

Participant Cardiovascular Risk Factors	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max	Change from BL to 2-YR F/UP	p-value
Systolic BP (mmHg)	123	110.09 (11.64)	109.00	83.00, 145.00	59	111.91 (10.28)	111.80	88.00, 145.80	1.82	**<0.001**
Diastolic BP (mmHg)	123	69.23 (9.31)	68.20	51.20, 104.33	59	68.48 (8.94)	68.80	50.00, 89.75	-0.75	**0.021**
SBP Percentile age-sex-height	122	52 (27)	51	4, 100	57	47 (24)	45	3, 99	-5	0.271
DBP Percentile age-sex-height	122	64 (23)	67	13, 100	57	56 (24)	53	11, 99	-8	0.073
Total Cholesterol (mmol/L)	113	4.20 (0.63)	4.09	2.87, 5.78	32	4.11 (0.71)	3.92	2.96, 6.25	-0.09	0.125
HDL Cholesterol (mmol/L)	113	1.14 (0.21)	1.13	0.78, 1.64	32	1.04 (0.18)	1.01	0.71, 1.32	-0.10	**0.030**
LDL Cholesterol (mmol/L)	113	2.50 (0.59)	2.48	1.23, 4.30	32	2.45 (0.68)	2.38	1.47, 4.58	-0.05	0.130
Triglycerides (mmol/L)	113	1.31 (0.68)	1.13	0.40, 5.09	32	1.36 (0.70)	1.23	0.52, 3.19	0.05	0.461
Non-HDL-C (mmol/L)	113	3.06 (0.64)	2.96	1.85, 4.80	32	3.07 (0.80)	2.95	1.74, 5.33	0.01	0.419
TC/HDL Ratio	113	3.77 (0.81)	3.72	2.13, 5.97	32	4.12 (1.19)	4.04	2.43, 6.79	0.35	0.197
FPG (mmol/L)	113	4.77 (0.47)	4.70	4.00, 6.90	31	4.76 (0.51)	4.80	3.30, 5.60	-0.01	0.629
2-hr PG (mmol/L)	59	5.92 (1.27)	5.70	2.60, 10.90	10	5.46 (1.00)	5.30	4.00, 6.80	-0.46	0.104
HbA1c (%)	102	5.26 (0.35)	5.25	4.60, 6.50	30	5.29 (0.31)	5.30	4.70, 6.00	0.03	0.150

Participant cIMT Measures	N	Mean (SD)	Median	Min, Max	N	Mean (SD)	Median	Min, Max	Change from BL to 2-YR F/UP	p-value
Mean Far Wall Bulb cIMT (mm)	125	0.429 (0.039)	0.425	0.333, 0.585	59	0.467 (0.059)	0.465	0.377, 0.761	0.038	**<0.001**
Mean Near Wall Bulb cIMT (mm)	122	0.441 (0.044)	0.438	0.349, 0.563	57	0.475 (0.049)	0.466	0.395, 0.589	0.034	**<0.001**
Average Mean Bulb cIMT (mm)	122	0.435 (0.037)	0.433	0.349, 0.542	57	0.472 (0.045)	0.466	0.392, 0.615	0.037	**<0.001**
Mean Far Wall CCA (2-segment) cIMT (mm)	125	0.388 (0.033)	0.385	0.325, 0.490	60	0.405 (0.039)	0.403	0.324, 0.529	0.017	**0.001**
Mean Near Wall CCA cIMT (mm)	125	0.408 (0.043)	0.398	0.337, 0.521	60	0.422 (0.045)	0.413	0.336, 0.557	0.014	**0.003**
Average Mean CCA cIMT (mm)	125	0.398 (0.032)	0.390	0.338, 0.482	60	0.413 (0.035)	0.409	0.351, 0.505	0.015	**<0.001**
Mean Far Wall ICA cIMT (mm)	87	0.358 (0.033)	0.347	0.311, 0.508	34	0.369 (0.038)	0.366	0.324, 0.500	0.011	0.231
Mean Near Wall ICA cIMT (mm)	69	0.354 (0.031)	0.344	0.314, 0.496	24	0.358 (0.029)	0.351	0.319, 0.436	0.004	0.134
Average Mean ICA cIMT (mm)	69	0.356 (0.028)	0.350	0.315, 0.455	24	0.365 (0.029)	0.369	0.328, 0.432	0.009	**0.024**
Mean cIMT, 12-segments (mm)	69	0.400 (0.029)	0.397	0.359, 0.493	24	0.418 (0.035)	0.422	0.365, 0.492	0.018	**<0.001**

All measures are reported as mean (standard deviation) unless otherwise stated. P values in boldface indicate significance ($p<0.05$).



Appendix Figure 3. Annualized IMT progression rates over 1-year and 2-years of follow-up. Annualized progression rates (mm/year) for cIMT measures over 1-year and 2-years of follow-up are presented. Carotid IMT progression rates were greater at the carotid bulb than the CCA and ICA, over both 1-year and 2-years of follow-up (*$p<0.001$).

Appendix Table 4. Baseline Univariable Regression Analyses of cIMT Measures.

	Carotid Bulb - far wall only cIMT (n=125)			**Mean Carotid Bulb IMT (n=122)**			**CCA - far wall only cIMT (n=125)**			**Mean CCA IMT (n=125)**		
	Reg. Coeff. (SE)	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**
Age (years)	0.0058 (0.0011)	18.67	**<0.001**	0.0059 (0.0011)	20.68	**<0.001**	0.0025 (0.0010)	4.86	**0.013**	0.0024 (0.0010)	4.81	**0.014**
Sex (Male)	0.0160 (0.0069)	4.12	**0.023**	0.0180 (0.0066)	5.80	**0.008**	0.0074 (0.0059)	1.27	0.210	0.0084 (0.0057)	1.73	0.144
Height (in cm)	0.0010 (0.0002)	15.24	**<0.001**	0.0011 (0.0002)	20.29	**<0.001**	0.0005 (0.0002)	5.09	**0.012**	0.0006 (0.0002)	8.27	**0.001**
BMI (kg/m2)	0.0016 (0.0005)	6.99	**0.003**	0.0015 (0.0005)	6.76	**0.004**	0.0003 (0.0005)	0.40	0.484	0.0005 (0.0005)	0.97	0.277
WC (cm)	0.0007 (0.0003)	7.41	**0.014**	0.0007 (0.0003)	8.62	**0.009**	0.0006 (0.0003)	6.12	**0.027**	0.0005 (0.0002)	5.52	**0.035**
Body Fat %	-0.0004 (0.0005)	0.43	0.505	-0.0006 (0.0005)	1.36	0.238	-0.0008 (0.0004)	2.66	0.093	-0.0006 (0.0004)	1.52	0.206
LDL-C (mmol/L)	0.0073 (0.0063)	1.23	0.244	0.0049 (0.0060)	0.62	0.414	0.0059 (0.0054)	1.08	0.277	0.0090 (0.0051)	2.72	0.082
HDL-C (mmol/L)	-0.0367 (0.0173)	3.89	**0.036**	-0.0406 (0.0165)	5.25	**0.016**	-0.0385 (0.0147)	5.85	**0.010**	-0.0259 (0.0144)	2.81	0.076
Non-HDL-C (mmol/L)	0.0064 (0.0057)	1.12	0.265	0.0042 (0.0055)	0.52	0.451	0.0052 (0.0049)	1.01	0.289	0.0072 (0.0047)	2.03	0.132

TC/HDL-C	0.0086 (0.0045)	3.19	0.059	0.0083 (0.0043)	3.33	0.055	0.0081 (0.0038)	3.83	**0.038**	0.0079 (0.0037)	3.91	**0.036**
SBP (mmHg)	0.0009 (0.0003)	6.43	**0.005**	0.0010 (0.0003)	10.69	**<0.001**	0.0004 (0.0003)	1.58	0.166	0.0006 (0.0002)	4.22	**0.023**
DBP (mmHg)	0.0008 (0.0004)	3.98	**0.027**	0.0010 (0.0004)	6.13	**0.006**	0.0002 (0.0003)	0.26	0.575	0.0002 (0.0003)	0.23	0.602
FPG (mmol/L)	0.0194 (0.0079)	5.20	**0.015**	0.0138 (0.0075)	2.98	0.070	0.0115 (0.0066)	2.65	0.085	0.0157 (0.0064)	5.07	**0.016**
2-hr PG (mmol/L)	-0.0021 (0.0034)	0.65	0.543	-0.0023 (0.0036)	0.73	0.527	-0.0039 (0.0033)	2.37	0.245	-0.0034 (0.0035)	1.63	0.335
HbA1c (%)	-0.0062 (0.0108)	0.33	0.569	-0.0048 (0.0105)	0.21	0.649	-0.0095 (0.0095)	0.98	0.323	-0.0085 (0.0092)	0.83	0.362

	ICA - far wall only cIMT (n=87)			**Mean ICA IMT (n=69)**			**Mean 12-segment (mm) (n=69)**		
	Reg. Coeff. (SE)	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**
Age (years)	0.0021 (0.0012)	3.51	0.082	0.0026 (0.0012)	6.75	**0.031**	0.0036 (0.0012)	12.5	**0.003**
Sex (Male)	0.0113 (0.0071)	2.87	0.117	0.0108 (0.0067)	3.78	0.109	0.0138 (0.0068)	5.8	**0.047**
Height (in cm)	0.0006 (0.0001)	2.94	0.115	0.0005 (0.0002)	6.53	**0.035**	0.0007 (0.0002)	14.9	**0.001**
BMI (kg/m2)	0.0007 (0.0006)	1.76	0.224	0.0016 (0.0006)	11.03	**0.006**	0.0017 (0.0006)	11.9	**0.004**
WC (in cm)	0.0002 (0.0003)	0.67	0.538	0.0004 (0.0003)	3.90	0.183	0.0007 (0.0003)	9.29	**0.037**

Body Fat %	-0.0001 (0.0005)	0.02	0.900	0.0001 (0.0005)	0.10	0.811	0.0000 (0.0006)	0.00	0.970
LDL-C (mmol/L)	0.0019 (0.0067)	0.11	0.772	0.0023 (0.0061)	0.22	0.710	0.0062 (0.0064)	1.52	0.331
HDL-C (mmol/L)	-0.0120 (0.0179)	0.56	0.504	-0.0076 (0.0172)	0.31	0.660	-0.0231 (0.0178)	2.61	0.198
Non-HDL-C (mmol/L)	0.0013 (0.0057)	0.06	0.827	0.0002 (0.0052)	0.00	0.972	0.0037 (0.0054)	0.75	0.494
TC/HDL-C Ratio	0.0010 (0.0048)	0.05	0.838	-0.0002 (0.0045)	0.00	0.963	0.0047 (0.0046)	1.62	0.312
SBP (mmHg)	0.0004 (0.0003)	1.94	0.198	0.0008 (0.0003)	10.19	**0.007**	0.0011 (0.0003)	16.48	**0.001**
DBP (mmHg)	0.0001 (0.0004)	0.04	0.853	0.0002 (0.0004)	0.43	0.594	0.0007 (0.0004)	5.19	0.060
FPG (mmol/L)	0.0094 (0.0073)	2.09	0.198	0.0101 (0.0065)	3.75	0.125	0.0142 (0.0067)	6.71	**0.039**
2-hr PG (mmol/L)	-0.0039 (0.0052)	1.28	0.454	-0.0021 (0.0045)	0.58	0.639	-0.0016 (0.0043)	0.37	0.709
HbA1c (%)	-0.0105 (0.0109)	1.24	0.341	-0.0067 (0.0097)	0.80	0.494	-0.0029 (0.0101)	0.14	0.772

P values in boldface indicate significance ($p<0.05$).

Appendix Table 5. Univariable Regression Analyses of cIMT Measures at 1-year Follow-up.

	Carotid Bulb - far wall only cIMT (n=123)			**Mean Carotid Bulb IMT (n=120)**			**CCA - far wall only cIMT (n=124)**			**Mean CCA IMT (n=124)**		
	Reg. Coeff. (SE)	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**
Age (years)	0.0050 (0.0013)	11.21	**<0.001**	0.0046 (0.0011)	12.23	**<0.001**	0.0024 (0.0010)	4.61	**0.016**	0.0021 (0.0010)	3.12	**0.048**
Sex (Male)	0.0247 (0.0078)	7.63	**0.002**	0.0234 (0.0068)	9.01	**0.001**	0.0140 (0.0062)	4.00	**0.026**	0.0122 (0.0063)	3.01	0.055
Height (in cm)	0.0011 (0.0002)	14.04	**<0.001**	0.0010 (0.0002)	17.41	**<0.001**	0.0004 (0.0002)	4.54	**0.018**	0.0005 (0.0002)	5.02	**0.012**
Baseline cIMT (mm)	0.8977 (0.0631)	62.44	**<0.001**	0.8550 (0.0545)	67.42	**<0.001**	0.8452 (0.0597)	62.01	**<0.001**	0.9684 (0.0488)	76.20	**<0.001**
BMI (kg/m^2)	0.0017 (0.0006)	5.51	**0.009**	0.0015 (0.0006)	5.90	**0.007**	0.0027 (0.0030)	0.71	0.356	0.0013 (0.0030)	0.10	0.675
WC (cm)	0.0011 (0.0003)	10.91	**0.003**	0.0008 (0.0003)	9.21	**0.008**	0.0006 (0.0003)	6.11	**0.027**	0.0007 (0.0003)	8.42	**0.009**
Body Fat %	-0.0003 (0.0006)	0.25	0.609	-0.0006 (0.0005)	1.10	0.286	-0.0007 (0.0005)	2.13	0.136	-0.0003 (0.0005)	0.42	0.506
LDL-C (mmol/L)	0.0125 (0.0074)	2.5	0.098	0.0050 (0.0065)	0.52	0.448	0.0105 (0.0057)	3.0	0.068	0.0108 (0.0057)	3.2	0.061
HDL-C (mmol/L)	-0.0312 (0.0209)	2.04	0.140	-0.0324 (0.0182)	2.92	0.077	-0.0466 (0.0156)	7.51	**0.003**	-0.0387 (0.0159)	5.10	**0.017**

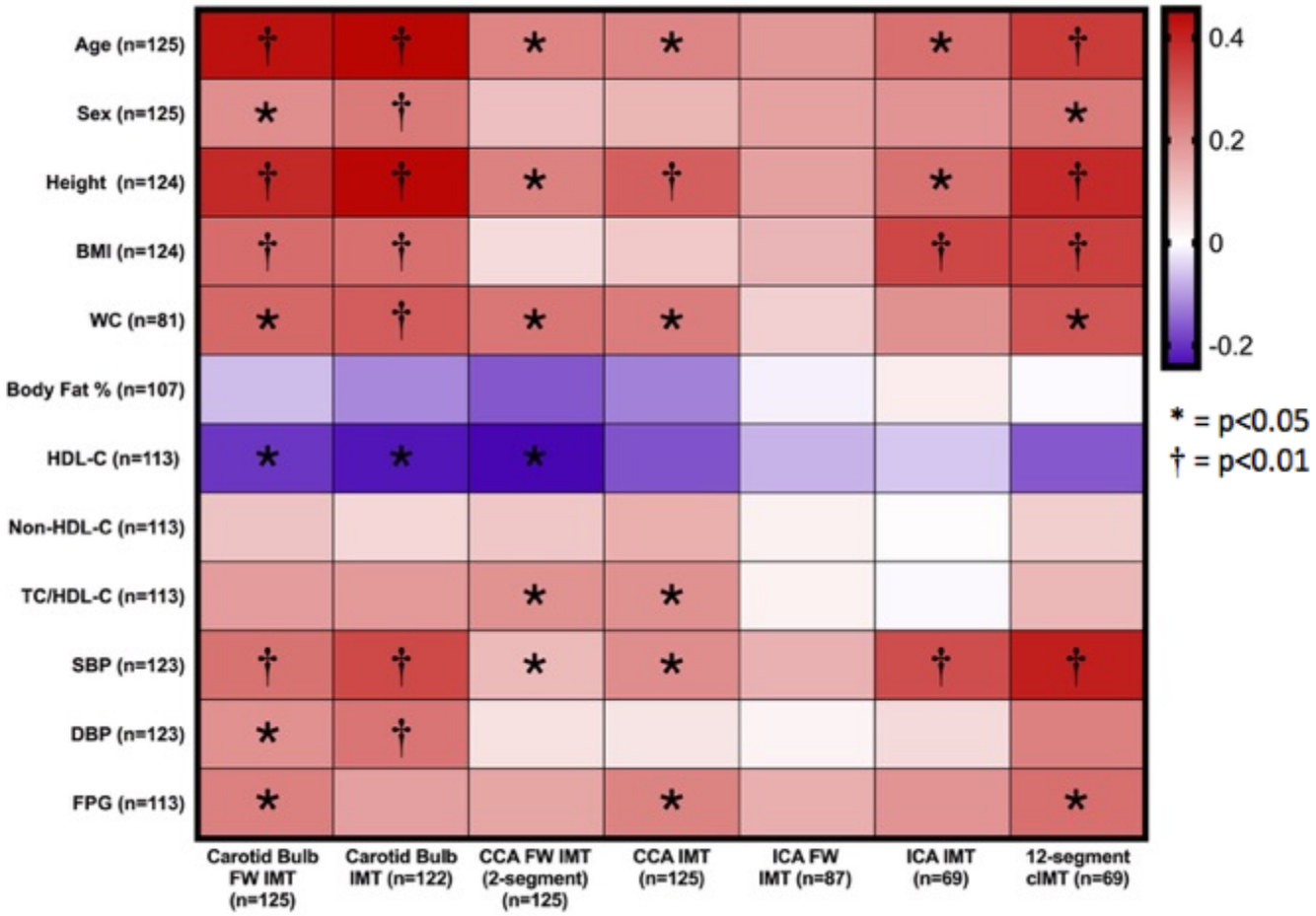
Non-HDL-C (mmol/L)	0.0146 (0.0067)	4.23	**0.031**	0.0068 (0.0060)	1.21	0.249	0.0101 (0.0052)	3.41	0.053	0.0080 (0.0053)	2.11	0.129
TC/HDL-C Ratio	0.0124 (0.0053)	4.81	**0.021**	0.0087 (0.0046)	3.13	0.065	0.0121 (0.0040)	7.60	**0.003**	0.0104 (0.0041)	5.52	**0.013**
Systolic BP (mmHg)	0.0011 (0.0003)	8.31	**0.001**	0.0010 (0.0003)	9.61	**0.001**	0.0005 (0.0003)	3.31	**0.044**	0.0006 (0.0003)	3.93	**0.028**
Diastolic BP (mmHg)	0.0011 (0.0004)	5.00	**0.014**	0.0007 (0.0004)	2.94	0.062	0.0004 (0.0003)	1.01	0.270	0.0003 (0.0003)	0.50	0.447
FPG (mmol/L)	0.0216 (0.0093)	4.74	**0.021**	0.0178 (0.0080)	4.40	**0.028**	0.0132 (0.0072)	3.01	0.068	0.0202 (0.0071)	6.82	**0.005**
2-hr PG (mmol/L)	0.0008 (0.0047)	0.1	0.854	-0.0026 (0.0043)	0.73	0.550	-0.0033 (0.0039)	1.2	0.406	-0.0028 (0.0040)	0.9	0.489
HbA1c (%)	-0.0088 (0.0135)	0.4	0.516	-0.0180 (0.0117)	2.41	0.129	-0.0112 (0.0103)	1.2	0.276	-0.0003 (0.0103)	0.0	0.980

	ICA - far wall only cIMT (n=83)			**Mean ICA IMT (n=63)**			**Mean 1-year cIMT, 12-segment (mm) (n=63)**		
	Reg. Coeff. (SE)	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**	**Reg. Coeff. (SE)**	**R^2 (%)**	**P-value**
Age (years)	0.0029 (0.0012)	6.87	**0.017**	0.0036 (0.0014)	9.57	**0.014**	0.0033 (0.0015)	7.70	**0.027**

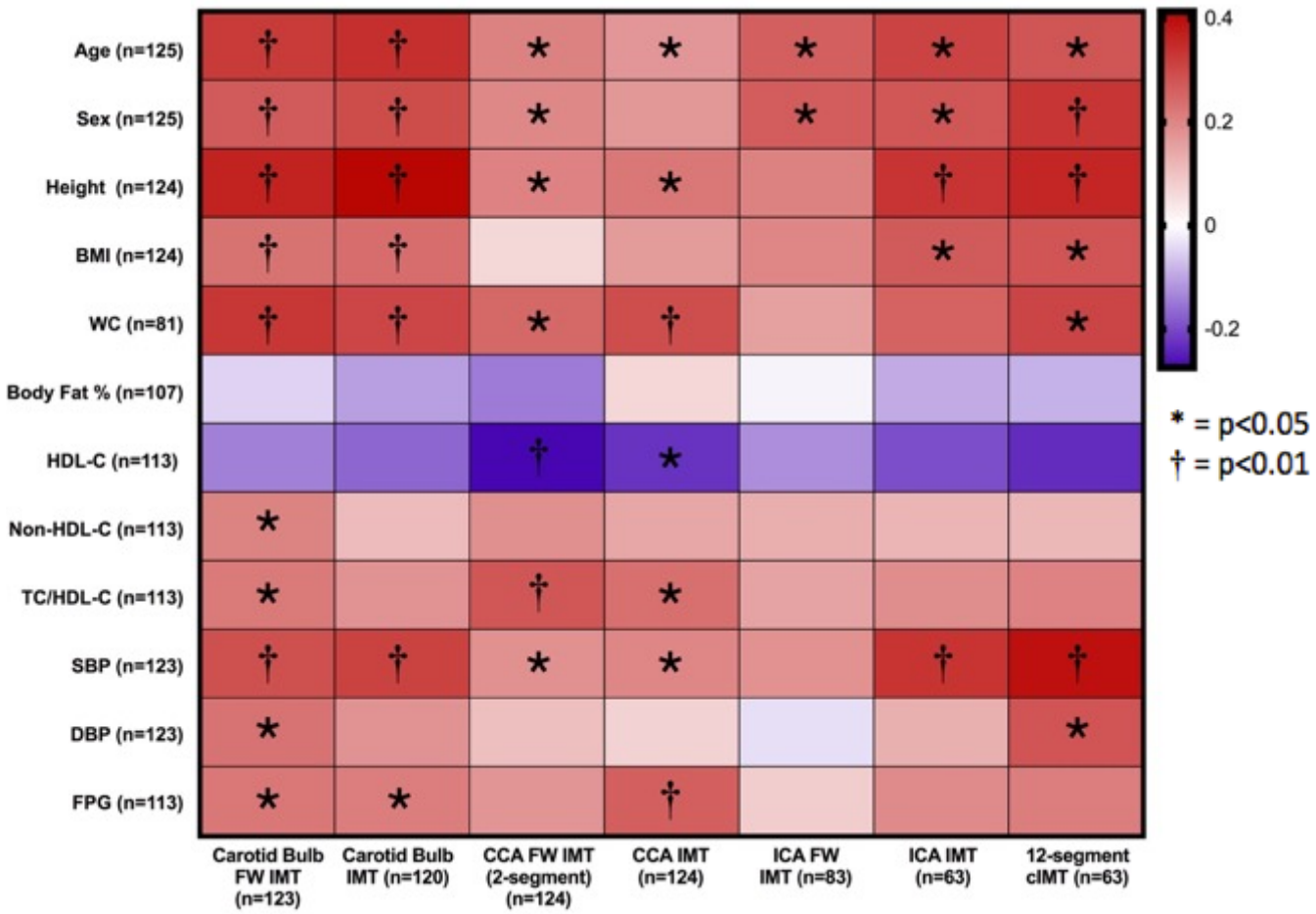
Sex (Male)	0.0176 (0.0071)	7.06	**0.015**	0.0180 (0.0080)	7.66	**0.028**	0.0222 (0.0081)	11.01	**0.008**
Height (in cm)	0.0004 (0.0002)	4.24	0.063	0.0007 (0.0003)	11.19	**0.008**	0.0008 (0.0003)	12.71	**0.004**
Baseline cIMT (mm)	0.7079 (0.0767)	51.3	**<0.001**	0.9037 (0.0885)	63.09	**<0.001**	1.0573 (0.0650)	85.12	**<0.001**
BMI (kg/m2)	0.0010 (0.0006)	3.88	0.076	0.0015 (0.0007)	7.29	**0.034**	0.0020 (0.0007)	7.91	**0.027**
WC (cm)	0.0004 (0.0003)	2.42	0.253	0.0006 (0.0004)	6.60	0.096	0.0007 (0.0004)	9.20	**0.048**
Body Fat %	-0.0001 (0.0006)	0.02	0.905	-0.0005 (0.0007)	0.88	0.488	-0.0004 (0.0007)	0.81	0.520
LDL-C (mmol/L)	0.0089 (0.0066)	2.34	0.184	0.0073 (0.0073)	1.75	0.322	0.0103 (0.0075)	3.3	0.173
HDL-C (mmol/L)	-0.0200 (0.0182)	1.56	0.276	-0.0304 (0.0202)	3.84	0.137	-0.0375 (0.0207)	5.51	0.075
Non-HDL-C (mmol/L)	0.0066 (0.0057)	1.74	0.249	0.0057 (0.0061)	1.49	0.356	0.0055 (0.0063)	1.30	0.385
TC/HDL-C Ratio	0.0064 (0.0048)	2.25	0.190	0.0075 (0.0052)	3.53	0.154	0.0084 (0.0053)	4.11	0.123
Systolic BP	0.0005 (0.0003)	3.21	0.105	0.0010 (0.0004)	11.23	**0.007**	0.0012 (0.0004)	15.51	**0.001**

(mmHg)									
Diastolic BP (mmHg)	-0.0001 (0.0004)	0.13	0.749	0.0005 (0.0005)	1.66	0.314	0.0010 (0.0005)	7.81	**0.026**
FPG (mmol/L)	0.0053 (0.0075)	0.66	0.482	0.0118 (0.0082)	3.60	0.154	0.0136 (0.0084)	4.52	0.111
2-hr PG (mmol/L)	0.0011 (0.0053)	0.10	0.842	-0.0010 (0.0053)	0.10	0.848	-0.0008 (0.0052)	0.1	0.872
HbA1c (%)	-0.0088 (0.0111)	0.90	0.432	-0.0123 (0.0116)	2.10	0.291	-0.0082 (0.0121)	0.9	0.500

P values in boldface indicate significance ($p<0.05$).



Appendix Figure 4. Pearson correlation heat map for baseline cIMT measures. Heat map of the Pearson correlations between baseline participant characteristics and measures of cIMT at baseline. *P < .05 and †P < .01. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

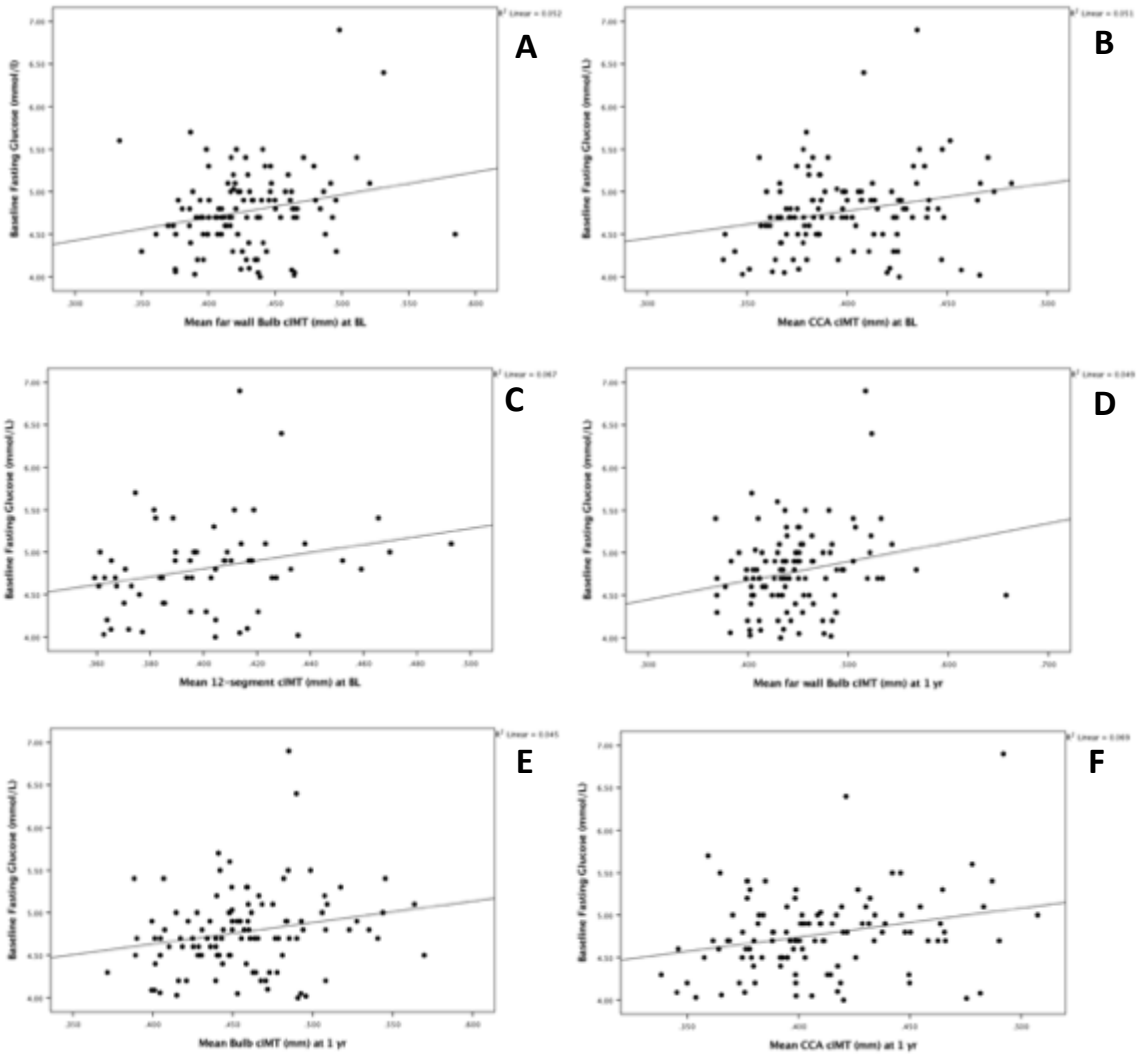


Appendix Figure 5. Pearson correlation heat map for 1-year cIMT measures. Heat map of the Pearson correlations between baseline participant characteristics and measures of cIMT at 1-year follow-up. *P < .05 and †P < .01. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

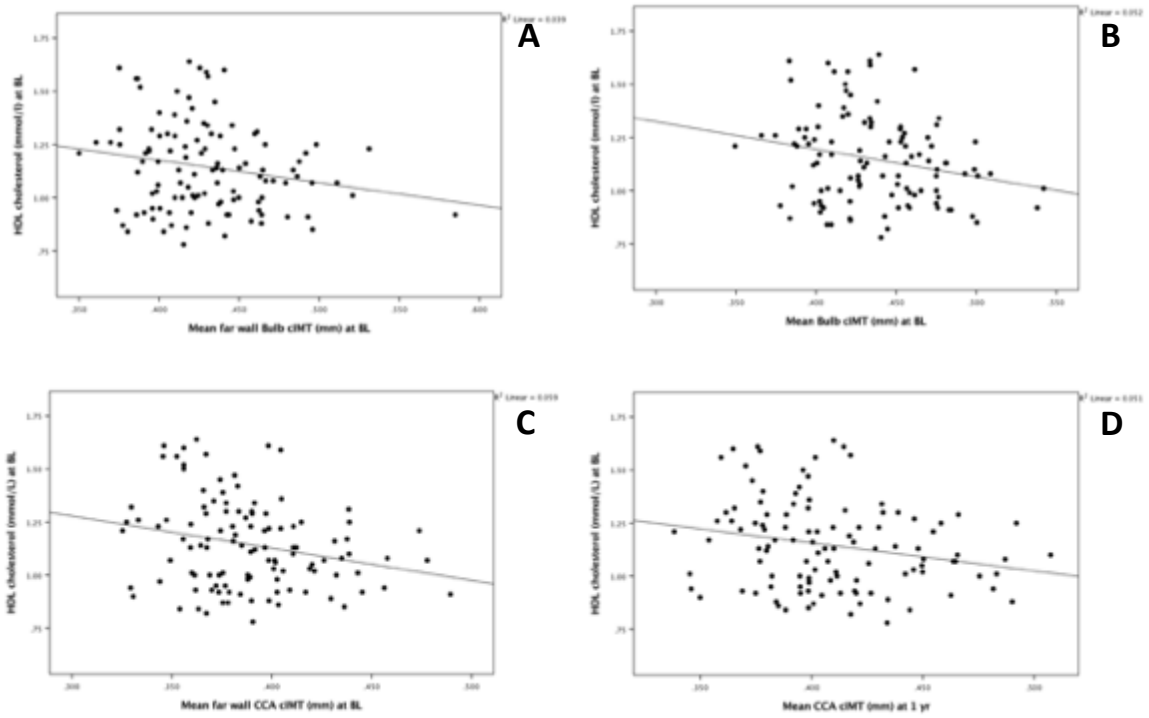
A	12-segment cIMT	Carotid bulb far wall IMT	Mean carotid bulb IMT	CCA far wall IMT	Mean CCA IMT	ICA far wall IMT	Mean ICA IMT
Age	0.354	0.432	0.455	0.221	0.219	0.187	0.260
Sex	0.240	0.203	0.241	0.113	0.131	0.169	0.194
Height	0.386	0.390	0.450	0.226	0.288	0.171	0.256
Race	0.006	0.052	-0.025	-0.043	-0.083	-0.022	0.059
BMI	0.344	0.264	0.260	0.063	0.098	0.133	0.332
WC	0.305	0.272	0.294	0.247	0.235	0.082	0.198
Body fat %	-0.005	-0.065	-0.117	-0.163	-0.123	-0.014	0.031
LDL-C	0.123	0.111	0.079	0.104	0.165	0.033	0.047
HDL-C	-0.162	-0.197	-0.229	-0.242	-0.168	-0.075	-0.056
Non-HDL-C	0.086	0.106	0.072	0.101	0.143	0.025	0.004
TC/HDL-C	0.127	0.178	0.183	0.196	0.198	0.023	-0.006
SBP	0.406	0.254	0.327	0.126	0.205	0.139	0.319
DBP	0.228	0.200	0.248	0.051	0.047	0.020	0.065
FPG	0.259	0.228	0.173	0.163	0.225	0.144	0.194

B	12-segment cIMT	Carotid bulb far wall IMT	Mean carotid bulb IMT	CCA far wall IMT	Mean CCA IMT	ICA far wall IMT	Mean ICA IMT
Age	0.278	0.323	0.341	0.205	0.171	0.262	0.309
Sex	0.332	0.270	0.294	0.195	0.169	0.266	0.277
Height	0.356	0.365	0.413	0.202	0.220	0.206	0.334
BMI	0.280	0.231	0.239	0.063	0.163	0.197	0.270
WC	0.304	0.330	0.303	0.247	0.290	0.155	0.257
Body fat %	-0.087	-0.050	-0.107	-0.146	0.065	-0.014	-0.094
LDL-C	0.181	0.159	0.074	0.174	0.178	0.153	0.132
HDL-C	-0.234	-0.141	-0.170	-0.274	-0.226	-0.125	-0.196
Non-HDL-C	0.115	0.204	0.111	0.183	0.144	0.132	0.122
TC/HDL-C	0.203	0.219	0.177	0.276	0.235	0.150	0.188
SBP	0.394	0.288	0.310	0.181	0.198	0.179	0.335
DBP	0.280	0.229	0.177	0.104	0.072	-0.036	0.129
FPG	0.212	0.221	0.213	0.175	0.263	0.081	0.190

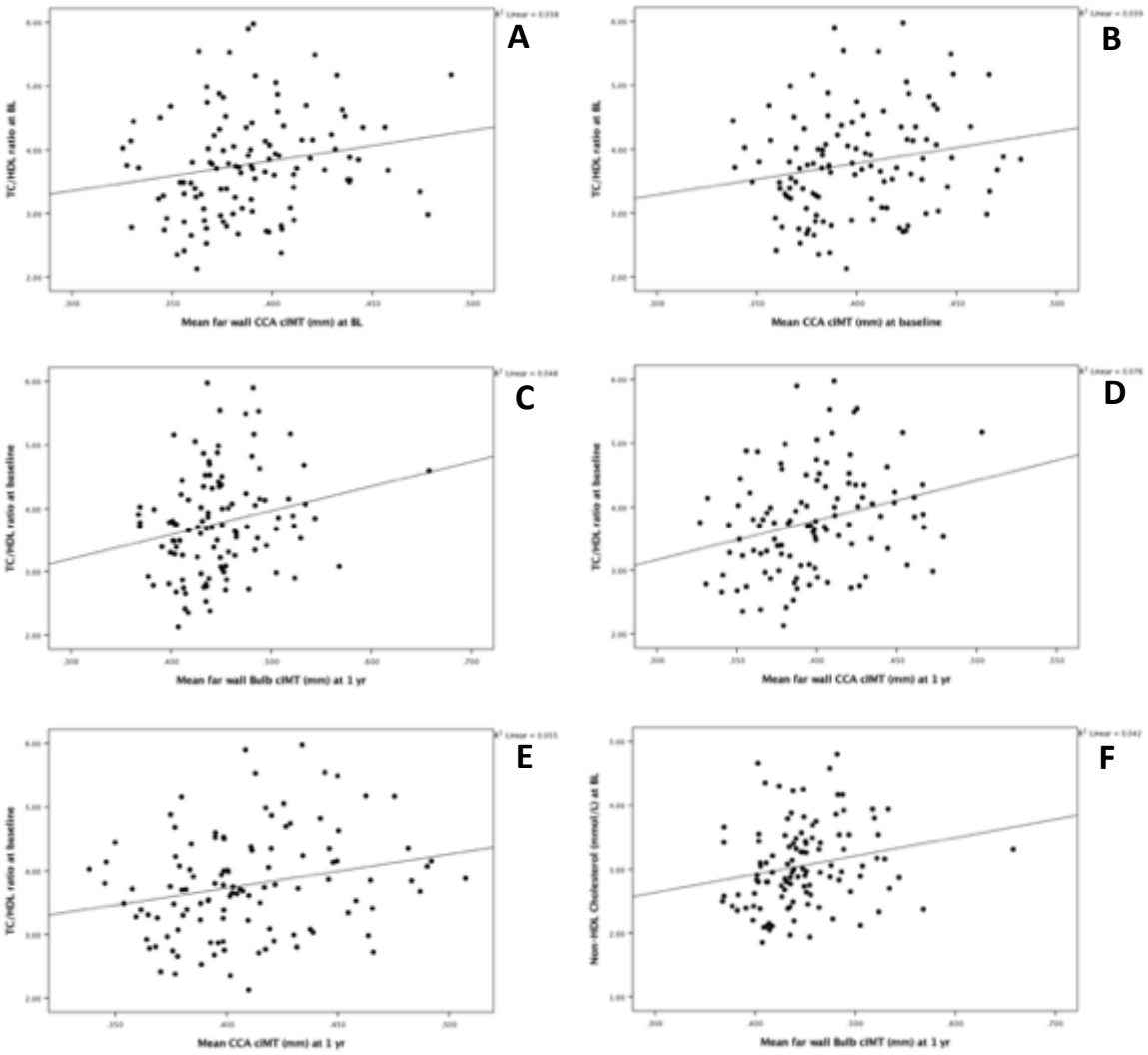
Appendix Table 6. Pearson correlation values between baseline CVRFs and measures of cIMT at (A) baseline and (B) 1-year follow-up. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-HDL cholesterol; TC/HDL-C, total cholesterol-to-HDL cholesterol ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.



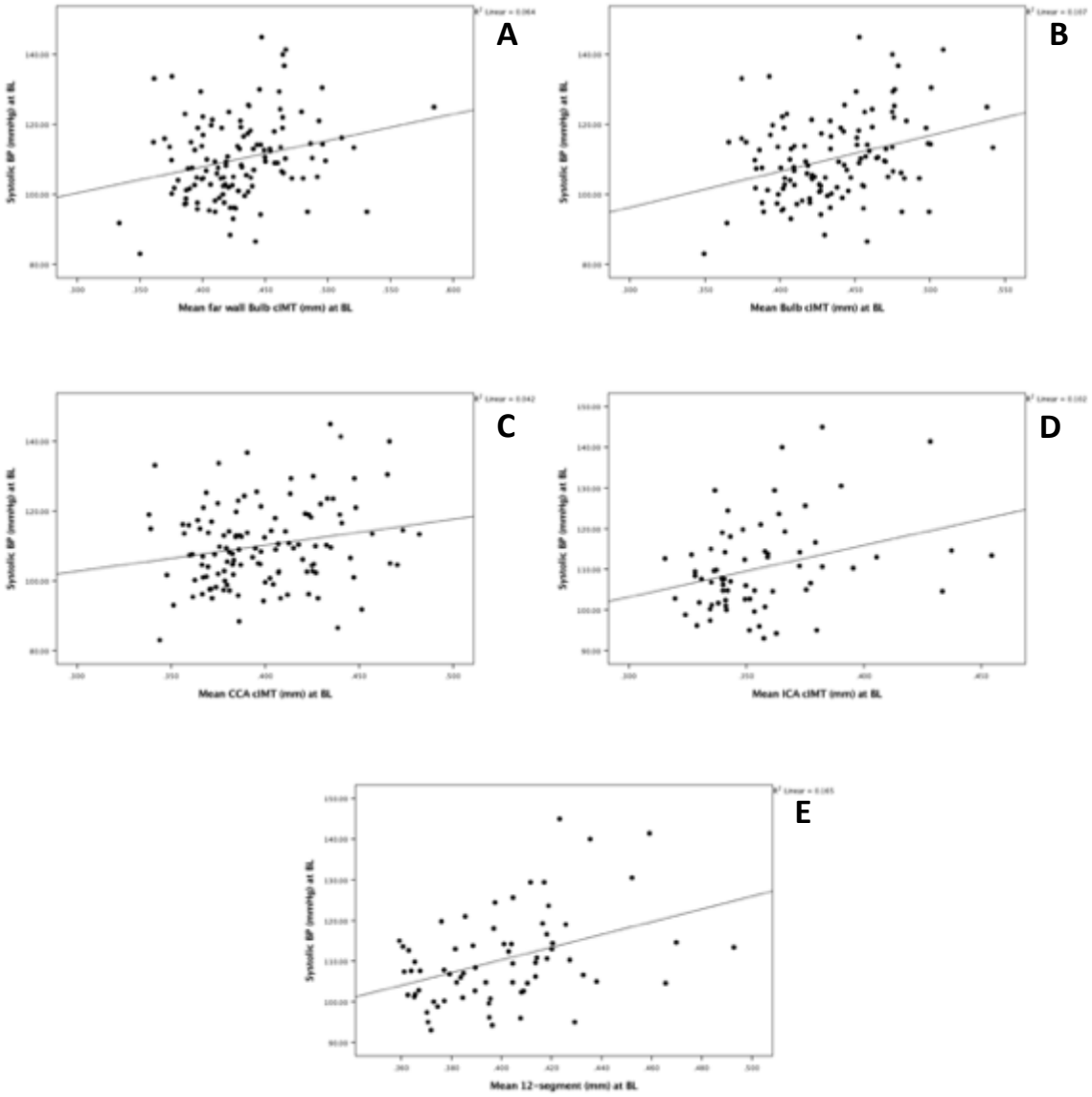
Appendix Figure 6. Distribution of baseline FPG values and measures of cIMT at baseline and 1-year follow-up. Baseline FPG was associated with: **(A)** baseline carotid bulb far wall IMT (mm) (r=0.228, p=0.015), **(B)** baseline mean CCA IMT (r=0.225, p=0.016), **(C)** 12-segment cIMT (r=0.259, p=0.039), **(D)** carotid bulb far wall IMT at 1 year (r=0.221, p=0.021) **(E)** mean carotid bulb IMT at 1-year (r=0.213, p=0.028) and **(F)** mean CCA IMT at 1-year (r=0.263, p=0.005).



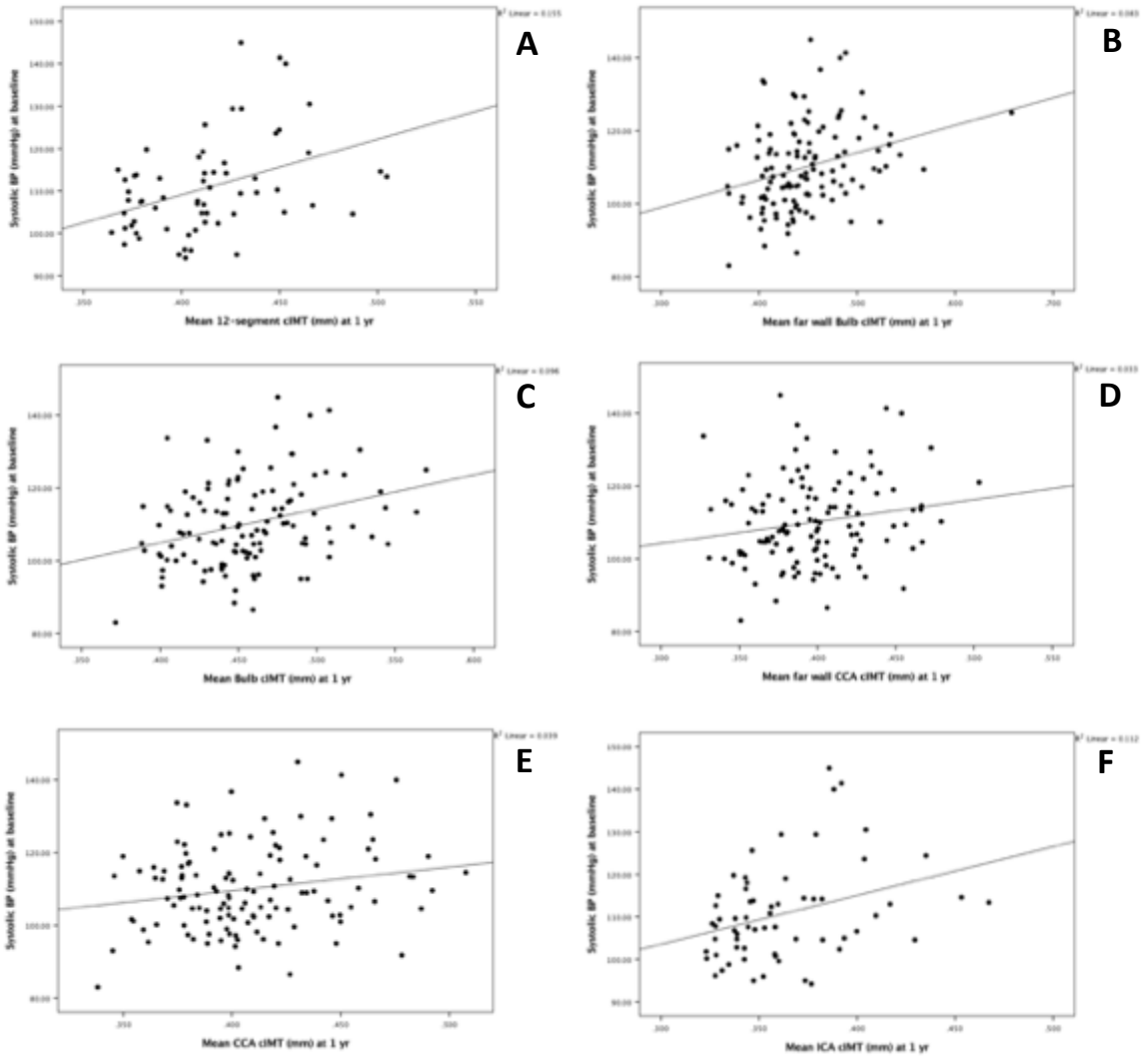
Appendix Figure 7. Distribution of baseline HDL cholesterol values and measures of cIMT at baseline. Baseline HDL cholesterol was associated with: **(A)** carotid bulb far wall IMT at baseline (r=-0.197, p=0.036), **(B)** mean carotid bulb IMT at baseline (r=-0.229, p=0.016), **(C)** CCA far wall (2-segment) IMT at baseline (r=-0.242, p=0.010), **(D)** mean CCA IMT (r=-0.226, p=0.017) at 1 year.



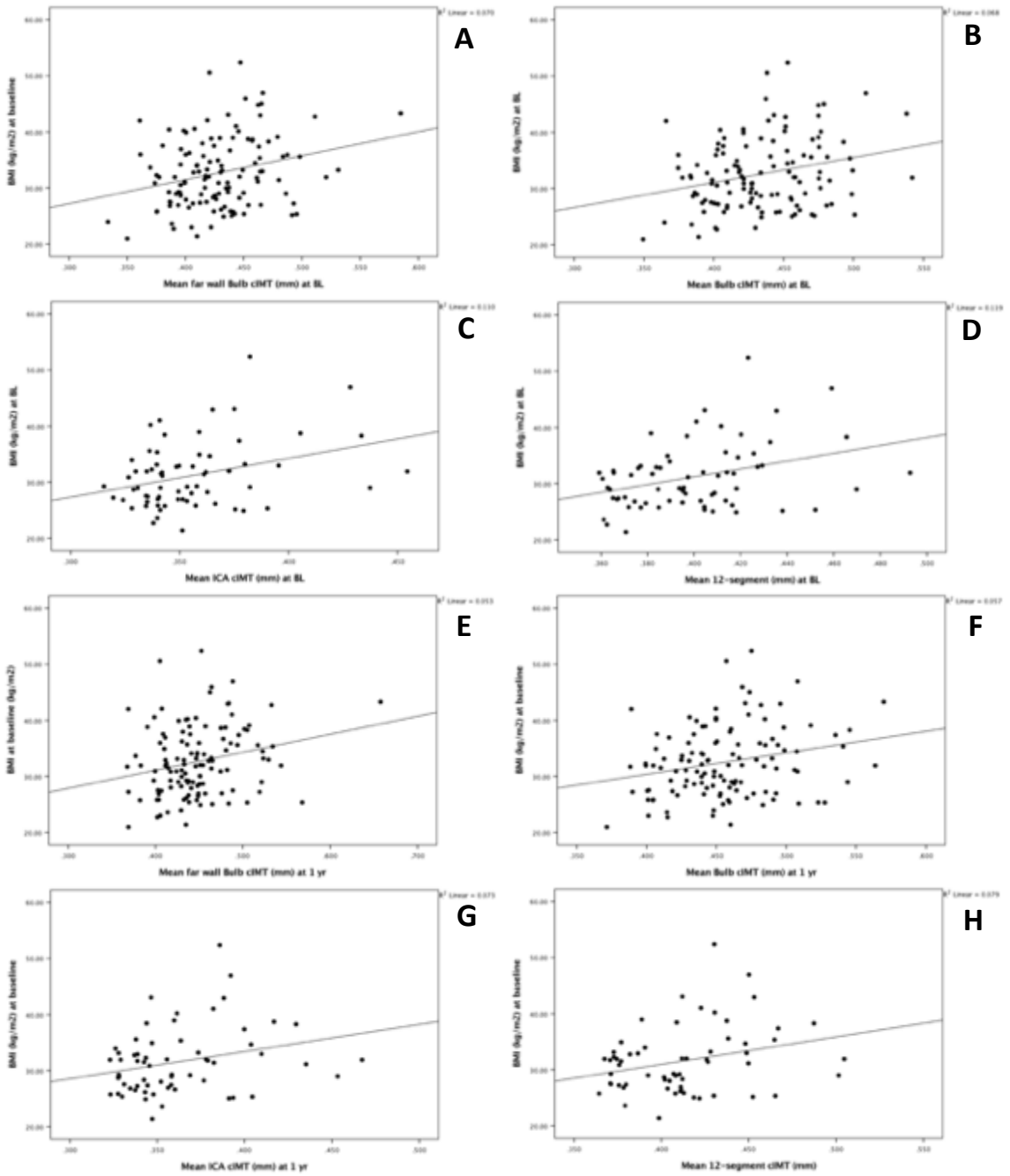
Appendix Figure 8. Distribution of baseline TC/HDL and non-HDL-C values and measures of cIMT at baseline and 1-year follow-up. Baseline TC/HDL ratio was associated with: **(A)** CCA far wall (2-segment) IMT at baseline (r=0.196, p=0.038), **(B)** mean CCA IMT at baseline (r=0.198, p=0.036), **(C)** carotid bulb far wall IMT at 1 year (r=0.219, p=0.021), **(D)** CCA far wall (2-segment) IMT at 1 year (r=0.276, p=0.003) and **(E)** mean CCA IMT at 1 year (r=0.235, p=0.013). Baseline Non-HDL-C was associated with: **(F)** carotid bulb far wall IMT at 1 year (r=0.204, p=0.031).



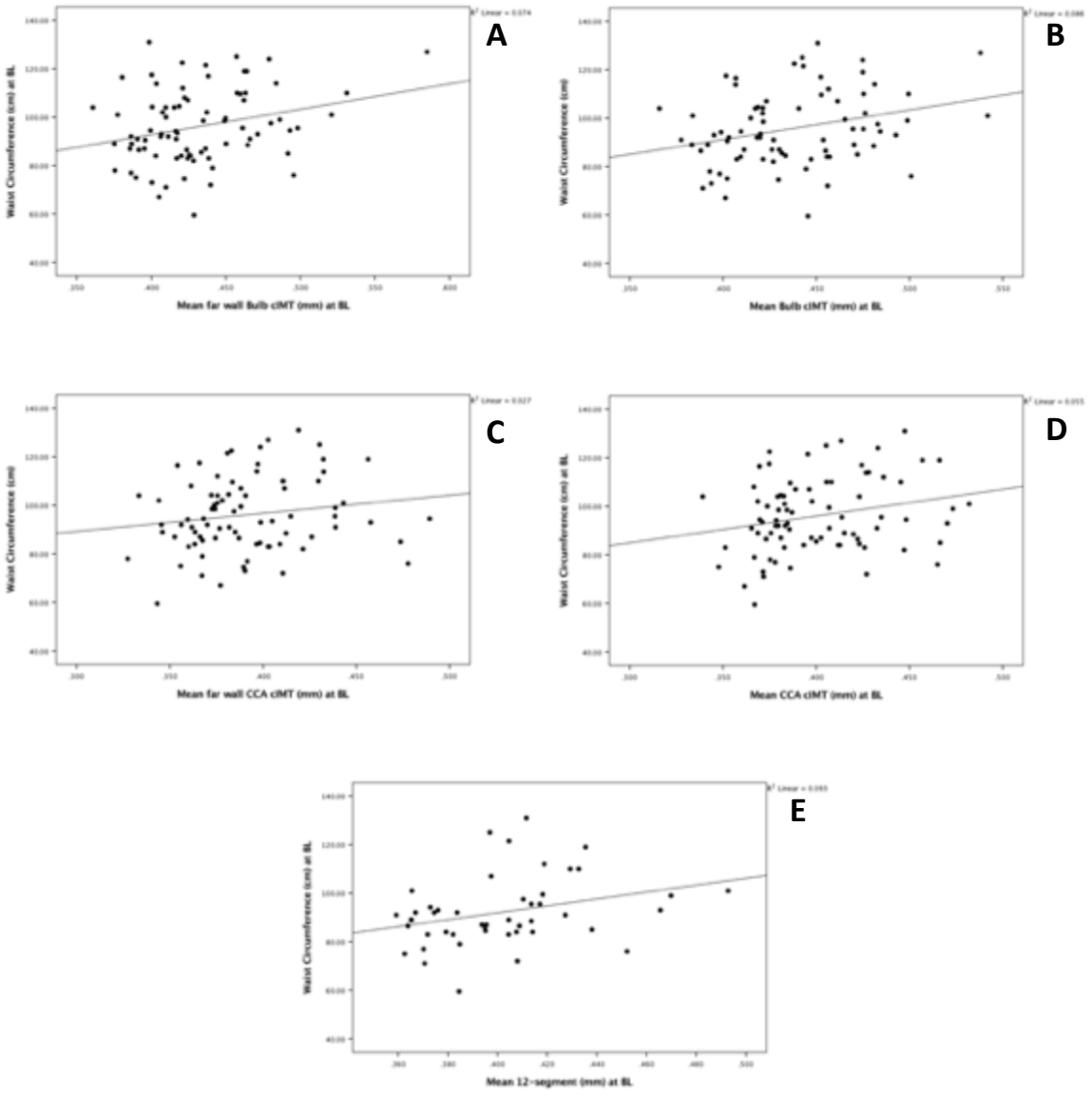
Appendix Figure 9. Distribution of baseline SBP values and measures of cIMT at baseline. Baseline SBP was associated with: **(A)** carotid bulb far wall IMT at baseline (r=0.254, p=0.005), **(B)** mean carotid bulb IMT at baseline (r=0.327, p=0.001), **(C)** mean CCA IMT at baseline (r=0.205, p<0.001), **(D)** mean ICA IMT at baseline (r=0.319, p=0.007), and **(E)** 12-segment cIMT at baseline (r=0.406, p=0.001).



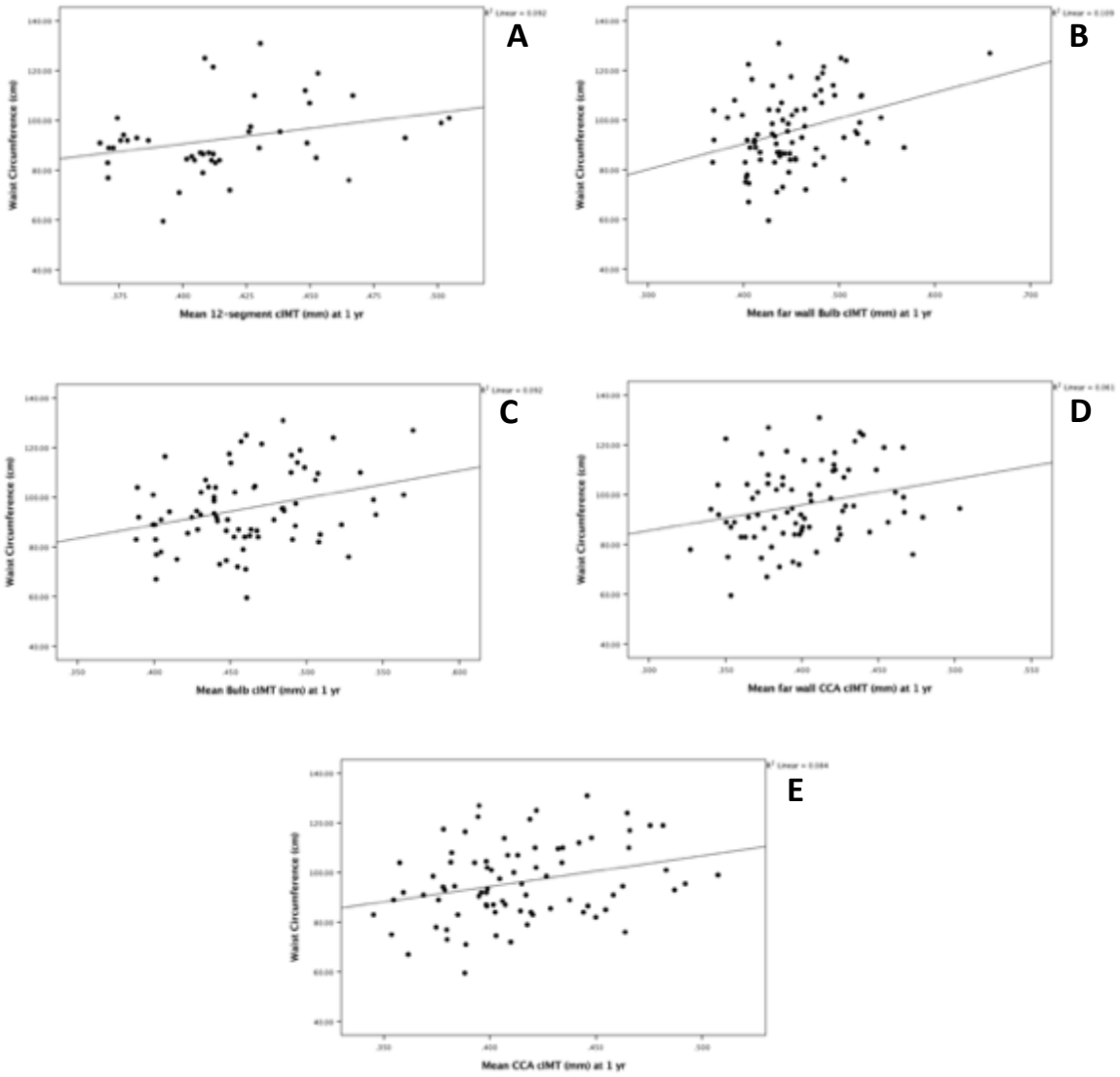
Appendix Figure 10. Distribution of baseline SBP and measures of cIMT at 1-year follow-up. Baseline SBP was associated with: **(A)** 12-segment cIMT at 1 year (r=0.394, p=0.001), **(B)** carotid bulb far wall IMT at 1 year (r=0.288, p=0.001), **(C)** mean carotid bulb IMT at 1 year (r=0.310, p=0.001), **(D)** CCA far wall (2-segment) IMT at 1 year (r=0.181, p=0.044), **(E)** mean CCA IMT at 1 year (r=0.198, p=0.028) and **(F)** mean ICA IMT at 1 year (r=0.335, p=0.007).



Appendix Figure 11. Distribution of baseline BMI and measures of cIMT at baseline and 1-year follow-up. Baseline BMI was associated with: **(A)** carotid bulb far wall IMT at baseline (r=0.264, p=0.003), **(B)** mean carotid bulb IMT at baseline (r=0.260, p=0.004), **(C)** mean ICA IMT at baseline (r=0.332, p=0.006), **(D)** 12-segment cIMT at baseline (r=0.344, p=0.004), **(E)** carotid bulb far wall IMT at 1 year (r=0.231, p=0.009), **(F)** mean carotid bulb IMT at 1 year (r=0.239, p=0.007), **(G)** mean ICA IMT at 1 year (r=0.270, p=0.034) and **(H)** 12-segment cIMT at 1 year (r=0.280, p=0.027).



Appendix Figure 12. Distribution of baseline waist circumference and measures of cIMT at baseline. Baseline waist circumference was associated with: **(A)** carotid bulb far wall IMT at baseline (r=0.272, p=0.014), **(B)** mean carotid bulb IMT at baseline (r=0.294, p=0.009), **(C)** CCA far wall (12-segment) IMT at baseline (r=0.247, p=0.027), **(D)** mean CCA IMT at baseline (r=0.235, p=0.035), and **(E)** 12-segment cIMT at baseline (r=0.305, p=0.037).



Appendix Figure 13. Distribution of baseline waist circumference and measures of cIMT at 1-year follow-up. Baseline waist circumference was associated with: **(A)** 12-segment cIMT at 1 year (r=0.304, p=0.048), **(C)** carotid bulb far wall IMT at 1 year (r=0.330, p=0.003), **(D)** mean carotid bulb IMT at 1 year (r=0.303, p=0.008), **(E)** CCA far wall (2-segment) IMT at 1 year (r=0.247, p=0.027) and **(F)** mean CCA IMT at 1 year (r=0.290, p=0.009).

Appendix Table 7. Multivariable regression analyses of cIMT measures at baseline.

Variable	Reg. Coeff. (SE)	P-value	R^2 (%)	Variable	Reg. Coeff. (SE)	P-value	R^2 (%)
Carotid Bulb far wall IMT at baseline (n=110)			**27.39%**	**Mean Carotid Bulb IMT at baseline (n=108)**			**28.79%**
Intercept	0.2121 (0.0553)	**p<0.001**		Intercept	0.2197 (0.0522)	**p<0.001**	
Age (y) at BL	0.0045 (0.0020)	**0.026**		Age (y) at BL	0.0036 (0.0019)	0.059	
Sex: Male	0.0122 (0.0072)	0.093		Sex: Male	0.0100 (0.0068)	0.144	
Height (cm) at BL	0.0000 (0.0004)	0.923		Height (cm) at BL	0.0003 (0.0004)	0.511	
BMI (kg/m^2) at BL	0.0000 (0.0007)	0.976		BMI (kg/m^2) at BL	-0.0002 (0.0006)	0.803	
Non-HDL-C (mmol/L) at BL	0.0053 (0.0052)	0.311		Non-HDL-C (mmol/L) at BL	0.0024 (0.0049)	0.623	
Systolic BP (mmHg) at BL	0.0001 (0.0005)	0.806		Systolic BP (mmHg) at BL	0.0000 (0.0004)	0.892	
Diastolic BP (mmHg) at BL	0.0007 (0.0005)	0.137		Diastolic BP (mmHg) at BL	0.0007 (0.0004)	0.115	
FPG (mmol/L) at BL	0.0207 (0.0076)	**0.007**		FPG (mmol/L) at BL	0.0127 (0.0071)	0.076	
CCA far wall IMT at baseline (n=110)			**12.12%**	**Mean CCA IMT at baseline (n=110)**			**19.59%**

Intercept	0.2725 (0.0523)	**p<0.001**		Intercept	0.2354 (0.0490)	**p<0.001**	
Age (y) at BL	0.0026 (0.0019)	0.169		Age (y) at BL	0.0017 (0.0018)	0.337	
Sex: Male	0.0082 (0.0068)	0.232		Sex: Male	0.0076 (0.0064)	0.237	
Height (cm) at BL	0.0000 (0.0004)	0.990		Height (cm) at BL	0.0002 (0.0004)	0.629	
BMI (kg/m^2) at BL	-0.0008 (0.0007)	0.211		BMI (kg/m^2) at BL	-0.0006 (0.0006)	0.293	
Non-HDL-C (mmol/L) at BL	0.0041 (0.0049)	0.412		Non-HDL-C (mmol/L) at BL	0.0056 (0.0046)	0.231	
Systolic BP (mmHg) at BL	0.0005 (0.0004)	0.256		Systolic BP (mmHg) at BL	0.0009 (0.0004)	**0.034**	
Diastolic BP (mmHg) at BL	-0.0003 (0.0004)	0.479		Diastolic BP (mmHg) at BL	-0.0006 (0.0004)	0.123	
FPG (mmol/L) at BL	0.0110 (0.0072)	0.128		FPG (mmol/L) at BL	0.0117 (0.0067)	0.086	
ICA far wall IMT at baseline (n=80)			**7.40%**	**Mean ICA IMT at baseline (n=63)**			**20.41%**
Intercept	0.3017 (0.0634)	**p<0.001**		Intercept	0.2570 (0.0571)	**p<0.001**	
Age (y) at BL	0.0029 (0.0024)	0.230		Age (y) at BL	0.0025 (0.0023)	0.288	
Sex: Male	0.0113 (0.0084)	0.183		Sex: Male	0.0121 (0.0074)	0.109	
Height (cm) at BL	-0.0004 (0.0005)	0.401		Height (cm) at BL	-0.0004 (0.0004)	0.410	
BMI (kg/m^2) at BL	-0.0002 (0.0008)	0.834		BMI (kg/m^2) at BL	0.0004 (0.0009)	0.665	

Non-HDL-C (mmol/L) at BL	-0.0017 (0.0062)	0.785		Non-HDL-C (mmol/L) at BL	-0.0045 (0.0054)	0.404	
Systolic BP (mmHg) at BL	0.0005 (0.0005)	0.403		Systolic BP (mmHg) at BL	0.0008 (0.0005)	0.149	
Diastolic BP (mmHg) at BL	-0.0003 (0.0005)	0.584		Diastolic BP (mmHg) at BL	-0.0004 (0.0005)	0.447	
FPG (mmol/L) at BL	0.0098 (0.0080)	0.229		FPG (mmol/L) at BL	0.0099 (0.0069)	0.157	
12-segment cIMT (n=63)			**31.03%**				
Intercept	0.2017 (0.0555)	**0.001**					
Age (y) at BL	0.0020 (0.0023)	0.370					
Sex: Male	0.0129 (0.0072)	0.081					
Height (cm) at BL	0.0000 (0.0004)	0.843					
BMI (kg/m^2) at BL	0.0002 (0.0009)	0.842					
Non-HDL-C (mmol/L) at BL	-0.0026 (0.0052)	0.626					
Systolic BP (mmHg) at BL	0.0006 (0.0005)	0.241					
Diastolic BP (mmHg) at BL	0.0002 (0.0005)	0.700					
FPG (mmol/L) at BL	0.0129 (0.0067)	0.059					

P values in boldface indicate significance ($p<0.05$).

Appendix Table 8. Multivariable regression analyses of cIMT at 1-year follow-up (corrected for BL cIMT).

Variable	Reg. Coeff. (SE)	P-value	R^2 (%)		Reg. Coeff. (SE)	P-value	R^2 (%)
Carotid Bulb far wall IMT at 1-year (n=108)			**71.57%**	**Mean Carotid Bulb IMT at 1-year (n=106)**			**73.46%**
Intercept	-0.0398 (0.0461)	0.389		Intercept	0.0204 (0.0392)	0.604	
Age (y) at BL	-0.0019 (0.0016)	0.246		Age (y) at BL	-0.0018 (0.0014)	0.185	
Sex: Male	0.0109 (0.0056)	0.053		Sex: Male	0.0078 (0.0047)	0.098	
Height (cm) at BL	0.0004 (0.0003)	0.283		Height (cm) at BL	0.0003 (0.0003)	0.312	
Baseline cIMT (mm)	0.9372 (0.0762)	**p<0.001**		Baseline cIMT (mm)	0.9032 (0.0687)	**p<0.001**	
BMI (kg/m^2) at BL	0.0002 (0.0005)	0.644		BMI (kg/m^2) at BL	0.0002 (0.0004)	0.617	
Non-HDL-C (mmol/L) at BL	0.0081 (0.0040)	**0.045**		Non-HDL-C (mmol/L) at BL	0.0033 (0.0033)	0.327	
Systolic BP (mmHg) at BL	0.0002 (0.0004)	0.529		Systolic BP (mmHg) at BL	0.0003 (0.0003)	0.251	
Diastolic BP (mmHg) at BL	0.0000 (0.0004)	0.829		Diastolic BP (mmHg) at BL	-0.0006 (0.0003)	0.065	
FPG (mmol/L) at BL	-0.0030 (0.0060)	0.621		FPG (mmol/L) at BL	0.0000 (0.0049)	0.995	
CCA far wall (2-segment) IMT at 1-year (n=109)			**70.15%**	**Mean CCA IMT at 1-year (n=109)**			**81.57%**

Intercept	0.0311 (0.0372)	0.405		Intercept	-0.0023 (0.0290)	0.936	
Age (y) at BL	0.0008 (0.0012)	0.485		Age (y) at BL	-0.0007 (0.0009)	0.454	
Sex: Male	0.0105 (0.0044)	**0.017**		Sex: Male	0.0071 (0.0034)	**0.043**	
Height (cm) at BL	0.0000 (0.0002)	0.844		Height (cm) at BL	0.0000 (0.0002)	0.788	
Baseline cIMT (mm)	0.8199 (0.0628)	**p<0.001**		Baseline cIMT (mm)	0.9752 (0.0531)	**p<0.001**	
BMI (kg/m^2) at BL	-0.0003 (0.0004)	0.511		BMI (kg/m^2) at BL	0.0007 (0.0003)	**0.032**	
Non-HDL-C (mmol/L) at BL	0.0046 (0.0031)	0.147		Non-HDL-C (mmol/L) at BL	0.0011 (0.0025)	0.650	
Systolic BP (mmHg) at BL	0.0002 (0.0003)	0.526		Systolic BP (mmHg) at BL	-0.0002 (0.0002)	0.358	
Diastolic BP (mmHg) at BL	0.0000 (0.0003)	0.849		Diastolic BP (mmHg) at BL	0.0001 (0.0002)	0.605	
FPG (mmol/L) at BL	0.0018 (0.0046)	0.700		FPG (mmol/L) at BL	0.0035 (0.0036)	0.343	
ICA far wall IMT at 1-year (n=76)			**58.20%**	**Mean ICA IMT at 1-year (n=57)**			**66.11%**
Intercept	0.1315 (0.0507)	**0.012**		Intercept	-0.0327 (0.0543)	0.550	
Age (y) at BL	0.0029 (0.0017)	0.095		Age (y) at BL	0.0001 (0.0020)	0.960	
Sex: Male	0.0138 (0.0060)	**0.025**		Sex: Male	0.0032 (0.0065)	0.623	
Height (cm) at BL	-0.0004 (0.0003)	0.223		Height (cm) at BL	0.0003 (0.0004)	0.472	

Baseline cIMT (mm)	0.6446 (0.0818)	**p<0.001**		Baseline cIMT (mm)	0.8370 (0.1099)	**p<0.001**	
BMI (kg/m^2) at BL	0.0000 (0.0006)	0.963		BMI (kg/m^2) at BL	-0.0007 (0.0007)	0.322	
Non-HDL-C (mmol/L) at BL	0.0035 (0.0042)	0.412		Non-HDL-C (mmol/L) at BL	0.0044 (0.0043)	0.303	
Systolic BP (mmHg) at BL	0.0005 (0.0004)	0.220		Systolic BP (mmHg) at BL	0.0003 (0.0004)	0.467	
Diastolic BP (mmHg) at BL	-0.0007 (0.0004)	0.055		Diastolic BP (mmHg) at BL	0.0000 (0.0004)	0.947	
FPG (mmol/L) at BL	-0.0011 (0.0056)	0.842		FPG (mmol/L) at BL	0.0042 (0.0058)	0.479	
Mean 12-segment cIMT at 1-year (n=57)			**87.62%**				
Intercept	-0.0422 (0.0330)	0.207					
Age (y) at BL	-0.0015 (0.0013)	0.240					
Sex: Male	0.0053 (0.0041)	0.203					
Height (cm) at BL	0.0003 (0.0002)	0.258					
Baseline cIMT (mm)	1.0288 (0.0721)	**p<0.001**					
BMI (kg/m^2) at BL	-0.0003 (0.0005)	0.556					
Non-HDL-C (mmol/L) at BL	0.0015 (0.0027)	0.579					

Systolic BP (mmHg) at BL	0.0003 (0.0003)	0.359	
Diastolic BP (mmHg) at BL	-0.0002 (0.0003)	0.474	
FPG (mmol/L) at BL	0.0002 (0.0037)	0.961	

P values in boldface indicate significance ($p<0.05$).

Appendix Table 9. Summary of Cross-Sectional and Longitudinal cIMT Studies in Children, Youth or Young Adults.

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Cross-Sectional	Shah, A. S., Dabelea, D., Fino, N. F., Dolan, L. M., Wadwa, R. P., D'Agostino, R., …& Urbina, E. M. (2015). Predictors of increased carotid intima-media thickness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care,39*(3), 418-425. doi:10.2337/dc15-1963	298 youth with T1DM -Mean baseline age: 13.3±2.9y -Mean follow-up age: 19.2±2.7y -53.7% M and 46.3% F - 87.6% non-Hispanic white - Participants enrolled are enrolled in SEARCH CVD (PTs from SEARCH for Diabetes in Youth) - PTs were adolescents that had type one diabetes diagnosis	- Only measured at follow-up - Right and left side neck at CCA, Bulb, ICA (longitudinal and transverse views) - Looked at far wall mean cIMT by manual trace method - Took readings from six different angles for each carotid segment (CCA, ICA and bulb) - Mean IMT value calculated by averaging IMT measurements from 6 angles for each carotid segment	Right and left carotid	CCA, Bulb, ICA (far wall only)	- cIMT was only measured at follow up (not baseline) - Follow-up mean cIMT for youth with T1DM: o Mean cIMT (CCA): 0.60±0.10mm o Mean cIMT (Bulb): 0.62±0.10mm o Mean cIMT (ICA): 0.55±0.12mm - Risk factors associated with follow up cIMT, which were: ▪ CCA: older age, male sex, HDL-C AUC, MAP, insulin sensitivity AUC, BMIz AUC ▪ Bulb: older age, male sex, BMIz AUC ▪ ICA: older age, male sex, HDL-C AUC, insulin sensitivity AUC, BMIz AUC - Multivariate Linear Regression: independent predictors of cIMT were: ▪ CCA: BMIz AUC ▪ Bulb: BMIz AUC ▪ ICA: BMIz AUC - Higher BMIz over time was the only modifiable risk factor associated with follow-up carotid IMT - Using AUC measurements -> shows that a higher BMIz exposure over ~5 years was significantly associated with IMT at follow-up

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Longitudinal	Toledo-Corral et al. (2011), J Pediatr. "Subclinical atherosclerosis in Latino youth: Progression of carotid intima media thickness (cIMT) and its relationship to cardiometabolic risk factors."	72 OW adolescents (healthy otherwise): -Mean baseline age: 14.5±1.7y -Mean follow-up age: 16.6±1.7y	- Mean cIMT measured from computer processed images of the right distal common carotid artery (1-2cm from the bifurcation into the external and internal carotids)	Right carotid	CCA (far wall only)	- Simple and partial correlations between baseline cardiovascular risk factors and CIMT change revealed that LDL-cholesterol, fasting insulin and insulin AUC were positively correlated to change in CIMT ($r=0.21 – 0.24$, $p<0.05$) with glucose effectiveness the only factor negatively correlated with change in CIMT ($r= -0.30$, $p=0.01$) - BL LDL and Total Cholesterol were significantly higher in the advanced CIMT progression group (92.6±4.4 and 152.9±5.1 mg/dL) versus those in the CIMT non-progression group (77.7±3.7 and 135.5±4.2 mg/dL, $p<0.05$) - Two logistic regression models (Table III) were used to determine the independent predictors of CIMT progression, which was evident in 53% of the sample. In model 1, LDL cholesterol was the sole predictor of any type of CIMT progression (CIMT>0.000mm) - Odds for cIMT progression over a 2-year period was 1.03 for each 1mg/dL higher baseline LDL cholesterol [95% CI 1.004-1.006, $p=0.03$]
Cross-Sectional	Toledo-Corral et al. (2009), Atherosclerosis. "Persistence of the metabolic syndrome and its influence on carotid artery	90 OW Latino children (mean age at baseline: 11.0±1.8y) Classified according to	- B-mode ultrasound images CIMT measured from computer processed images of right distal common	Right	CCA	- Mean waist circumference, systolic blood pressure and triglycerides were significantly higher in the PERSISTENT MetS group whereas mean HDL-cholesterol was significantly lower than in the other MetS groups ($p < 0.05$)

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
	intima media thickness in overweight Latino children."	persistence of MetS - 53 NEVER (0 visits with MetS) - 28 INTERMITTENT (1-2 visits with MetS) 16 PERSISTENT (16 visits with MetS)	carotid artery approx. 1-2 cm from bifurcation into ICA and ECA			- Significantly higher cIMT with increasing persistence of MetS (p = 0.01) and significance remained after adjusting for covariates - Post hoc analyses revealed a significantly higher mean CIMT in the PERSISTENT than in the NEVER group (ANOVA means: 0.647 ± 0.018 mm vs. 0.600 ± 0.007 mm, $p < 0.01$) and a marginally significantly higher mean CIMT in PERSISTENT than in the INTERMITTENT group (0.647 ± 0.018 mm vs. 0.611 ± 0.008 mm, $p = 0.09$). Statistical significance remained in ANCOVA analyses. - cIMT was significantly related with baseline systolic blood pressure (p=0.018) and 2-hour glucose (p=0.02) independent of all other MetS components
Cross-Sectional	Tonstad S, Joakimsen O, Stensland-Bugge E, leren TP, Ose L, Russell D, Bonaa KH. Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. Arterioscler	90 children with FH: 61 boys and 29 girls with FH (ages 10-19 y) 30 control subjects matched for age and sex - In all FH subjects, FH was caused by a specific mutation in the LDL-R gene	- Right carotid artery scanned - Mean and maximum cIMT of the CCA far wall and of the carotid bulb far wall → primary outcome measures	Right carotid	CCA (far wall only) Carotid Bulb (far wall only)	- Mean carotid bulb cIMT (far wall): FH group (0.54 mm) > Control group (0.50 mm) - Carotid bulb cIMT → positively associated with apoB and fibrinogen levels, after control for pubertal stage (r=0.19-0.24; p<0.05) - Plasma total homocysteine was similar in FH and control groups and was associated with mean and max CCA and carotid bulb cIMT, after controlling for pubertal stage (r=0.22 to 0.28, p<0.05) - These relationships were unchanged in stepwise multiple regression analyses

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
	Thromb Vasc Biol 1996;16: 984-991.					
Cross-Sectional	Davis PH, Dawson JD, Riley WA, Lauer RM: Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation, 2001; 104: 2815-2819	Cohort of children in Muscatine, Iowa, followed since 1971: - Cardiovascular risk factors measured in childhood (ages 8-18 y), young adulthood (20-33 y) and finally, at age of 33-42 y cIMT was obtained for: - 346 men - 379 women (n= 725) (ages 33-42 y)	Primary outcome of interest: - Mean of max cIMT measured at 12 locations (3 sites * 2 sides * 2 walls)	Right and left carotid	CCA, carotid bulb, internal carotid artery (near and far wall)	- **Results:** - Mean maximum cIMT was 0.79±0.12 mm for men and 0.72±0.10 mm for women - Data completeness for cIMT: - ICA NW: 74.0%; ICA FW: 88.0%; Bulb NW: 92.7%; Bulb FW: 92.8%; CCA NW: 98.9%, CCA FW: 99.7% - Multivariable analysis: - **Significant predictors of IMT**: age and LDL-C (both sexes) and DBP (women) - Total cholesterol → significant childhood predictor of cIMT in both men ($r= 0.17$, $p<0.01$) and women ($r= 0.14$, $p<0.01$) - Childhood BMI → significant childhood predictor of cIMT in women ($r= 0.18$, $p<0.001$) - **Risk factor load model**: - In the multivariable analysis using only measurements performed at ages of 8 to 11 years, total cholesterol was a significant risk factor in men odds ratio of 1.47 (95% confidence interval: 1.02, 2.13), and in women, with an odds ratio of 1.71 (95% confidence interval: 1.16, 2.50).

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
						- Demonstrated that childhood total cholesterol (measured here at ages 8 to 11 years) is a significant risk factor for carotid IMT measured in young adulthood The following risk factors (measured in childhood or young adulthood) were significant predictors of cIMT at 33-42 years of age - Men: LDL-C (OR: 1.39) and HDL-C (OR: 0.70) and DBP (OR: 1.58) at young adulthood, predictive of cIMT - Women: LDL-C (OR: 1.54) and Triglycerides (OR: 1.49) at young adulthood, predictive of cIMT; childhood BMI (OR: 1.47) predictive of cIMT Overall: Higher cIMT in young adults demonstrates an association with childhood and current CVRFs along with risk factor load.
Longitudinal	Wunsch R, de Sousa G, Toschke AM, Reinehr T. Intima-media thickness in obese children before and after weight loss. Pediatrics. 2006; 118 (6): 2334-40.	N= 56 prepubertal obese children - Population: median age = 9 years old - Control group: 10 non-obese children of same age and gender - Nonsyndromally obese white children participating in	cIMT Method: - B-mode ultrasound -Measured at common carotid artery at the FAR wall - Measured 4 values on each side and took maximum value - Measured cIMT for participants at baseline and at	Left and Right	FW CCA	**Results:** - Children with obesity had significantly ($P<0.001$) thicker cIMT than the control group - OB cIMT (0.60 mm) > control (0.47 mm) - BP, TG, insulin and insulin resistance was significantly ($p<0.05$) higher in children with obesity vs control group - HDL-C was significantly ($p<0.05$) lower in children with obesity vs control group - In the 24 children with obesity with substantial weight loss → cIMT, BP, TG, insulin and IRI decreased significantly ($p<0.05$)

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
		the 1 year obesity intervention program 'Obeldicks' between 2004/5 at BL and one year later – compared profiles with 10 prepubertal non-obese healthy children in a prospective study	the 1-year follow up period			- Specifically: - Decrease in cIMT: Baseline cIMT (0.62 mm) > 1 YR F/UP cIMT (0.55 mm) - In the 32 children with obesity without substantial weight loss-> no significant changes apart from an increase in insulin and insulin resistance index **Overall Summary:** - Children with obesity demonstrated a thicker cIMT → thus, vascular changes seemed to occur **ALREADY** in childhood obesity - For the obese children with substantial weight loss-> cIMT decreased along with the cardiovascular risk factor profile, which improved as well - **This suggests that there is possible reversibility of early atherosclerotic changes**
Cross-Sectional	Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. JAMA 2003;290(17):2271-2276.	N=486 adults - Ages 25-37 → 4-17 years of age and median follow-up period was 22.2 years - At follow up, young adults were between ages of 18-38	- 7.5-MHz linear array transducer - Images recorded at CCA, Carotid bulb and Internal carotid arteries for both left and right neck - Single reader for scans using semi-automatic US image processing program	Left and Right sides of neck	Common Carotid artery (CCA), Internal Carotid Artery (ICA) and Carotid Bulb	- Multivariable logistic regression analyses were used to assess risk factors measured since childhood and their association with cIMT in the upper quartile vs lower 3 quartiles - Elevated childhood LDL-C levels and elevated childhood BMI were found to be significant risk factors for having an elevated cIMT in adulthood - Mean cIMT for participants in top quartile of LDL-C level in childhood was 0.761 mm (95% CI, 0.743- 0.780 mm) versus a mean cIMT of 0.724 mm (95% CI, 0.715-0.734 mm) for

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
			- Mean of the maximum cIMT readings of the 3 right and 3 left far walls for the CCA, bulb and ICA segments			participants in the lower 3 quartiles (P<0.001) - LDL-C measured in childhood and adulthood, was a consistent independent predictor of cIMT in adulthood -
Longitudinal	Koskinen, J., Kahonen, M., Viikari, J. S., Taittonen, L., Laitinen, T., Ronnemaa, T., . . . Juonala, M. (2009). Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in Young Finns study. Circulation, 120(3), 229-236. doi:10.1161/circulationaha.108.845065	- N= 1809 participants - Cardiovascular Risk Cohort in Young Finns Study - Study baseline at in 1980 (ages 3-18 years) - Study Follow up in between 2001 and 2007 (subjects aged 24-39 years)	- 13.0-MHz linear array transducer - Left common carotid artery scanned on far wall - Moving scan with duration of 5 seconds incident with R wave recorded for offline analysis - Scans manually analyzed by a single reader - At least 4 measurements of CCA taken for derivation of maximal cIMT	Left side of neck	Common Carotid Artery (approximately 10 mm proximal to the carotid bifurcation)	- Background: evaluated relations of conventional CV risk factors and MetS to the 6-year progression of carotid intima-media thickness in young adults (longitudinal study) **Important Findings:** - Waist circumference (P 0.0001), low-density lipoprotein cholesterol (P 0.01), and insulin (P 0.003) were directly associated with IMT progression in a multivariable model adjusted for age, sex, and baseline IMT (model R^2 = 24%) - Obesity, high low-density lipoprotein cholesterol, and high insulin level predicted IMT progression in young adults. All MetS definitions identified young adults with accelerated IMT progression, but we found no evidence that MetS would predict IMT progression more than expected from the sum of its risk components

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Longitudinal	Juonala, M., Viikari, J. S., Kähönen, M., Taittonen, L., Laitinen, T., Hutri-Kähönen, N., ... & Telama, R. (2010). Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. European heart journal, ehq141.	Cardiovascular Risk in Young Finns - N=1809 participants - Follow-up period of 27 years since baseline (1980, ages 3-18 y) - Carotid IMT was measured in 2001 and 2007 follow ups	Left common carotid artery scanned at the common carotid artery (far wall only) Manual caliper method used for analyses Four measurements of the CCA far wall taken to determine maximal cIMT	Left neck	Common Carotid Artery (Far wall only)	- Childhood HDL/LDL-C ratio was associated with IMT progression in the childhood multivariable model (-5 (-9 to -1) um, p=0.01 - Changes in lipid profile and status of obesity, that were regarded as favorable, demonstrated an association with a lower ATH progression rate - Ex. In the participants with low HDL/LDL-C ratio in childhood, only participants with a low ratio as adults had increased IMT progression in adulthood - Also, children and youth with obesity, that became non-obese adults demonstrated lower cIMT progression rates than consistently obese participants - Thus, may intervene to address obesity and lipid profile for participants between youth and adulthood, in order to decrease the progression rate of ATH Findings from the study → indicate that children with risk factors have increased ATH progression in adulthood - Also support the proposition that ATH prevention can be effective if life style modification when initiated in childhood.
Longitudinal	Nguyen, Q. M., Toprak, A., Xu, J., Srinivasan, S. R., Chen, W., & Berenson, G. S. (2011). Progression of segment-specific carotid artery	- Cohort of N= 824 participants who underwent ultrasound scans at BL (2001-2002) and follow-up (2003-2005)	- 7.5-MHz linear array transducer - Images recorded at CCA, Carotid bulb and Internal carotid arteries	Left and Right sides of neck	Common Carotid artery (CCA), Internal Carotid Artery	**Important Findings:** - Segment-specific cIMT progression rates were adjusted for covariates of age, race, sex, and corresponding baseline cIMT in young adults - Segment specific cIMT differences: rate of change in Bulb cIMT showed a significantly greater progression in

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
	intima-media thickness in young adults (from the Bogalusa Heart Study). The American Journal of Cardiology, 107(1), 114-119. doi:10.1016/j.amjcard.2010.08.054	- mean ages between approximately 36 and 39 years - Surveys conducted in Bogalusa, Louisiana (biracial community)	for both left and right neck - Single reader for scans using semi-automatic US image processing program - Mean of the maximum cIMT readings of the 3 right and 3 left far walls for the CCA, bulb and ICA segments		(ICA) and Carotid Bulb	comparison to other carotid segments ($p<0.0001$), with the ICA cIMT displaying greater values vs CCA cIMT ($p<0.0001$) - Consistent predictors of cIMT progression among carotid segments → age, mean arterial pressure and cigarette smoking (independent of other traditional CVRFs) - WC, HOMA-IR and HDL-C→ associated with ICA, Bulb and HDL-C, respectively, but no detected during short follow-up period - cIMT progression→ site specific and predictable using a different risk factor composition - cIMT progression → highest at carotid bulb, then ICA and then CCA - Explanation: cIMT progression is site specific and is governed by different cardiometabolic RF profiles - Greatest observed progression at carotid bulb, followed by ICA and CCA - Differences explained by fact that: bulb and ICA are more sensitive to segmental ATH → bulb and ICA are also more prone to local plaque formation - Association of BP and age reported to be associated with increasing cIMT – demonstrated by this study - - Adverse effects of age and hemodynamic factors → reflect the arterial endothelial dysfunction from both aging and hypertension

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Cross-Sectional	Ryder et al. (2016), J Pediatr. "Relations among adiposity and insulin resistance with flow-mediated dilation, carotid intima-media thickness, and arterial stiffness in children."	- 252 children (age 15.1±2.4 yrs) - BMI percentile: 68.2±26.5% Cross-sectional study	- CIMT images obtained at end-diastole (gated by R wave on ECG) - B-mode images of far wall of left common carotid artery Measurement obtained at distal 10 mm of the common carotid artery	Left	CCA	- Obese children exhibited: significantly greater cIMT that normal weight children - No significant difference was seen by BF% tertile - Children in most insulin resistant tertile had a greater cIMT than those in the least insulin resistant tertile - Multiple linear regression: - VAT (visceral adipose tissue) – positively associated with cIMT (β (SE) = 0.01 ± 0.01, p=0.002, R2= 0.083) - No significant associations between cIMT and insulin resistance or fasting insulin - BF%-> positively associated with cIMT (β (SE) = 0.01 ± 0.01, p=0.028, R^2= 0.048) - Obesity (BMI) and higher VAT are associated with higher cIMT OVERALL: CIMT was significantly, positively related to obesity, VAT, and insulin resistance (p<0.05 all)
Cross-Sectional	Melo et al. (2016), Pediatr Obes. "Single and combined effects of body compositio n phenotypes on carotid intima-media thickness."	- N= 349 children (183 girls) - Age: betw 11-12 yrs old - Recruited from six schools in Portugal - No specific exclusion criteria other than being	2 segment cIMT method - cIMT defined as the distance between the leading edge of the lumen–intima interface to the leading edge of the media–adventitia	Right	CCA	- 34% children in study were overweight or obese NOTE: TBFI => total body fat index; ABFMI => abdominal body fat mass index; TBLSTI => total body lean soft tissue (total body lean mass) - Significant diff. existed for all variables (refer to Table 1) between BMI categories - Body composition phenotypes (TBFI, ABFMI, TBLSTI) -> were dichotomized and examined individually -> children from

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
		apparently healthy (did not target children that were overweight or obese)	interface of the far wall of the right carotid artery - SECTION of carotid artery used: 1 cm before the flow divider – ie CCA far wall thickness - cIMT automatic measurement (software)			all high-risk categories had increased cIMT (+0.03mm to +0.04mm; P<0.05) except between TBLSTI categories - Significant differences in cIMT remained even after adjustments for carotid artery diameter and pulse pressure - Highest odds ratio (OR) for increased cIMT was observed for participants with a higher waist circumference (WC) compared with PTs in the normal WC group - Adjustment for PP increased OR in all variables - NO predictive ability of increased cIMT by TBLSTI - PTs with BOTH high total body fatness (BMI, TBFI) and high central fat accumulation (WC, WHtR, ABFMI) or only one of these increased had cIMT ≥P85 (+0.03mm to +0.04mm; P< 0.05) - Highest OR for increased cIMT was found among children who were over-weight or obese and had high WC compared with those with normal body fat phenotype - The highest potential to discriminate increased cIMT came from combined effect of BMI + WC

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Cross-Sectional	Hao G, Wang X, Tieber F, Harshfield G, Kapuku G, Su S. Blood pressure trajectories from childhood to young adulthood associated with cardiovascular risk. Hypertension. 2017; doi: 10.1161/hypertensionaha.116.08312.	- Participants from GSH study (Georgia Stress and Heart) – longitudinal study to evaluated development of CVRFs in youth and young adults - N= 551 participants (with cIMT) - At baseline – adolescents were between ages of	- 7.5 MHz linear array probe - Common carotid artery IMT - Left and right CCA, carotid bulb, ICA, and ECA Measurement made at point 2 cm proximal to bifurcation on both near and far wall that showed the intima–media boundaries clearly	Left neck	CCA, Carotid bulb, ICA, ECA (near and far wall) Primary outcome: mean cIMT for left neck far wall	- Trajectory of SBP was a significant predictor of cIMT with increased rate of growth in SBP being associated with elevated cIMT - 3 trajectory groups recognized in BP during childhood of participants (ages ≤ 18 years) – participants in high increasing group had an elevated cIMT (0.55 mm) ($p<0.001$) when compared to the low increasing group (0.50 mm) - Increased rate of growth in SBP was significantly associated with elevated cIMT in adulthood ($P<0.001$). Compared with the LI group, individuals in the MI and HI groups showed higher IMT ($\beta=0.019$; $P=0.007$ for the MI group and $\beta=0.051$; $P=0.012$ for the HI group) - Study reported an association between childhood SBP trajectories and subclinical CV risk (measured via cIMT) in adulthood → suggests that keeping track of BP trajectories starting in childhood, could aid in detecting a high CV risk population earlier on

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
Cross-Sectional	Yan et al. (2017), J Hypertens. "Childhood body mass index and blood pressure in prediction of subclinical vascular damage in adulthood: Beijing blood pressure cohort."	1252 individuals aged 27-42	- Right and left side neck at CCA - cIMT measured for anterior and posterior wall at 1-1.5cm proximal to bifurcation of each CCA - Mean IMT calculated from: average of four measurements on two sides used for analysis	Right and Left	CCA	- BMI and SBP were weakly but significantly associated with adult cIMT for both sexes ($p<0.05$) - In cross-sectional multivariate models for participants between 27-42 years of age, risk factors of high cIMT were: ▪ BMI, SBP, LDL-C for both sexes - Multivariate logistic regression of high cIMT: ▪ With respect to childhood and cumulative values-> BMI and SBP predicted high cIMT in adulthood ▪ Incremental BMI and SBP from childhood to adulthood predicted high cIMT
Cross-Sectional	Menezes et al. (2016), Atherosclerosis. "Adiposity during adolescence and carotid intima-media thickness in adulthood: Results from the 1993 Pelotas Birth Cohort."	3264 children and adolescents Children followed up at age of 11, 15 and 18 years	B mode ultrasound imaging used to measure CIMT CIMT measured at posterior wall of the right and left common carotid arteries in longitudinal planes CCA imaged proximal to carotid bulb – automatically calculated	Left and Right	CCA	- Adjusted analysis showed statistically significant association between BMI and cIMT among males obese at 11 and 15 years but NOT in females - Females in highest tertile of subscapular skinfold at 18 years showed higher cIMT after adjustment for cofounders - Males and females exposed to the highest tertiles of BMI at 11, 15 and 18 years showed higher cIMT at 18 years compared to the individuals in lowest tertiles of BMI (similar pattern observed when considered subscapular skinfold) - In males, subscapular skinfold had mainly direct effects on cIMT (60 to 99%)

Study Type	Author, Year, Journal	Participants	Measurement of cIMT	Left or Right	Segments	Important Findings
						- Direct effects of subscapular skinfold over cIMT were large for both sexes (between 59.3 and 99.2%) - Diastolic BP was largest mediator (M and F) besides fat mass-> mediating almost 40% of effects between subscapular skinfold and cIMT

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