RELATIONSHIP BETWEEN ADVERSE CHILDHOOD EXPERIENCES AND ARTERIAL STIFFNESS OVER TIME FROM CHILDHOOD INTO EARLY ADULTHOOD

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ABSTRACT

It is well established in the literature that there is an association among adults between adverse childhood experiences (ACEs) and arterial stiffness, and between arterial stiffness and cardiovascular disease. However, recent cross-sectional evidence suggests that ACEs may play an important role in the development and progression of arterial stiffness, but it remains unclear when these changes begin to manifest. Therefore, the purpose of this research was to examine the relationship between ACEs and arterial stiffness from childhood into adulthood using population-based longitudinal data. A total of 76 young adults (females = 44), with an average age of 21 years (SD = 1) were included in this study. Overall, a total of 71 respondents reported to have experienced at least one ACE. The findings of this study showed ACEs-exposed individuals have a greater increase in arterial stiffness over time from childhood into young adulthood. This increase was similar for both males and females. Also, differences in heart rate, systolic blood pressure, body mass index, and physical activity did not mediate the relationship between ACEs and arterial stiffness over time. It is therefore important to recognize individuals with exposure to ACEs early on in life in an effort to lower the risk of arterial stiffness and in turn the cascade of events leading to cardiovascular disease.

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LIST OF ABREVIATIONS

ACEs – Adverse Childhood Experiences

BMI – Body Mass Index

CCA – Common Carotid Artery

cfPWV – Carotid-Femoral Pulse Wave Velocity

cIMT – Carotid Intima Media Thickness

CTES – Child Trust Event Survey

DBP – Diastolic Blood Pressure

HPA – Hypothalamic-Pituitary-Adrenal axis

HR – Heart Rate

IMT – Intima Media Thickness

MET – Metabolic Equivalent Scores

PP – Pulse Pressure

PWV – Pulse Wave Velocity

RRI – R-R Interval

SBP – Systolic Blood Pressure

CHAPTER 1: INTRODUCTION

1.1 Preamble

Cardiovascular disease is the second leading cause of mortality in the Canadian population and the leading cause of death worldwide (Statistics Canada, 2017). It accounts for 17.3 million deaths per year worldwide, which is projected to increase to more than 23.6 million by 2030 (Benjamin et al., 2017; Statistics Canada, 2009). Cardiovascular disease is a term encompassing diseases of the heart and blood vessels including coronary heart disease, coronary artery disease, stroke, and congenital heart disease (Fuster & Kelly, 2010). Some of the traditional risk factors for heart disease include age, dyslipidemia, family history, hypertension, obesity, physical inactivity, smoking, and diabetes mellitus (deGoma et al., 2012). However, it is now becoming apparent that arterial stiffness may also contribute to cardiovascular disease. Arterial stiffness is defined as the artery's capacity to expand and contract during a cardiac cycle, and relies on the structural properties of the arterial wall and on the distending pressure (Cecelja & Chowienczyk, 2012). Studies have shown that stiffening of arteries is associated with various clinically important cardiovascular outcomes including hypertension, left ventricular hypertrophy, atherosclerosis, stroke, coronary artery disease, and coronary heart disease (Chae et al., 1999; Franklin et al., 1997; Herrington et al., 2004; Sutton-Tyrrell et al., 2005; Urbina et al., 2011).

Age is an important intermediate marker to identify progression of cardiovascular disease. Recent studies have shown that changes in arterial structure and function may begin to develop early on in childhood, suggesting that progression of arterial stiffness may begin in childhood (Batista et al., 2015; Çelik et al., 2011; Donald et al., 2010; McGill et

al., 2000). Therefore, it is important to identify risk factors that affect arterial stiffness early in life so that the cascade of events leading to cardiovascular disease can be prevented. Recent evidence among adults suggests that individuals who experienced adversity in childhood may have a greater risk of developing cardiovascular disease in adulthood (Alastalo et al., 2009; Alastalo et al., 2013; Dong et al., 2004; Felitti et al., 1998; Su et al., 2014). Research studies examining childhood adversity including maltreatment, trauma, and household dysfunctions have referred to these early life experiences as adverse childhood experiences (ACEs) (Felitti et al., 1998; Klassen et al., 2016; Su et al., 2014). ACEs are stressful and traumatic events that occur during childhood and have been associated with physical and psychological health problems and poor well-being (Felitti et al., 2002; Hughes et al., 2016). ACEs can take several forms, for example, abuse and maltreatment includes neglect, physical, sexual, or emotional abuse, and household dysfunctions such as separation from parents or family, a household member engaging in substance abuse, suffering from a serious mental illness, experiencing parental separation or divorce, involvement of a household member in criminal activity, or a child witnessing his or her mother being treated violently (Felitti et al., 2002). Recent estimates show that approximately 32% of adults in Canada report having experienced abuse during childhood, with physical abuse being the most common, followed by sexual abuse (Afifi et al., 2014; MacMillan et al., 2013). Another study by MacMillan and colleagues (1997) found the rate of physical abuse to be higher among males (31% vs. 21%), and the rate of sexual abuse to be higher among females (13% vs. 4%). Further, the Adverse Childhood Experiences Study found that individuals who have experienced at least one ACE have an 87% chance of experiencing 2 or more ACEs, indicating that ACEs often occur in clusters and not in

isolation (Friedman, Keane, & Resick, 2007). Studies have found exposure to ACEs to be associated with various negative health outcomes including psychological health, health behaviours, chronic diseases including heart disease, and premature mortality (Anda et al., 2002; Bellis et al., 2014; Loucks et al., 2014; Waite & Shewokis, 2012; Su et al., 2015). However, recent studies are now showing that ACEs may also play an important role in the development and progression of arterial stiffness at an earlier age, leading to future cardiovascular problems.

To date, only four studies have examined the association between ACEs and arterial stiffness and two of these were cross-sectional (Hakulinen et al., 2016; Klassen et al., 2016; Loucks et al., 2014; Su et al., 2014). A study by Klassen and colleagues (2016) found that boys 10-14 years old who experienced 4 or more ACEs showed greater arterial stiffness when compared to their peers. Likewise, a study by Su and colleagues (2014) found that those who had experienced two or more ACEs showed increased peripheral arterial stiffness in adulthood compared to those who did not experience any ACEs. A 20-year longitudinal study among adults examined changes in carotid intima media thickness (cIMT) and found that those exposed to an adverse childhood family psychosocial environment had a larger cIMT after adjusting for age (Loucks et al., 2014). Finally, a large cohort study involving 2,265 young adults aged 24-39 years assessed cIMT in 2001 and again in 2007. Psychosocial risk factors including childhood adversity were assessed at baseline in 1980. This study found that a higher baseline psychosocial risk score was associated with a higher cIMT in 2001, as well as increased cIMT progression from 2001 to 2007 (Hakulinen et al., 2016). The study by Klassen and colleagues (2016) and by Su and colleagues (2014) are cross-sectional in design, and the two longitudinal studies, one

by Loucks and colleagues (2014) and the other by Hakulinen and colleagues (2016) include adult population and differences in arterial stiffness between groups (higher among those with ACEs) was already present at baseline, making it difficult to identify whether ACEs can lead to changes in arterial stiffness and when these changes begin to occur. Thus, no study to date has examined the longitudinal association between ACEs and arterial stiffness from childhood into adulthood.

It is also unclear whether the relationship between ACEs and arterial stiffness differs between males and females. Some studies have investigated the moderating effect of sex on the relationship between early life adversity and arterial stiffness but the findings are equivocal. One study recruited adults 42 years of age on average, and found early life adversity to be associated with higher risk of coronary heart disease among females only (Almeida et al., 2010), while another study done in children aged 10-14 years found that only males who experienced 4 or more ACEs have a higher arterial stiffness as measured by pulse wave velocity (Klassen et al., 2016). On the contrary, some studies did not find any significant interactions between ACEs and sex on pulse wave velocity (Su et al., 2014) or cIMT (Loucks et al., 2014). Finally, a large cohort study (n=2,265) found that a higher childhood psychosocial cumulative risk was associated with a higher cIMT among men but not among women when assessed in 2001, while no such interaction was present when cIMT was assessed in 2007 (Hakulinen et al., 2016). As seen from review of the literature, there is limited research examining sex differences in the relationship between ACEs and arterial stiffness and the results from existing research are conflicting. In addition, it is unclear if traditional risk factors including heart rate (HR), systolic blood pressure (SBP),

body mass, and/or physical activity explain the relationship between ACEs and arterial stiffness.

1.2 Study Rationale

Few studies have examined the association between ACEs and arterial stiffness, and those that have are either cross-sectional in design, focused on longitudinal data in adults only and/or required participants to recall exposure decades later. Thus, it remains unclear whether differences in arterial stiffness in response to ACEs begin to emerge early on in life. Also, it is still unclear whether the association between ACEs and arterial stiffness differs between males and females. Lastly, no study to date has examined the potential pathways between ACEs and arterial stiffness. It is unclear as to whether the connection between ACEs and arterial stiffness goes through commonly identified risk factors, specifically HR, SBP, BMI, and physical activity, or whether there are different pathways that account for this relationship. Therefore, the purpose of this study was to examine the relationship among ACEs, arterial stiffness, sex, HR, SBP, body mass index (BMI), and physical activity over time from childhood to adulthood, while carefully addressing the limitations of previous studies.

1.3 Research Hypotheses

1. Individuals who have experienced a greater number of ACEs, will experience a greater increase in arterial stiffness over time from childhood into early adulthood.
2. The relationship between ACEs and changes in arterial stiffness will not differ between males and females over time from childhood into early adulthood.
3. Changes in HR, SBP, BMI, and/or physical activity will mediate the association between ACEs and arterial stiffness over time from childhood into early adulthood.

CHAPTER 2: LITERATURE REVIEW

2.1 Social Stress and Health Problems

Stress has been described as a state of arousal resulting from the presence of socio-environmental demands, which can lead to wear and tear on the body if it were to exceed the adaptive capacity of an individual (Lazarus 1966, Pearlin 1983, Menaghan 1983). Much of the earlier research on the physiological consequences of stress was investigated by Hans Seyle, the "father of stress", who emphasized that "stress is not what happens to you, but how you react to it (Selye 1974; Selye 1977)." In the mid-1930s, he identified three stages of physiological reaction to harmful and stressful events: the alarm, resistance, and exhaustion stages, and later went on to define stress as "the non-specific neuroendocrine response of the body (Selye, 1936; Selye, 1956; Selye, 1976)." However, Seyle's later work found that these stages of stress will not only lead to neuroendocrine response, but they also lead to various health problems including high blood pressure (BP) and heart disease (Selye, 1970). Despite the ample evidence in in-vitro and animal models to support the role of stress in the development of cardiovascular disease, research examining cardiovascular reactions to psychosocial stress in human participants was limited until the 1960s.

Two psychiatrists, Thomas Holmes and Richard Rahe created the Social Readjustment Rating Scale to assess whether stress contributes to illness in humans and found a dose-response relationship between behavioural readjustments (e.g., after death of a spouse) and the likelihood of illness among adults (Holmes & Rahe, 1967). Thereafter, a number of studies found an association between stress factors such as work stress, lack of social support, and isolation and coronary artery disease (Blazer, 1982; Siegrist et al., 1990). Work by Ruberman and colleagues (1984) reported that cardiac patients who

experienced high levels of life stress or social isolation have a twofold increased risk of experiencing mortality, and a fourfold higher risk among those who experienced the two factors together. A more recent meta-analysis found anxiety to be an independent risk factor for coronary heart disease and cardiac deaths (Roest, Martens, de Jonge, & Denollet, 2010). Anxiety has also been correlated with palpitations, abnormal heartbeat, and muscle tension (Suls & Bunde, 2005). Further, lack of social support and social isolation also predicted the onset and prognosis of coronary heart disease among males and females with the risk being 3-5 times higher in adult males and 2-3 times higher in adult females of various age groups (Bunker et al., 2003; Sorensen & Wang, 2009). Cohort studies have also established the association between more severe psychological trauma and posttraumatic stress disorder and cardiovascular events with hazard ratios ranging from 1.5 to 3.5 (Boscarino, 2008; Edmondson & Cohen, 2013; Jordan et al., 2011; Kubzansky, Koenan, Spiro, Vokonas, & Sparrow, 2007; Scherrer et al., 2010; Vaccarino et al., 2013).

Not only have studies examined the effect of long-term stress on cardiovascular health, but they have also examined the association between acute stress and adverse cardiovascular events (Carroll, Ebrahim, Tilling, Macleod; Leor, Poole, & Kloner, 1996; Meisel et al., 1991). For example, a number of studies have found an association between major events (i.e., natural disasters, terrorist attacks, and major sporting events) and increased rate of cardiac events and cardiac mortality among adults (Carroll, Ebrahim, Tilling, Macleod, & Smith, 2002; Meisel et al., 1991; Steptoe & Brydon, 2009; Suzuki et al., 1997). Overall, literature in the area suggests that psychological stress caused by social factors and/or emotional experiences in adulthood increases the risk for cardiovascular disease and mortality.

Although studies have extensively examined the relationship between psychosocial stress and cardiovascular disease in adults, relatively little research is conducted among children. Some studies in the 1980s and early 1990s started to understand the frequency and long-term behavioural consequences of child abuse (Belsky, 1980; Malinosky-Rummell & Hansen, 1993); however, the health consequences of these exposures were yet to be examined. It was in 1998 that a landmark study by Felitti and colleagues (1998) examined the influence of adverse and stressful experiences in childhood, focusing specifically on child maltreatment and household dysfunction, on psychological and physical health in adults. The results showed that adults who had experienced 4 or more adverse events in childhood had increased rates of depression, drinking, substance abuse, and chronic diseases such as ischemic heart disease, chronic lung disease, cancer, and liver disease compared to those with no experience of adverse events in childhood.

2.2 Adverse Childhood Experiences

ACEs are stressful and traumatic events that occur during childhood. The experiences tend to occur in the context of a child's immediate family environment, vary in severity, and may be acute, intermittent, or chronic in nature. Examples of ACEs based on Felitti's work focused on two types: child maltreatment, specifically neglect, physical, sexual, or emotional abuse, and household dysfunction, specifically separation from parents or family, a household member engaging in substance abuse, a family member suffering from serious mental illness, experiencing parental separation or divorce, involvement of a household member in criminal activity, or a child witnessing his or her mother being treated violently (Felitti et al., 2002). While much of the literature includes these aforementioned conventional ACEs, some studies have expanded these to include

other childhood adversities both within and outside the family including bullying, feel discriminated, living in foster care, or family member killed by soldiers, police, military, or gangs (Cronholm et al., 2015; Naal, Jalkh, & Haddad, 2018).

2.2.1 Prevalence of ACEs

ACEs are prevalent in the population regardless of sex and cultural settings. Recent estimates show that approximately 702,000 (9.4 victims per 1,000) children in the United States have experienced some form of maltreatment per year (Sugaya et al., 2012). It is estimated that 4-16% of individuals have experienced physical abuse during childhood, meanwhile 15-30% of girls and 5-15% of boys have experienced some form of sexual abuse, and 10% have experienced psychological abuse or neglect in developed countries including the U.S., U.K., New Zealand, Canada, Australia, and Finland (Gilbert et al., 2009). Specifically, in Canada past estimates suggest that 31% of males and 21% of females have experienced physical abuse, while 4% of males and 13% of females have experienced sexual abuse in childhood (MacMillan et al., 1997). More recent estimates show that approximately 32% of young adults in Canada have experienced abuse during childhood, with physical abuse (26-32%) being the most common, followed by sexual abuse (10-15%) (Afifi et al., 2014; MacMillan et al., 2013). Studies conducted in developed countries have also shown that while the rates of physical and psychological abuse are higher in boys compared to girls, the rates of sexual abuse are higher among girls (Afifi et al., 2014; Finkelhor, Hotaling, Lewis, & Smith, 1990; Titus et al., 2003). Furthermore, evidence shows that ACEs do not occur in isolation. Individuals who have experienced one ACE are at a greater risk of experiencing other ACEs. This was evident in the Adverse Childhood Experiences Study, which found that individuals who experienced at least one

ACE have an 87% chance of experiencing 2 or more ACEs (Friedman, Keane, & Resick, 2007). Such high prevalence of ACEs and the fact that they are present in clusters is of concern due to their association with poor health outcomes.

2.2.2 Health Implications of ACEs

It is well known that early life adversities have a significant influence on adult health (Afifi et al., 2014; Benedetti et al., 2011; Su et al., 2014). ACEs are associated with poor physical and psychological health outcomes across the life course (Afifi et al., 2014; Benedetti et al., 2011; Hughes et al., 2017; Monnat & Chandler, 2015). There is some evidence of a dose-response relationship between exposure to ACEs and risk of negative health outcomes (Chapman et al., 2004; Dong et al., 2004; Felitti et al., 1998). Studies have found exposure to ACEs to be associated with various negative health outcomes including psychological health (e.g. depression and anxiety), health behaviours (e.g. smoking and substance misuse), chronic diseases (e.g. heart disease, type 2 diabetes, and cancer), and premature mortality (Anda et al., 2002; Bellis et al., 2014; Loucks et al., 2014; Waite & Shewokis, 2012; Su et al., 2015).

2.2.2.1 ACEs and Psychological Health

Research has examined the long-term impacts of ACEs on mental/psychological health among adults. A positive association has been found between the number of ACEs experienced and depression, anxiety, panic reaction, hallucinations, psychosis, suicide attempt, and overall mental well-being (Benedetti et al., 2011; Chan & Yeung, 2009; Dube et al., 2001; Felitti et al., 1998; Waite & Shewokis., 2012; Whitfield et al., 2005; Young et al., 1997). Various explanations have been proposed to explain this relationship. It is proposed that maltreatment during childhood can lead to the development of attachment

difficulties, poor control over emotions, fear, and lack of trust (Anda et al., 2006; Riggs, 2010). Children who experience adverse events also hold a negative image of themselves, lack self-worth, and feelings of incompetency, which can lead to poor psychological well-being in adulthood (Hillis et al., 2004). While evidence suggests that adverse events in childhood may influence the development and mental health, most studies are retrospective and rely on recall of exposure in the adult population (Benedetti et al., 2011; Dube et al., 2001; Felitti et al., 1998; Waite & Shewokis., 2012; Whitfield et al., 2005; Young et al., 1997).

2.2.2.2 ACEs and Poor Lifestyle and Behaviours

Studies have found an association between ACEs and unhealthy lifestyle such as physical inactivity, and consequently, obesity. A study by Felitti and colleagues (1998) found that obesity rates were significantly higher among adults who experienced 4 or more ACEs compared to those with less than 4 ACEs. Studies have also examined the relationship between ACEs and body mass in children. Work by Pretty and colleagues (2013) found a dose-response relationship between ACEs and BMI, and between ACEs and waist circumference among children aged 11-14 years. The effect of ACEs on obesity has also been examined prospectively in 11-year-old girls as they grew into adults (Noll et al., 2007). The results showed that by the age of 20-27 years, those who had experienced childhood abuse were more likely to be obese compared to those who did not experience childhood abuse. The reasoning behind this weight gain was investigated by Felitti and Williams (1998) who found that individuals who experienced sexual abuse in childhood may avoid weight loss as it may trigger post-traumatic stress disorder symptoms as they approach the weight when they were abused (Felitti & Williams, 1998). Felitti and

colleagues (2010) also found that participants who had previously experienced abuse reported that they felt ‘protected’ and ‘safe’ by their obesity since they believed themselves to be physically unattractive and less-noticed by their partner and/or abuser (Felitti et al., 2010).

It is also possible that higher BMI and waist circumference scores and higher rates of obesity among individuals who experienced ACEs may be explained by differences in physical activity levels among this group. Adults who have experienced 4 or more ACEs are more likely to be physically inactive compared to those that did not experience ACEs (Bellis et al., 2014; Dong et al., 2004; Felitti et al., 1998). Consistent physical inactivity may lead to overweight/obesity, which is associated with various health conditions including cardiovascular disease (Blair & Brodney, 1999).

Studies conducted among adults have shown that adverse events experienced during childhood are also linked to engagement in aggressive behaviour, risky sexual behaviour, smoking, drinking, and substance abuse in adulthood (Bellis et al., 2014; Dietz et al., 1999; Douglas et al., 2010; Felitti et al., 1998; Ford et al., 2011; Hahm et al., 2010; Ramiro et al., 2010). Evidence also suggests that the relationship between ACEs and poor behaviour may be mediated by depression. ACEs have been found to be associated with depression and anxiety (Chapman et al., 2004; Mersky et al., 2013; Reiser et al., 2014) and it is known that depressed individuals are more likely to engage in smoking, drinking, and substance abuse as a form of self-medication to deal with mental health issues (Crocq, 2003; Johannessen et al., 2017, Skogen et al., 2014). Consequently, adults who have experienced childhood adversities may become dependent on these behaviours over time, which is indicated by the higher rate of poor health behaviours in this population (Fanti &

Henrich, 2010). Felitti describes this situation as the public health paradox where ACEs are often hidden and not discussed openly because of the shame and social stigma/taboo associated with these experiences (Felitti, 2009). In order to deal with these experiences, people rely on other behaviours such as smoking, overeating, alcohol, and drugs because it brings them immediate (but temporary) relief. In this case, the public health problems such as smoking, drinking, overeating, and substance abuse are often serving as the "solution". This is the paradox as something that is problematic unconsciously ends up being used to address the situation and provide temporary relief. Therefore, it is important to intervene in the early stages of life and focus on encouraging children to share adverse experiences, thereby breaking the stigma and taboos in order to address these public health problems before they manifest into long-term negative health outcomes.

2.2.2.3 ACEs and Hypertension

Previous studies have examined the association between ACEs and cardiovascular risk factors and outcomes. The Georgia Stress and Heart Study examined the long-term effects of ACEs on BP from childhood to young adulthood, where ACEs were grouped into 4 groups: none (0), low (1-2), moderate (3), and severe ($\geq$4) (Su et al., 2015). The results showed a significant ACEs group by age interaction, suggesting that participants who experienced multiple adverse events before 18 years of age showed a rapid increase in their BP levels in young adulthood when compared to those who did not experience any traumatic events (Su et al., 2015). However, the study did not find an ACEs group by sex interaction, suggesting that increases in BP levels were similar for both males and females. Other studies have also reported a positive association between adverse and stressful events during childhood and BP in adulthood (Alastalo et al., 2013; Riley, Wright, Jun, Hibert, &

Rich-Edwards, 2010; Stein et al., 2009). A study involving nurses reported a positive association between maltreatment in childhood and hypertension in adulthood (Riley et al., 2010). Another study found that children who were separated from their parents had higher systolic and diastolic blood pressures (DBP) as adults compared to children who were not separated from their parents (Alastalo et al., 2013). In contrast, two cross-sectional studies, one by Gooding and colleagues (2014) among adults, and the other by Pretty and colleagues (2013) among 11-13 year olds, did not find any significant relationship between exposure to ACEs and systolic and DBP. However, the study by Pretty and colleagues (2013) did find that children who had experienced 4 or more ACEs showed a significantly higher HR compared to children with less than 4 ACEs. While ACEs is found to be associated with high BP (Alastalo et al., 2013; Riley, Wright, Jun, Hibert, & Rich-Edwards, 2010; Stein et al., 2009; Su et al., 2015), it is now becoming apparent that ACEs may also play an important role in the development and progression of arterial stiffness, leading to future cardiovascular problems.

Arterial stiffness is defined as the artery's capacity to expand and contract during a cardiac cycle, and relies on the structural properties of the arterial wall and on the distending pressure (Cecelja & Chowienczyk, 2012). Studies have shown that stiffening of arteries is associated with cardiovascular risk factors such as physical inactivity and obesity and various clinically important cardiovascular outcomes including hypertension, left ventricular hypertrophy, atherosclerosis, stroke, coronary artery disease, and coronary heart disease (Chae et al., 1999; Franklin et al., 1997; Herrington et al., 2004; Sutton-Tyrrell et al., 2005; Urbina et al., 2011). In addition, recent studies have shown that changes in arterial structure and function may begin to develop early on in childhood, suggesting

that progression of arterial stiffness may begin in childhood (Batista et al., 2015; Çelik et al., 2011; Donald et al., 2010; McGill et al., 2000). Also, given the evidence linking ACEs and cardiovascular disease in adults (Alastalo et al., 2009; Alastalo et al., 2013; Dong et al., 2004; Felitti et al., 1998; Su et al., 2014), as well as the evidence linking arterial stiffness and cardiovascular disease in adults (Cecelja & Chowienczyk, 2012), it is important to identify whether ACEs leads to greater arterial stiffness early in life so that the cardiovascular trajectory can be altered at an earlier age to prevent negative outcomes.

2.3 The Arterial System

The systemic arterial system is comprised of a large number of vessels such as arteries and arterioles that are responsible for the delivery of blood throughout the body. The unique elastic properties of the arterial system allow for pulsatile flow, generated by the pumping action of the left ventricle, to be converted into continuous steady flow as blood travels to the periphery. However, arteries tend to stiffen with age (Lee & Oh, 2010; Sun, 2015; Mirea, Donoiu, & Plesea, 2012) and arterial stiffness has been found to be associated with hypertension (Franklin et al., 1997), obesity (Wildman et al., 2003), physical inactivity (Pandit et al., 2014), dyslipidemia (Pannier et al., 1994), coronary artery disease (Sutton-Tyrrell et al., 2005), stroke (Sutton-Tyrrell et al., 2005), heart failure (Chae et al., 1999), atrial fibrillation (Mitchell et al., 2007) and cardiovascular mortality (Shoji et al., 2010). Considering that arterial stiffness is associated with many cardiovascular risk factors and cardiovascular disease, it is important to understand the structural, functional, and mechanical properties of the arterial system.

2.3.1 Arterial Wall Structure & Function

Arterial walls are comprised of three distinct layers, namely, the tunica intima, tunica media, and tunica adventitia. The intima is the innermost layer of the artery and is mainly composed of one layer of endothelial cells and a supporting layer of elastin rich collagen fibres, which anchor it to the internal elastic lamina (Gasser, Ogden, & Holzapfel, 2006). The internal elastic lamina separates the tunica intima from the tunica media. Tunica media forms the middle layer of the wall and is the primary determinant of the mechanical properties of the vessel. The medial layer is mainly composed of smooth muscle fibres and a thick elastic connective tissue that allow vessels to constrict or dilate. The outer elastic lamina separates the media from the adventitia. Tunica adventitia is the outer most layer and is composed of collagen and some elastin tissue that blend with the connective tissue containing nerves, blood vessels, and fibroblasts (Gasser et al., 2006).

The arterial system is divided into three anatomical regions: 1) large arteries, 2) muscular arteries, and 3) arterioles (Nichols, O'Rourke, & Vlachopoulos, 2011). Each region serves a distinct function with the overall goal to deliver blood to the peripheral vascular network. The large elastic arteries, such as the aorta and common carotid artery (CCA) act as a cushioning reservoir to help cope with pressure changes and pressure waves generated by the ejection of blood from the left ventricle, thereby ensuring laminar flow and reducing pulsatile flow. These large arteries store blood during systole and expel it to the tissues during diastole (Nichols & Edwards, 2001). While large elastic arteries are located closest to the heart, the muscular arteries such as the brachial and femoral artery act as conduits as they are responsible for supplying blood to the extremities (Nichols & Edwards, 2001). Further, these muscular arteries are capable of altering smooth muscle

tone and diameter, which allows them to modify wave propagation (Nichols & Edwards, 2001). The muscular arteries end in arterioles, which supply continuous blood to the organs and tissues. Arterioles are capable of regulating peripheral resistance by changing their diameter through contraction of circular smooth muscle cells in the wall (Nichols & Edwards, 2001). The greater the vasoconstriction, the smaller the diameter and greater the peripheral resistance, resulting in increased arterial BP. Aging, direct injury, atherogenic factors, and long-term changes in hemodynamic conditions are some of the factors that may modify the structure and function of the arterial wall (Safar, 2010). Structural modifications include widening and elongation of large arteries and thickening of the vessel wall, while functional modifications include a decrease in arterial compliance and distensibility, in other words an increase in stiffness, of the large elastic arteries (Bortolotto et al., 1999).

2.4 Arterial Stiffness

The primary functional role of large arteries is to transform pressure and flow oscillations caused by left ventricular ejection into steady blood flow. With increased stiffness, the ability of arteries to dilate in response to the volume of blood ejected by the left ventricle is decreased. Arterial stiffness is commonly used to express the viscoelastic properties of the arterial wall. Arterial stiffness (E) is defined as the relationship between changes in pressure (ΔP) over changes in volume (ΔV) (Briet, Boutouyrie, Laurent, & London, 2012; London & Pannier, 2010). The relationship between pressure and volume is non-linear and stiffness represents the instantaneous slope of this relation (O'Rourke, Staessen, Vlachopoulos, & Duprez, 2002). Over the years, a number of ways to measure

arterial stiffness have been developed and include arterial compliance, arterial distensibility, IMT and pulse wave velocity (PWV).

2.4.1 Pulse Wave Velocity

PWV is a function of pressure, diameter, and speed of blood flow through the vasculature. The force at which blood is ejected by the left ventricle is transmitted into a pulse wave, which then travels through the arterial vessels to the distal sites of the body. The speed of the pulse wave is inversely related to the viscoelastic properties of the arterial wall. Hence, the higher the PWV, the greater the arterial wall stiffness (Boutouyrie, Briet, Collin, Vermeersch, & Pannier, 2009). PWV is calculated by dividing the distance between the two sites (ΔD) of pulse wave measurement, over the delay in travel time between the two measurement sites (ΔT). PWV is calculated using the following equation (Laurent et al., 2006):

$$PWV = \frac{\Delta D \text{ (metres)}}{\Delta T \text{ (seconds)}}$$

PWV is an ideal method for assessing arterial stiffness in a research setting as it is non-invasive and is relatively easy to obtain. There are several tools that can be used to obtain PWV: applanation tonometry, Doppler ultrasound, ultrasound wall tracking system, magnetic resonance imaging, and photoplethysmography (Cheung, 2010). The two sites commonly used are the CCA and femoral arteries. Carotid-femoral PWV (cfPWV) is considered the 'gold standard' for assessing arterial stiffness non-invasively (Laurent et al., 2006). The validity and reliability of cfPWV has been established (Hwang et al., 2014). Table 2.1 displays the normative values for cfPWV by age categories (Reference Value for Arterial Stiffness' Collaboration, 2010). However, obtaining femoral pressure waveform can be difficult at times in obese individuals and those with peripheral artery disease (Van

Bortel et al., 2002). Therefore, other methods have been investigated such as carotid-toe, carotid-radial, brachial-ankle, and ECG-to-toe PWV (Bulpitt et al., 1999; Klassen et al., 2016; Lee et al., 2006, Munakata, 2015), and while some of these methods such as carotid-to-toe and brachial-ankle PWV have shown to be reliable and valid (Cheng et al., 2015; Klassen et al., 2018), validity and reliability of others are yet to be established.

Table 2.1 Distribution of PWV (m/s) according to age. Taken from the Reference Values for Arterial Stiffness' Collaboration, 2010. (n=1,455)

Age category (years)	Mean (±2 SD)	Median (10–90 pc)
<30	6.2 (4.7–7.6)	6.1 (5.3–7.1)
30–39	6.5 (3.8–9.2)	6.4 (5.2–8.0)
40–49	7.2 (4.6–9.8)	6.9 (5.9–8.6)
50–59	8.3 (4.5–12.1)	8.1 (6.3–10.0)
60–69	10.3 (5.5–15.0)	9.7 (7.9–13.1)
≥70	10.9 (5.5–16.3)	10.6 (8.0–14.6)

SD, standard deviation; 10 pc, the upper limit of the 10th percentile; 90 pc, the lower limit of the 90th percentile.

2.4.2 Common Carotid Artery Compliance and Distensibility

Arterial compliance and distensibility is the ability of an artery to expand and contract. Arterial compliance is defined as the absolute change in area per unit of pressure (Tziomalos et al., 2007) and is calculated as follows:

$$\frac{(sCSA - dCSA)}{P_s - P_d}$$

Whereas arterial distensibility is defined as the relative change in area per unit of pressure and is calculated as:

$$\frac{((sCSA - dCSA)/\ dCSA))}{P_s - P_d}$$

Where sCSA and dCSA are systolic and diastolic arterial cross-sectional area (cm^2), and Ps and Pd are systolic and diastolic pressures, respectively.

The CCA is commonly used to measure compliance and distensibility due to its location, shape, and parallel walls. Both distensibility and compliance can be estimated using a high-resolution ultrasound, where diameter and area of the arterial walls can be measured throughout the cardiac cycle as the expansion and contraction of arteries occurs with every pulsation and relaxation (Fernhall & Agiovlasitis, 2008). Arterial compliance is the change in arterial blood volume for a given change in arterial pressure, and is dependent on artery size, whereas, arterial distensibility is the relative change in area for a given pressure change independent of the size of the artery.

A decrease in arterial distensibility and compliance indicates a reduced ability to dilate in response to the volume of blood ejected by the left ventricle. Reduced arterial compliance and distensibility may lead to increased systolic pressure and ventricular afterload, which are known to increase the risk for various cardiovascular events including atherosclerosis, left ventricular hypertrophy, and cardiac arrest (Marchais et al., 1992).

2.4.3 Carotid Intima-Media Thickness

Common carotid artery IMT is typically measured with a high-resolution B-mode ultrasound (Fernhall & Agiovlasitis, 2008) and the intima-media complex (Figure 2.1) is identified as a double line density of intima-luminal and media-adventitia interfaces on the near (anterior) as well as the far wall (posterior) of the CCA (Shin, Tajbakhsh, Todd Hurst, Kendall, & Liang, 2016).

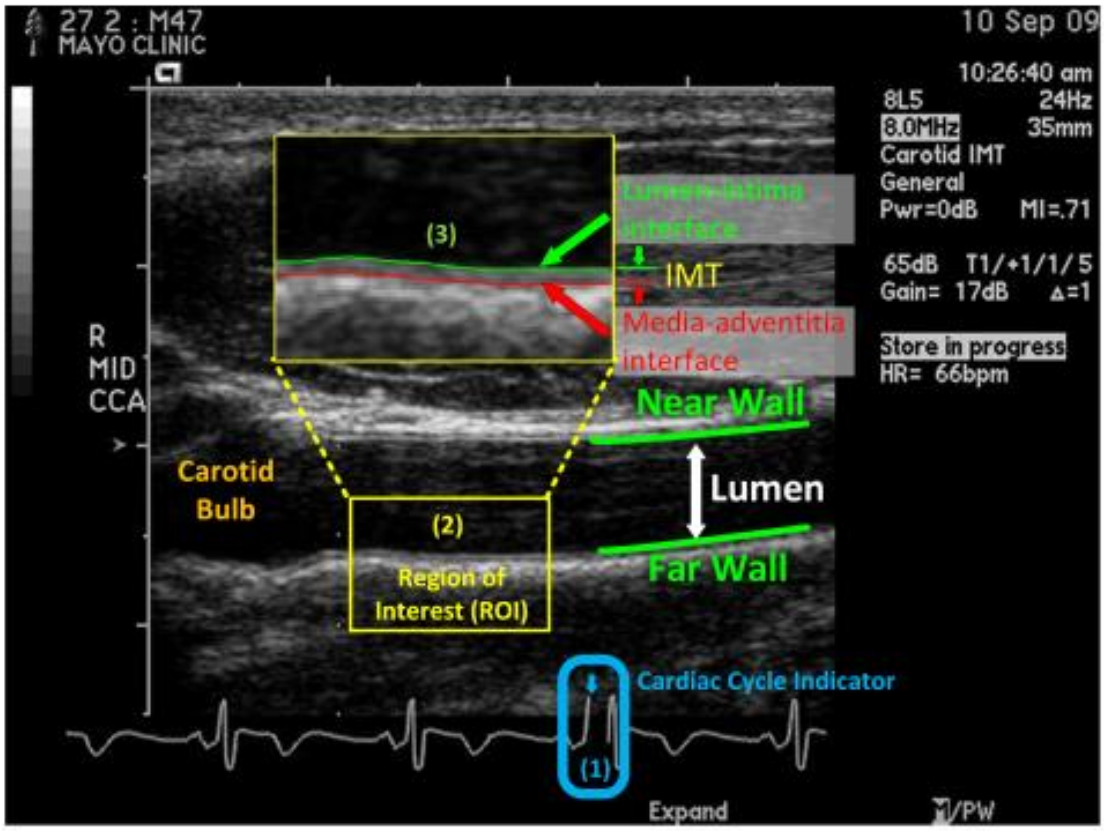

Figure 2.1: *Longitudinal view of the common carotid artery using an ultrasound B-scan image*. Taken from Shin et al., 2016.

Obtaining cIMT of the near wall may be inaccurate and difficult to reproduce due to technical considerations in discerning the IMT. Meanwhile, there is limited movement on the far wall, and typically, it is measured at end-diastole (minimal arterial pressure) to ensure lowest possible wall tension. Also, the double-line pattern of the far wall has better detail than the near wall. Therefore, it is recommended to limit cIMT measurements to the far wall since it provides a more accurate and reliable assessment of the IMT in comparison to the near wall (Stein, Korcarz, & Post, 2009).

Population based studies have shown that cIMT varies from 0.4 to 0.5 mm in young individuals to 0.8 mm in older populations (Lim, Lim, Dwivedi, Kooner, & Senior, 2008).

Also, a cIMT of 1.0 mm is typically considered abnormal, and values of 1.2 mm or higher are associated with increased risk of vascular disease (Lim et al., 2008).

2.4.4 Mechanisms of Arterial Stiffness

Arterial stiffening occurs as a result of many factors including age related changes in hemodynamic forces, hormonal fluctuations, deterioration of the cellular systems and their functions over time, increased salt intake and glycemic levels, and diseases such as atherosclerosis and diabetes (Benetos et al., 2002; Schram et al., 2004; Sun, 2014; Zieman, Melenovsky, & Kass, 2005; van Popele et al., 2001). Mechanisms for arterial stiffness can be discussed in terms of factors that lead to structural and functional changes to the endothelium or the medial layer of the arterial wall.

Collagen, elastin, glycoproteins, and proteoglycans make up the extracellular matrix of the arterial wall (Zieman et al., 2005). Normally, there is a tight regulation of collagen and elastin levels through their synthesis and breakdown by metalloproteases (Johnson, Baugh, Wilson, & Burns, 2001). However, abnormalities in the regulatory process that result in increased collagen levels and decreased elastin levels is known to contribute to stiffening of the arteries. Research shows that an imbalance in collagen and elastin levels may be due to inflammation of the arterial wall or increased pressure in the lumen, for example, in case of hypertension (Johnson et al., 2001; Xu, Zarins, Pannaraj, Bassiouny, & Glagov, 2000). When the vessel wall is inflamed, inflammatory cells including polymorphonuclear neutrophils and macrophages produce various metalloproteases and elastase, which breakdown the extracellular matrix by producing weaker collagen and degradation of elastin fibres, thus leading to a stiffer vessel wall (Visse & Nagase, 2003; Dollery, McEwan, & Henney, 1995). Moreover, degradation of

extracellular matrix may also play an important role in the development and progression of atherosclerotic lesions and therefore, studies have suggested that higher levels of metalloproteases are associated with increased cIMT (Galis & Khatri, 2002).

In addition to degradation of elastin fibres, advanced glycation end products have also been reported to influence arterial stiffness by receptor mediated-endothelial dysfunction and inflammation. Advanced glycation end products are formed by a mechanism where prolonged tissue exposure to hyperglycemia can result in glycation of proteins within the extracellular matrix, causing them to rearrange and in turn reducing arterial compliance (Bailey, 2001; Katsuda & Kaji, 2003; Quinn, Tomlinson, Cockcroft, 2012). Research suggests that accumulation of advanced glycation end products over time forms cross-links among collagen fibres as well as among elastin fibres. The formation of cross-links is an irreversible process and once cross-links are formed, they alter the interaction of collagen and elastin within the extracellular matrix, resulting in a stiffer vessel wall (Quinn et al., 2012). Adverse vascular effects of advanced glycation end products may also include endothelial modulation of vasomotor tone, platelet adhesion and aggregation, thrombogenicity, and cell proliferation (Zieman & Kass., 2004), which may coincide with cross-linking and increase the progression of arterial stiffness. This increase in stiffness may create a vicious cycle of arterial stiffness, that is, accumulation of advanced glycation end products may promote the development of IMT, which may lead to a decrease in compliance and an increase in SBP and pulse pressure, and this in turn may further increase IMT thereby accentuating arterial stiffening. Studies have shown that levels of advanced glycation end products increase with age (Monnier et al., 1999),

smoking (Cerami et al., 1997), diet (Yamagishi, Ueda, & Okuda, 2007), and diabetes (Brownlee, 1995), which are important risk factors for arterial stiffness.

The extracellular matrix provides support for the vascular endothelium. Specifically, through the formation of adhesive interactions with proteins on the endothelial cell surface, the extracellular matrix provides structural support that is required for maintaining the organization of endothelial cells in the blood vessels (Davis & Senger, 2005). The endothelium covers the inner surface of the artery and is responsible for producing a variety of contracting and relaxing factors that influence the structure and tone of the artery (Cockcroft, Wilkinson, & Webb, 1997). Nitric oxide is synthesized and released by the endothelium. Nitric oxide counteracts the action of vasoconstricting factors such as angiotensin-II and endothelin-1, and acts to relax the vessel walls and therefore plays an important role in regulating basal arterial tone and BP (Anderson, 2006; Cockcroft et al., 1997). Nitric oxide also maintains arterial tone by inhibiting platelet and white cell activation (Anderson, 2006). Therefore, a balance between contracting and relaxing factors is required in maintaining normal arterial function. Imbalances between nitric oxide, endothelium-derived hyperpolarizing factor, vasoconstricting factors, and oxygenases (e.g. heme oxygenases act as an antioxidant, protect endothelial cells from apoptosis, help in regulating arterial tone, and lower the inflammatory response in the vessel wall) alter smooth muscle tone of the medial layer of the vessels and are responsible for endothelial dysfunction (Shirwany & Zou, 2010). This is because when there is an imbalance, the arteries are more prone to vasoconstriction, leukocyte adherence, platelet activation, thrombosis, inflammation and atherosclerosis (Verma & Anderson, 2002). Studies have found that an increase in endothelin-1 production significantly increased iliac PWV, and

administration of endothelin-1 receptor antagonist reduced large artery stiffness (McEniery et al., 2003). In fact, research shows that there is a bidirectional relationship between endothelial dysfunction and arterial stiffening, where arterial stiffening leads to endothelial dysfunction and in turn, endothelial dysfunction further stiffens the arteries (Shirwany & Zou, 2010). Overall, due to stiffness, less volume of blood can be stored in these arteries during systole, which can lead to an increase in the left ventricle load, reduced coronary flow, and increased risk for cardiovascular disease (Belz, 1995).

Leptin levels are also associated with arterial stiffness, especially among overweight and obese individuals (Valle et al., 2003; Considine et al., 1996). Studies have shown that serum leptin levels are significantly higher in obese individuals and are known to be associated with reduced arterial distensibility (Singhal et al., 2002), increased smooth muscle cell proliferation and migration (Oda, Taniguchi, & Yokoyama, 2001), vascular cell calcification (Parhami, Tintut, Ballard, Fogelman, & Demer, 2001), and oxidative stress in endothelial cells (Bouloumie, Marumo, Lafontan, & Busse, 1999). Hence, a combination of these changes may promote arterial stiffness over time.

Another factor associated with arterial stiffness is C-reactive protein, which is secreted by the liver in response to trauma, inflammation, or infections by activating an adaptive immune response (Du Clos, 2000). C-reactive protein has been associated with insulin resistance (Yudkin et al., 1999), diabetes mellitus (Pradhan et al., 2001), and hypertension (Chae, Lee, Rifai, & Ridker, 2001), Studies have also found increased levels of C-reactive protein among older individuals to be associated with higher cfPWV, a measure of central arterial stiffness after adjusting for age, sex, SBP, pulse pressure, glucose levels, and lipid profile (Kim et al., 2007; Mattace-Raso et al., 2004). It is possible

that an increase C-reactive protein level is associated with endothelial dysfunction. For example, two studies, one by Yudkin and colleagues (1999), the other by Fichtlschere and colleagues (2000) found that increased C-reactive protein induces endothelial dysfunction, thereby blocking the synthesis of nitric oxide, which in turn may inhibit endothelium-dependent vasodilation and contribute to atherosclerosis (Kinlay et al., 2001). Inhibiting the release of nitric oxide may also influence basal arteriolar tone and BP (Hanes, Noon, Walker, Webb, 1993; Vallance, Collier, Moncada, 1989), thereby contributing to arterial stiffening. Research has also reported that an elevated C-reactive protein during childhood may promote increased cIMT (Jarvisalo et al., 2002). Overall, there are a number of mechanisms that have been proposed in the literature linking arterial stiffness to a variety of cardiovascular risk factors, both modifiable and non-modifiable, as well as disease outcomes.

2.5 Determinants of Arterial Stiffness

2.5.1 Non-Modifiable Risk Factors

2.5.1.1 Age and Sex

Age is one of the most important determinants of cardiovascular health (Lee & Oh, 2010). Previous research shows that changes in both arterial structure and function take place as individuals get older (Lee & Oh, 2010; Sun, 2015; Mirea, Donoiu, & Plesea, 2012). The most consistent changes that occur with aging are luminal enlargement, arterial wall thickening, and reduction in elastic properties (Izzo & Shykoff, 2001). Also, research has demonstrated that there is a decline in endothelium function with increased age. Consequently, there is a reduction in nitric oxide availability and an increase in formation of reactive oxygen species, further facilitating vascular aging (Balaban, Nemoto, & Finkel,

2005; Donato et al., 2009; Harrison, 1997). A study by Virmani and colleagues (1991) showed that individuals over the age of 65 years had a 15-20% increase in aortic diameter compared to younger adults, independent of BP (Virmani et al., 1991). Similar trends were also reported by Dinenno and colleagues (2000), and supported by a laboratory animal study that found arterial dilation despite completely blocking the renin-angiotensin system, suggesting that arterial remodeling occurs with age independent of BP (Levy, Duriez, Phillipe, Poitevin, & Michel, 1994). Further, a study by Wang and colleagues (2007) reported that thickening of the arterial wall with age is caused by smooth muscle cell hypertrophy, collagen synthesis, and elastin degradation (Wang et al., 2007).

The effect of vascular aging is not homogenous since the central elastic arteries are more likely to experience structural changes with increased age as opposed to peripheral muscular arteries (McVeigh et al., 1999). Vessel wall compliance is dependent on the contribution of two scaffolding proteins: collagen and elastin (Marchais et al., 1992; Xu et al., 2000; Zieman et al., 2005). Normally, the balance, stability, and compliance of arteries are regulated by the synthesis and breakdown of these proteins. However, there is an increased degradation of elastin and accumulation of collagen with aging (Mirea et al., 2012) explaining why central arteries become stiffer with age, since they contain more elastin and less smooth muscle to begin with. This reduction in elastin to collagen ratio might be a consequence of enhanced activity of extracellular matrix metalloproteinases, which are present in significantly greater amounts in older individuals (Wang et al., 2007). Moreover, a study found that aortic PWV increased faster after the age of 50 years, suggesting that progression of arterial stiffness increases with older age (McEniery et al., 2005). Similarly, studies that conducted a histological examination of arterial tissue found

that the tunica media layer of the artery is 2-3 times thicker in older individuals compared to younger individuals indicating the deterioration of cellular systems and functions as individuals age (Nagai, Metter, & Fleg, 1999; O'Leary et al., 1999). This finding may also be linked to the increased prevalence of metabolic syndrome factors including abdominal obesity, hypertension, hyperglycemia, and dyslipidemia in older individuals, which are thought to accelerate vascular aging (Koskinen et al., 2009). Also, work by Safar and colleagues (2006) found that individuals with three or more risk factors had significantly higher aortic PWV, supporting the finding that stiffness increases in presence of metabolic risk factors.

Studies have also examined differences in arterial stiffness between males and females. Typically, average cfPWV (in children and adolescents aged 8-17) is between 4.7-5.3 m/s and 4.5-5.1 m/s for males and females, respectively (Diaz et al., 2018; Mora-Urda et al., 2017; Reusz et al., 2010). Among young adults, cfPWV is reported to approximate between 5.5-6.0 m/s in males and between 5.4-5.8 m/s in females aged 18-25 years, and approximately 8.5 m/s in males and 8.1 m/s in females after the age of 64 years (Diaz et al., 2018; Reusz et al., 2010). In a 25-year longitudinal study by AlGhatrif and colleagues (2013) among 943 individuals between the ages of 21-94 years, these researchers found steeper longitudinal increases in cfPWV in males compared to females over time as participants aged, resulting in substantially higher cfPWV in males after the fifth decade. On the other hand, a large cross-sectional study consisting of a population of 11,092 European adults found statistically significant differences in cfPWV by sex, but the difference (0.1 m/s) was clinically negligible (The Reference Values for Arterial Stiffness Collaboration, 2010). In contrast, two longitudinal studies, one by Benetos and colleagues

(2002) (6-year follow-up), the other by Wildman and colleagues (2005) (2-year follow-up), did not find any sex difference in cfPWV. Furthermore, a study among 2,225 individuals between the ages of 24-39 years found greater cIMT and lower CCA compliance among males compared to females (Juonala et al., 2005). However, the difference in both cIMT and arterial compliance by sex became non-significant after adjusting for other cardiovascular risk factors. Meanwhile, another study examined differences in CCA compliance and distensibility between males and females in children and adult populations and found significant gender differences in compliance in adults, where females had greater compliance than males (Marlatt, Kelly, Steinberger, & Dengel, 2013). However, no significant sex difference in compliance and distensibility were observed in children, therefore suggesting that differences in arterial stiffness between males and females may possibly emerge later in adulthood. Overall, only a handful of studies have investigated changes in arterial stiffness early on in life between males and females and findings from these studies are equivocal (Ahimastos et al., 2003; Hidvégi et al., 2012; Thurn et al., 2015). Since the literature in this area is still conflicting, further research is required to clarify sex-related differences as they pertain to the progression of arterial stiffness.

2.5.1.2 Growth and Maturation

Studies have also examined the effects of growth on arterial stiffness. The results of some studies have found an increase in cIMT from childhood to early adulthood (Hansen et al., 1995; Jourdan et al., 2005), which may be partly attributed to natural changes in height and body mass from childhood to early adulthood (Hardy et al., 2015). There is also evidence suggesting that changes in arterial stiffness are due to maturation effects, rather

than age alone. A study by Hidvégi and colleagues (2012) examined changes in aortic PWV among children between the ages of 3-18 years and found that aortic PWV remained constant until early childhood, after which increases in aortic PWV was observed at the age of 10 years in girls and 12 years in boys, suggesting that changes may be due to maturation effects and not age. It is possible that sex hormones may be responsible for the progression of arterial stiffness from childhood to early adulthood. A study found that females consistently had lower aortic PWV compared to males from childhood into adulthood (Thurn et al., 2015). Whereas, another study found that females had a higher central (carotid-femoral) and peripheral (femoral-dorsal pedis) PWV compared to males' pre-puberty (Ahimastos et al., 2003). However, this was reversed post-puberty as both central and peripheral PWV increased in males, whereas both types of PWV decreased in females (Ahimastos et al., 2003). An explanation of this finding may be that reduced arterial stiffness post-puberty in females is due to increased levels of estrogen, since it is known to be associated with inhibition of smooth muscle cell proliferation (Vargas, Wroblewska, Rego, Hatch, & Ramwell, 1993), and modulation of extracellular matrix composition (Cox & Fischer, 1978; Fischer & Swain, 1977). On the other hand, elevation in androgen levels (i.e., testosterone) may explain increased arterial stiffness during post-puberty in males. Studies have shown that androgens promote smooth muscle cell proliferation (Fujimoto et al., 1994), and monocyte adhesion to endothelial cells (McCrohon, Jessup, Handelsman, & Celermajer, 1999) contributing to arterial stiffness.

2.5.2 Modifiable Risk Factors

2.5.2.1 Hypertension

In addition to non-modifiable risk factors, several modifiable factors are associated with arterial stiffness. Various studies have examined the link between hypertension and arterial stiffness. Results show that elevated BP and hypertension are associated with increased cIMT (Di Bello et al., 2009; Ferreira et al., 2016; Puato et al., 2008). It is possible that at a normal arterial BP, wall stress is supported by distensible elastin fibres of the arteries but at a higher pressure, less distensible collagen fibres are recruited (Wagenseil & Mecham, 2009). As a result, the concentration of collagen increases in the arterial wall replacing vascular smooth muscle cells, resulting in stiffer arteries. In addition, this passive change in the structure of the arteries also increases PWV since the timing of the pulse wave is dependent on the length and elastic properties of the arteries. A 26.5-year longitudinal study by Li and colleagues (2004), and a 21-year longitudinal study by Juonala and colleagues (2005) examined the effects of hypertension on brachial-ankle PWV over time from childhood to adulthood. Results showed that increased SBP during childhood and adolescence was an independent predictor of increased brachial-ankle PWV during adulthood. Research has also shown that hypertensive children are more likely to have reduced arterial compliance and distensibility (Litwin et al., 2004), and carotid-to-toe PWV (Philips et al., 2014). A constant elevation in BP may accelerate the progression of atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, which may in turn promote arterial stiffness (Chobanian, 1990; Safar & Frohlich, 1995; Arnett, Evans, & Riley, 1994). There is also evidence that the relationship between BP and arterial stiffness is bi-directional. Research suggests that increased BP not only

leads to arterial stiffness but that arterial stiffness may also lead to increased pressure pulsatility, which in turn may increase BP (Mitchell, 2014). However, the temporal evidence between hypertension and arterial stiffness is still unclear.

2.5.2.2 Obesity

Research has also shown that increased body mass is associated with arterial stiffness. A study by Wildman and colleagues (2003) examined the effects of obesity on arterial stiffness in younger and older adults and found body mass to be an independent predictor of aortic PWV. In other words, overweight and obese individuals have a greater risk of arterial stiffness. Studies have also examined the effects of waist circumference, BMI, and percent body fat on arterial stiffness and have shown that increased BMI, waist circumference, and percent body fat are associated with increased risk of arterial stiffness in adults (Yamada et al., 2008; Zebekakis et al., 2005), and in children population (Celik et al., 2011; Pandit et al., 2014). In addition, a study examining changes in arterial compliance and distensibility in healthy children found that greater body mass is associated with lower arterial compliance (Tounian et al., 2001) and distensibility (Banach et al., 2010), and similar findings were identified between body mass and compliance or distensibility in adults (Acree, Montgomery, & Gardner, 2007; Orr et al., 2008). It is possible that differences in leptin levels may explain changes in arterial structure among overweight and obese individuals since serum leptin levels are found to be significantly higher in obese individuals and are known to be associated with reduced arterial distensibility (Singhal et al., 2002). Further, increased serum C-reactive protein levels may also explain stiffening of arteries among overweight and obese individuals. C-reactive protein levels were reported to be higher among obese individuals (Visser et al., 1999), and

positively correlate with carotid-femoral and carotid-radial PWV (Yasmin et al., 2004; Yucel et al., 2015), indicating that arterial stiffness in overweight and obese individuals may be manifested by increased C-reactive protein levels. However, some studies have not been able to confirm the association between body mass and PWV (Faintuch et al., 2008; Ounis-Skali, Bentley-Lewis, Mitchell, Solomon, & Seely, 2007; Rodrigues et al., 2012). The reason for these conflicting findings may be due to an inaccurate calculation of the traveled distance of the pulse wave, which is measured over the body surface using a tape measure. This traveled distance measured over the body surface may be overestimated as a result of excessive abdominal fat. This explanation is supported by a study done by Canepa and colleagues (2014) who examined the association between central obesity and cfPWV among adult participants. Canepa and colleagues investigated different measures of adiposity to determine whether central obesity influenced cfPWV values. The results showed a positive correlation between cfPWV and waist circumference, total body fat, subcutaneous fat, and visceral fat when total distance over the body surface was used to calculate cfPWV. However, only visceral fat was found to be correlated with increased cfPWV when total distance was measured using radiological images, suggesting that PWV is greatly overestimated in overweight or obese individuals when total distance is measured over the body surface using a measuring tape. Therefore, it is recommended that a measure of visceral fat should be used and not overall adipose tissue when predicting cfPWV.

2.5.2.3 Physical Activity and Cardiovascular Fitness

Studies have examined the relationship between physical activity and arterial stiffness. Results show that regular physical activity has various beneficial effects on arterial health. For example, physical activity has beneficial effects on endothelial function

(Di Francescomarino, Sciartilli, Di Valerio, Di Baldassarre, & Gallina, 2009), IMT (Pahkala et al., 2013), and PWV (Boreham et al., 2004). In addition, a study by Pandit and colleagues (2014) examined the relationship between adiposity, physical activity and arterial stiffness and found that high adiposity and low physical activity were associated with increased cfPWV, elasticity modulus, and decreased CCA compliance (Pandit et al., 2014). As noted previously, the primary determinant of arterial stiffness is age, therefore, studies have also examined whether physical activity can blunt age-related increases in arterial stiffness. Results showed that increased participation in physical activity attenuates arterial stiffness associated with aging (DeSouza et al., 2000; Tanaka et al., 1998). Further, another study found high levels of cardiorespiratory fitness (i.e., VO_{2max}) to be associated with reduced brachial-ankle PWV (Zhu et al., 2014). Additionally, work by Otsuki and colleagues (2007) examined the effects of regular endurance and strength training on arterial stiffness and found that men who engaged in regular endurance training had a significantly lower aortic PWV compared to strength-trained and sedentary men. In the same study, endurance-trained men also demonstrated a greater cardiorespiratory fitness, reduced SBP and endothelin-1 levels compared to strength-trained and sedentary men. These results also indicate that not only is it important to participate in physical activity but the type (endurance vs. strength) of activity is also a key factor in maintaining or improving arterial elasticity. Moreover, the beneficial effects of aerobic fitness on arterial stiffness have also been examined in children. Several studies have found aerobic fitness to be a strong predictor of arterial stiffness, suggesting that aerobic exercise may prevent hardening of the arteries in children (Boreham et al., 2004; Meyer et al., 2006; Reed et al.,

2005; Sakuragi et al., 2009). Overall, these results indicate that physical activity, particularly cardiorespiratory fitness is inversely associated with arterial stiffness.

2.6 Consequences of Arterial Stiffness

There are several detrimental physiological consequences of atrial stiffness including increased BP, ventricular hypertrophy, atherosclerosis, myocardial infarction and stroke, and therefore arterial stiffness is considered to be a marker of cardiac morbidity and mortality.

2.6.1 Adverse Hemodynamic Consequences

Stiffening of the aorta leads to pathophysiological changes in circulation. A stiffened aorta has a reduced capacity to accommodate the volume of blood ejected by the left ventricle. This places greater pressure on the myocardium during systole resulting in increased SBP (London, Marchais, Guerin, Metivier, & Pannier, 1993). The increased workload will eventually lead to left ventricular hypertrophy (London et al., 1993). The reduced capacity of the aorta to stretch and accommodate blood volume is also linked to lower diastolic pressure. As a result, increased systolic and decreased diastolic pressure causes widened pulse pressure. This is of concern as vasculature of the brain and kidneys may experience greater pressure fluctuations associated with increased risk of stroke and renal failure (O'Rourke & Safar, 2005). Moreover, a low diastolic pressure may reduce coronary artery perfusion, resulting in the development of subendocardial ischemia (Ohtsuka, Kakihana, Watanabe, & Sugishita, 1994).

In addition, arterial stiffness causes changes in pulsatile flow and leads to an increase in shear stress (Zhao et al., 2002). This is due to decreased flow dampening during systole in stiffer arteries as a result of decreased elasticity. This decrease in elasticity

eventually results in irregular and increased pulsatile flow causing increased shear stress. Shear stress is a function of blood flow pattern where different layers of blood move at different velocities. The blood travelling in the middle of the artery tends to move faster compared to the side layers, generating a shearing action (friction) between them (Zhao et al., 2002). Shear stress (t) is directly related to blood flow (Q) and viscosity (μ) and inversely related to vessel radius (r), according to the Hagen-Poiseuille's formula (Cheng & Wagenseil, 2012):

$$t = \frac{4Q\mu}{\pi r^3}$$

Therefore, increased shear stress may be a result of factors such as increased blood viscosity and blood flow, and decreased arterial lumen diameter. An increase in shear stress affects the production of nitric oxide by the endothelium (Glagov et al., 1988). However, an abnormal increase in shear stress causes changes in vessel wall structure and may promote atherosclerotic plaque development over time (Glagov et al., 1988).

2.6.2 Left Ventricular Hypertrophy

Several studies have found a significant relationship between arterial stiffness and left ventricular mass, especially among hypertensives (Kumaran et al., 2002; Urbina et al., 2011). Research suggests that arterial stiffness increases SBP, which in turn increases left ventricular afterload. Increased afterload may cause structural changes of the left ventricle, ultimately leading to left ventricular hypertrophy (Kahan & Bergfeldt, 2005). Left ventricular hypertrophy is considered to be an independent risk factor of morbidity and mortality as it is associated with increased risk of congestive heart failure, atrial fibrillation, ventricular tachycardia, and stroke (Katholi & Couri, 2011).

2.6.3 Atherosclerosis and Myocardial Infarction

Studies have also found a bi-directional association between arterial stiffness and atherosclerosis (Herrington et al., 2004; van Popele et al., 2001; Wada et al., 1994). Structural changes and vessel wall damage due to arterial stiffness promotes atherosclerosis and advanced atherosclerosis in turn may worsen arterial stiffness (Arnett et al., 1994). A study by Farrar and colleagues (1991) found an increase in cfPWV in cynomolgus monkeys who were fed an atherogenic diet, while a decrease in cfPWV was found among low atherogenic diet monkeys. It is possible that greater levels of cholesterol may lead to the disruption of the internal elastic lamina, and increased production of collagen and non-fibrous connective tissues, thereby resulting in stiffer arteries. As well, a study by Demer (1991) found that an increase in arterial wall calcification may result in decreases in arterial distensibility. This may be because atherosclerotic vessels lose their shock absorbing capacity, and in turn, contribute to further stiffening of the affected vessel.

Studies have also found a relationship between arterial stiffness and myocardial infarction. Stiffening of the arteries leads to increased SBP and decreased DBP, thus resulting in a higher pulse pressure. Higher pulse pressure leads to increased workload and reduced coronary perfusion (Dart, 2017). These effects may lead to a myocardial infarction.

2.6.4 Stroke

Various studies have found a significant association between arterial stiffness and fatal stroke. For example, a cohort study with an 8-year follow-up period found that a 4 m/s increase in cfPWV was associated with a 72% greater risk of fatal stroke among middle-aged adults with essential hypertension (Laurent et al., 2003). Arterial stiffness also significantly predicts stroke among the elderly population (Mattace-Raso et al., 2006;

Sutton-Tyrrell, 2005). This relationship remained significant even after adjusting for other cardiovascular risk factors (Sutton-Tyrrell et al., 2005). One explanation for the relationship between arterial stiffness and stroke is that increased pulse pressure due to arterial stiffness leads to remodeling of the arterial walls, increases wall thickness, and promotes atherosclerotic plaque development (Witteman et al., 1994). The plaque may eventually break off and block one of arteries supplying blood to the brain, thus resulting in a stroke. Another pathway may be that stiffened vessel walls may reduce the capacity of the artery to regulate pulsatile flow, which means that unsteady turbulent flow can enter the cerebral vasculature and damage the arteries by causing structural changes such as breaking down elastic fibres and promoting fibrosis and calcification (Masawa et al., 1994). Finally, as discussed above, arterial stiffness is associated with other vascular diseases such as atherosclerosis and coronary artery disease, which are considered to be risk factors for stroke (Banerjee & Chimowitz, 2017; Conforto et al., 2013).

Considering arterial stiffness leads to a number of negative cardiovascular outcomes, it is important to identify factors that affect arterial stiffness so that appropriate measures can be taken to prevent arterial stiffening and lower the risk of cardiovascular diseases. As discussed above, age, hypertension, body mass/fat, and physical inactivity have been associated with arterial stiffness and heart disease. While some of these risk factors are non-modifiable, they may not be identified until later in life when significant structural and functional changes to the cardiovascular system have already taken place, thus making it difficult to establish temporal associations and implement preventative strategies. It is important to identify risk factors that are present in the early stages of life so that the cascade of events leading to cardiovascular disease can be identified and

prevented. Most studies on cardiovascular disease are focused on biological risk factors and lifestyle, however, recent evidence suggests that psychosocial factors such as ACEs may also play an important role in the development and progression of arterial stiffness.

2.7 ACEs and Arterial Stiffness

Only within the last decade have researchers started to examine the association between ACEs and stiffening of the large arteries. A cross-sectional study by Su and colleagues (2014) examined ACEs among 13 to 29-year-old males and females and found that those who had experienced 2 or more ACEs had increased peripheral arterial stiffness compared to those who did not experience any ACEs. A longitudinal study conducted by Loucks and colleagues (2014) reported that individuals who experienced poor family environment had increased cIMT. Work by Klassen and colleagues (2016) examined the relationship between ACEs and arterial stiffness among children aged 10-14 years and found that males with exposure to 4 or more ACEs was associated with greater systemic arterial stiffness when compared to their peers. Interestingly, they did not find the same effect for females. Finally, a large cohort study involving 2,265 young adults aged 24-39 years assessed cIMT in 2001 and again in 2007. Psychosocial risk factors including childhood adversity was assessed at baseline in 1980 when they were 3-18 years of age. This study found that those who experienced a greater number of stressful life events had a higher cIMT in 2001 and those with poorer health behaviours (e.g., physically inactive, smoker, and BMI$\geq$30) had increased cIMT in 2007 after adjusting for age, sex, and cardiovascular risk factors at baseline (Hakulinen et al., 2016). While these studies show an association between childhood stressors such as ACEs and arterial stiffness, two of these were cross-sectional in design (Klassen et al., 2016; Su et al., 2014), and three were

conducted among adults (Hakulinen et al., 2016; Loucks et al., 2014; Su et al., 2014). Cross-sectional studies are limited in that they do not provide insight into the temporal sequence between exposure and outcome. Moreover, the studies by Su and colleagues (2014) and Loucks and colleagues (2014) relied on self-reported recall of ACEs in adulthood, while studies by Klassen and colleagues (2016) and Hakulinen and colleagues (2016) identified ACEs through a parent-reported questionnaire.

2.7.1 Pathways for the Relationship between ACEs and Arterial Stiffness

To date, two ways in which ACEs can potentially lead to increased stiffening of the arteries in adulthood have been proposed in the literature. One pathway hypothesizes that exposure to ACEs increases the likelihood of engaging in negative health behaviours and risk factors such as smoking, overweight/obesity, physical inactivity, and high BP (Anda et al., 2002; Chapman et al., 2004; Dong et al., 2004; Felitti et al., 1998; MacMillan et al., 2001; Su et al., 2015), which in turn influences arterial wall structure and function (Boreham et al., 2004; Ferreira et al., 2016; Wildman et al., 2003). The other pathway proposes that ACEs affect the physiological functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in helping individuals adjust to internal and external stressors (Rhee & Pearce, 2011). Research shows that in the presence of chronic or repeated exposure to stress, the HPA axis remains constantly activated and there is an overexposure to stress hormones (Guilliams & Edwards, 2010), which in turn may promote arterial stiffness (Boutouyrie et al., 1994; Grassi et al., 1995). In addition to duration, intensity of stress also plays an important role in the activation of the HPA axis. A meta-analysis found that cortisol response to acute but intense traumas elicited a more pronounced alteration in HPA function (Miller et al., 2007).

2.8 Study Rationale

As discussed, studies have found exposure to ACEs to be associated with various negative health outcomes including poor psychological health, chronic diseases including those linked to the cardiovascular system, and premature mortality. Studies have also consistently shown arterial stiffness to be associated with various cardiovascular outcomes. Therefore, it is important to investigate if there is a causal association between ACEs and arterial stiffness as one potential pathway to identify those at greater risk for subsequent cardiovascular issues. Although limited, evidence shows that changes in arterial stiffness in response to ACEs may occur at an earlier stage in life, likely sometime in childhood and adolescence, but there are several gaps in the literature that need to be addressed. First, only four studies have examined the association between ACEs and arterial stiffness and two of these were cross-sectional in design, making it difficult to identify whether ACEs can lead to changes in arterial stiffness (a known marker for heart disease) and when these changes begin to manifest. Therefore, the current study addressed this limitation by examining the relationship between ACEs and arterial stiffness using a longitudinal study design (Figure 2.2). A longitudinal design would determine whether changes in arterial stiffness in response to ACEs begin to manifest at an earlier age than previously thought.

Second, it is unclear whether the relationship between ACEs and arterial stiffness differs between males and females. Only a handful of studies have investigated the moderating effect of sex on the relationship between early life adversity and arterial stiffness and findings from these studies are equivocal. Therefore, one of the objectives of this study was to examine whether the relationship between ACEs and arterial stiffness varies between males and females (Figure 2.2).

Finally, although studies have independently examined the association between ACEs and HR, SBP, body mass, and physical activity, and the association between arterial stiffness and HR, SBP, body mass, and physical activity, no previous study has examined the mediating role of these factors on the relationship between ACEs and arterial stiffness. Therefore, the final objective of this study was to examine if the relationship between ACEs and arterial stiffness is explained by these aforementioned factors that generally dominate the literature (Figure 2.2).

2.9 Study Purpose and Research Questions

The purpose of this research was to examine the relationship between ACEs and arterial stiffness among adults in a population-based longitudinal study. Specifically, the following research questions were examined:

1. Are there differences in the development of arterial stiffness from childhood to early adulthood among those exposed to ACEs compared to those not exposed to ACEs?
2. Does HR, SBP, BMI, and/or physical activity levels mediate the association between ACEs and arterial stiffness over time?
3. Does the relationship between ACEs and arterial stiffness differ between males and females over time?

2.9.1 Hypotheses

1. Individuals who have experienced a greater number of ACEs, will experience a greater increase in arterial stiffness over time from childhood into adulthood.
2. The relationship between ACEs and arterial stiffness will not differ between males and females over time.

3. Changes in HR, SBP, BMI, and/or physical activity levels will mediate the association between ACEs and arterial stiffness over time.

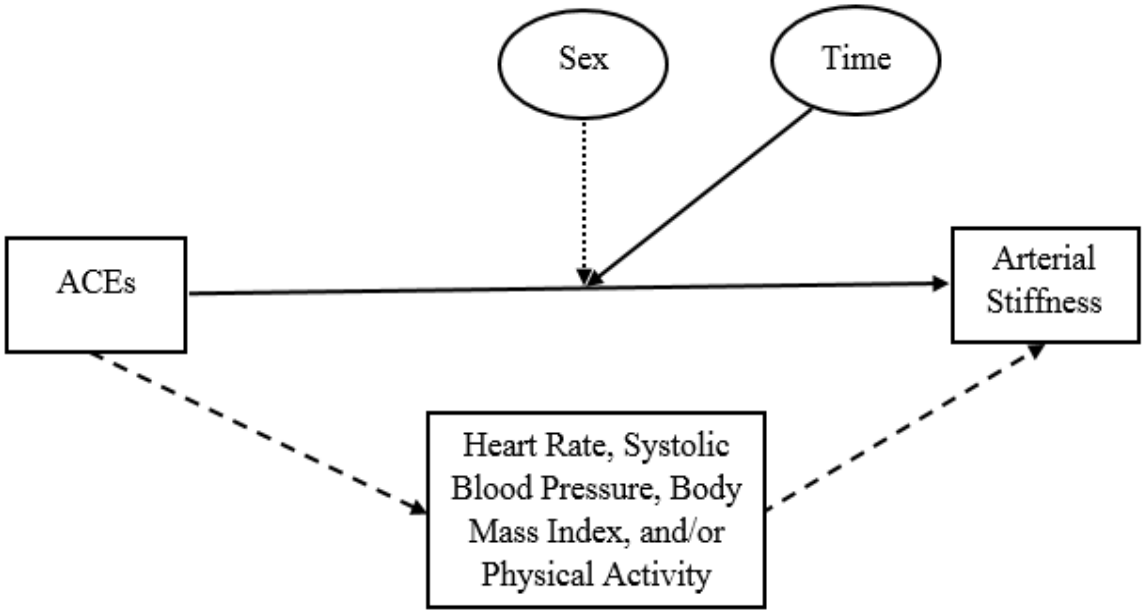

Figure 2.2: *A conceptual model of the study hypothesis*

Note: The solid dark lines represent the direct effect. Dashed lines represent the mediating pathways connecting variables together (indirect effects). Dotted lines represent the moderating or buffering effect of sex on the relationship between ACEs and arterial stiffness.

CHAPTER 3: METHODOLOGY

3.1 Study Design and Participants

The Niagara Longitudinal Heart Study (NLHS) is currently a pilot study that involves 76 participants (18 years or older) from the Niagara Region who previously participated in the Health Behavioural and Environmental Assessment Team [HBEAT] study. The HBEAT Study was a cross-sectional study which examined the relation between social determinants of health and childhood BP. It included a large community based sample of children aged 10-14 years (grades 5-8) from the Catholic School Board. The data collection for this study occurred in two phases. In phase 1, a total of 1,913 children completed the school-based testing procedures consisting of anthropometric, physical activity, and BP measurements. Afterwards, a subsample of 325 children underwent further laboratory testing in phase 2. At this time, children's structural and functional measures of cardiovascular health were obtained. Data collection for the HBEAT portion will be referred to as Time 1.

As for the NLHS pilot study, it will be referred to as Time 2. For this pilot study, a sub-sample of participants were randomly contacted using information available from the HBEAT study. All participants were 18 years of age or older at the time of contact. Upon contact, they are informed about the procedures including the amount of time for data collection, which was approximately 2 hours for lab testing and 1.5-2 hours to complete the self-reported questionnaire. They were also informed that they would be compensated ($100) for their complete participation. Upon agreeing to participate, the participants were emailed or mailed the information package explaining the study, directions to Brock University, where to obtain free parking, the scheduled testing time, as well as information

as to how to contact the lab in case they may need to cancel or reschedule. Also, they were asked to contact the lab if they fell ill 2 days following testing. Each participant was instructed to not consume food within 4 hours prior to testing, refrain from performing vigorous physical activity and avoid consuming caffeinated products for 12 hours prior to testing. These restrictions were followed as it has been shown that eating, exercising, and drinking beverages containing caffeine can influence BP readings (Ahuja, Robertson, & Ball, 2009; Karatzis et al., 2005; Pescatello & Kulikowich, 2001).

The study took place at the Human Hemodynamics Laboratory at Brock University. Upon arrival, participants were explained the study procedures and informed consent was obtained. Following the completion of the consent process, participants were asked to void their bladder as it has been shown that bladder distension can lead to changes in BP (Fagius & Karhuvaara, 1989). Six automated BP measures were then obtained while the participant remained seated. BP was recorded using the same BP monitor and protocol as Time 1. Afterwards, anthropometric measurements including body mass and height were taken.

Next, participants were asked to lie in a supine position on a padded table for cardiac structural and functional assessment. Participants were connected with a standard single-lead electrocardiogram (ECG) for beat-by-beat collection of R-R interval (RRI), a finger cuff on the left third digit for the assessment of beat-for-beat changes in BP, and a pulse oximeter on the second toe of the left foot. In addition, three resting BP measures were obtained manually using a sphygmomanometer and stethoscope on the right arm, while the participant remained in supine position.

Following BP measurement, each participant was asked to rest for 10 minutes in the supine position while beat-by-beat BP and RRI were recorded for autonomic

evaluation. Next, imaging of the right CCA was performed. Applanation tonometry was used to measure pulse pressure at the left CCA and femoral artery for a minimum of 15 beats. It is important to note that all measures of cardiac structural and functional indices were examined using the same equipment that was used in the HBEAT study (baseline measures).

Following cardiovascular assessment participants were given a short break along with a light snack (e.g., granola bar) and a beverage (e.g., juice box) before they began the self-report questionnaire that included questions on childhood maltreatment, trauma, and household dysfunctions, as well as physical activity levels. The questionnaire is a self-reported instrument to ensure confidentiality and minimize discomfort and social response bias due to the sensitive nature of some questions. Also, the questionnaire was handed out in an envelope with only the unique study ID to further facilitate confidentiality. Participants were told that a third party who has no access to personal identifiers would enter all the data. A research coordinator was present for the entire length of the questionnaire to assist with any questions that the participants might have but was not seated near the participant to avoid any unease. Upon completion, participants returned the questionnaire in the envelope, which was then sealed. At the end of the visit, participants were provided with medical contact information (i.e. trauma specialist) in case they felt any emotional stress or reported any concern or discomfort.

All data were collected by trained research assistants using the same testing procedures as Time 1. Lastly, an honorarium of $100 was given to each participant for participating in the study. The consent and data collection procedures visit took

approximately 3.5-4 hours to complete. Ethics approval for this study was obtained from the Research Ethics Board at Brock University (#16-078).

3.2 Study Measures

Although the HBEAT and NLHS studies collected a number of variables, only a subset of variables including measures of arterial stiffness, ACEs, BP, HR, physical activity, and BMI will be used in this study.

3.2.1 Anthropometrics

Height was measured in centimeters using a stadiometer (STAT 7X, Ellard Instrumentation Ltd., Monroe, WA, USA). Participants were asked to stand upright with feet together while height measurements were obtained. Body mass was measured in kilograms using a digital scale (BWB-800S, Tanita Corp., Tokyo, Japan). Measurements for height and body mass were obtained while wearing light clothing (e.g. tight fitted active wear) and without footwear. Body mass index (BMI;kg/m^2) was calculated by dividing body mass by height in metres squared.

3.2.2 Blood Pressure and Heart Rate

After 15 min of resting seated upright, BP and HR were obtained using an automated oscillometric device (BPM-300, VSM MedTech Devices Inc., Coquitlam, B.C., Canada). A total of 6 independent sequential measures for BP and HR were taken at 1-minute intervals while the participant remained quietly seated with both feet flat on the floor using an appropriate cuff size based on their arm circumference. The last 3 readings were averaged and used in the analysis.

Resting supine RRI was collected using a standard single-lead ECG. An appropriate size photoplethysmograph finger cuff was applied at the left middle finger to measure beat-

by-beat BP using a Nexfin ® monitoring system at heart level (BMEYE Monitor Series, BMEYE, Amsterdam, The Netherlands). Resting supine BP was also obtained manually using a stethoscope and sphygmomanometer. The appropriate cuff size was determined based on arm circumference (Veiga, et al., 2009). The stethoscope was placed at the right brachial artery for auscultation, 2 centimetres above the cubital fossa. An average of the 3 BP measures served as a reference point for the beat-by-beat BP data to ensure accuracy, since BP measured at the finger differs slightly from that taken at the arm (Imholz, Settels, van der Meiracker, Wesseling, & Wieling, 1990). Both beat-by-beat BP and RRI were sampled at 1000Hz using an online data analysis and acquisition system (PowerLab ® and LabChart ®; Version 7, ADInstruments Inc., Colorado Springs, CO, USA), to provide a resolution of 1ms.

3.2.3 Intima Media Thickness, Distensibility, and Compliance

Non-invasive ultrasonography (Vivid q, General Electric Medical Systems, The Netherlands) was used to measure the diameter, distensibility, compliance, and IMT of the right CCA. CCA images were obtained approximately 1-2 cm proximal to the bifurcation, using a 12 MHz linear array vascular transducer. A minimum of three images of 5 consecutive heartbeats were captured in longitudinal two-dimensional B-mode for all participants. The captured images were then stored in Digital Imaging and Communications in Medicine (DICOM) format (Sante DICOM Editor, V. 3.1.24; Santesoft, Athens, Greece). Thereafter, these stored images were further analyzed using a semi-automated edge tracking system (Maui Imaging, Inc). Applanation tonometry (Model SPT-301, Millar Instruments Inc., Houston, TX, USA) was used to measure pulse pressure for a minimum of 15 heartbeats at the left CCA and left femoral artery.

Carotid IMT and minimal and maximal arterial diameters were measured using five high quality heartbeats. To allow maximum access to the CCA, participants were in a supine position with neck extended and the head slightly contralateral to the side of measurement. The cIMT was measured at end-diastole on the far wall to ensure lowest possible wall tension. cIMT of the far wall was determined as the distance between the leading edge of lumen-intima interface and the leading ledge of intima-media interface.

The CCA lumen diameter was measured as the distance between lumen-intima interface of the near and of the far wall, and was used to calculate distensibility and compliance. Distensibility is the relative change in arterial diameter for a given change in pressure during the cardiac cycle. Distensibility ($mmHg^{-1}$) was calculated using the following equation (Tziomalos et al., 2007):

$$Distensibility = \frac{((sCSA - dCSA)/\ dCSA))}{(P_s - P_d)}$$

Where sCSA and dCSA indicate systolic and diastolic arterial cross-sectional area (cm^2), respectively, and Ps and Pd indicate systolic and diastolic finger pressures, respectively. Compliance is the absolute change in the cross-sectional area of an artery for a given pressure change. Arterial compliance was calculated using the following equation (Tziomalos et al., 2007):

$$Compliance = \frac{(sCSA - dCSA)}{(P_s - P_d)}$$

Although left CCA PP was obtained using tonometry, it was not used to calculate compliance and distensibility because it did not consistently provide a clear maximum amplitude and configuration to accurately estimate intra-arterial pressure changes (Chen et al., 1996). Although the finger BP is known to be higher than the central arterial BP, it still provides an accurate estimate of the beat-by-beat PP (Nichols and O'Rourke, 2005).

3.2.4 Pulse Wave Velocity

Pulse wave velocity was measured between the carotid-femoral and ECG-to-toe to estimate arterial stiffness. ECG-to-toe PWV was collected using the same method at both time points, but cfPWV was only assessed during Time 2. A minimum of three 15-pulse waveforms were recorded at each site. Pulse waveforms were recorded from the left CCA and femoral using applanation tonometry, while toe waveforms were obtained using pulse oximetry (Nellcor N-200 Tyco Healthcare Group LP, Pleasanton, CA, USA) from the second left toe. The fifteen consecutive pulse waveforms were band-pass filtered (15-30 Hz) in order to identify the foot of each wave. Since the CCA and femoral pulse pressures were not recorded simultaneously, the R-wave of the ECG was used as the initiation point to determine the time between the two pulse waves at 2 separate arterial sites (proximal and distal). The pulse transit time for the CCA, femoral artery and toe were calculated from subtracting the immediate minimal point prior to the upstroke of the pressure wave from the time of the R-wave on the ECG. Distance was measured (cm) using an inelastic tape from the sternal notch to the exact site where pulse pressure was measured at the left CCA, femoral artery, and toe. For cfPWV, the following equation was used:

$$PWV = \Delta D / \Delta T$$

Where the numerator is the difference in distance (ΔD) between proximal and distal arteries, divided by difference in time (ΔT) between the two pulse waves. As for ECG-to-toe PWV, distance from the sternal notch and time from the ECG-to-toe were used.

3.2.5 Physical Activity

Physical activity information was collected using two different questionnaires, where The Godin-Shephard Leisure – Time Exercise Questionnaire (4-item) was used

during Time 1 (Godin & Shephard, 1997), and The International Physical Activity Questionnaire – Short Form (9-item) was used during Time 2 (Craig et al., 2003). The total activity score for both questionnaires were converted into metabolic equivalent (MET) scores to get an estimate of energy expenditure. For the analysis, the MET scores were transformed into standardized scores (z-scores) in order to standardize the measurement scales between the two questionnaires. The validity and reliability of both questionnaires has been established previously (Craig et al., 2003; Sallis, Buono, Roby, Micale, & Nelson, 1993).

3.2.6 Adverse Childhood Experiences (ACEs)

The Child Trust Event Survey (CTES 2.0), a 26-item questionnaire appropriate for children and young adults based on the Kaiser ACEs questionnaire was used to identify ACEs among participants (Bernstein, Ahluvalia, Pogge, Handelsman, 1997; Pretty et al., 2013). Although the ACE data were collected at both Time 1 and 2, only data from Time 2 were used for analysis. This is because the ACE exposure at Time 2 was self-reported (versus parent-reported in Time 1) and included measures of extreme adverse experiences. Examples of items in the CTES 2.0 includes experiences of maltreatment such as physical, sexual, and emotional abuse, and experiences of household dysfunctions such as death of a family member or a parent, serious illness or injury in the family, serious argument between parents, a family member in jail or prison, divorce or separation of parents, a family member who abused alcohol or used street drugs, and separation from parents (Bernstein et al., 1994). This study also used a number of other ACEs, for example; been in a really bad accident, experienced a disaster such as a tornado, hurricane, fire, big earthquake, or flood, badly hurt or sick that a painful or scary medical treatment was

required, and been threatened or really picked on by a bully. CTES 2.0 was self-reported due to the sensitive nature of questions regarding ACEs, as well as to reduce any discomfort and social response bias. In addition, previous studies have reported a high response rate to self-reported questions concerning ACEs (Dube, Williamson, Thompson, Felitti, & Anda, 2004; Felitti et al., 1998), with kappas of 0.6 to 0.7 over one year (Dube et al., 2004).

The coding of ACEs for analyses has varied significantly across studies based on both quantity and type providing no clear approach. For example, several studies have previously dichotomized ACEs into those who experienced less than 4 ACEs and 4 or more ACEs (Felitti et al., 1998; Pretty et al., 2013), while one study dichotomized ACEs into less than 2 and 2 or more (Su et al., 2014). Another study examined childhood abuse separately from household dysfunction taking the approach that experience of abuse is fundamentally different than household dysfunction (Chartier, Walker, & Naimark, 2010). Yet another study dichotomized ACEs into acute versus chronic levels of exposure (Kliethermes, Schacht, & Drewry, 2014). Further, some have suggested that the cumulative effect of childhood psychosocial risk factors is a better indicator of total psychosocial risk burden than any single risk factor (Anda et al., 2006; Chartier, Walker, & Naimark, 2010) leading some studies to examine ACEs as a continuous, cumulative measure (i.e., a simple count of maltreatment, trauma, and household dysfunctions) (Chapman et al., 2004; Dong et al., 2004). Finally, one study constructed a 2x2 matrix comparing groups with high and low levels of abuse and household dysfunction to enable them to measure the qualitative difference between these two types of ACEs (MacDonald & Tough, 2014). In light of this variability across much of the previous work, the ACE variable was conceptualized in three ways for analysis: 1) ACE was treated as a continuous, cumulative variable, 2) ACEs were

dichotomized into participants who experienced less than 4 versus 4 or more ACEs, and finally 3) into a 2x2 matrix separating abuse and household dysfunction to compare those who experienced abuse and household dysfunction, those who experienced abuse but not household dysfunction, those who experienced household dysfunction but not abuse, and those who experienced neither abuse nor household dysfunction.

3.3 Statistical Analyses

Descriptive statistics including means and standard deviations (SD) are reported for continuous variables and frequency and proportions were reported for categorical variables. Mixed effects modeling was used to examine the effect of ACEs on changes in arterial stiffness (i.e., ECG-to-toe PWV, cIMT, compliance, and distensibility) over time (repeated measure) adjusted for change in age, sex, HR, SBP, BMI, and physical activity. A total of eight models were created. To determine if the change in arterial stiffness varied over time and by ACE (conceptualized in several ways described above), an ACE by time interaction term was tested (Model 1). A random intercept for participants and a random time for slope was included in the models for the measures of arterial stiffness. A time by ACEs interaction was also tested after adjusting to sex (Model 2). To identify if changes in arterial stiffness among the ACEs groups varied overtime between males and females, a 3-way interaction between time, arterial stiffness, and sex was tested (Model 3). Next, the effect of ACEs on arterial stiffness was examined after adjusting separately for SBP (Model 4), BMI (Model 5), physical activity (Model 6), HR (Model 7), and all variables adjusted for in the previous models (Model 8). Models 4 through 7 examined each potential mediating factor separately, while model 8 assessed the combined effects of all covariates. Finally, a multiple linear regression was used to cross-sectionally predict cfPWV (only

obtained at Time 2) from ACEs, while adjusting for sex, age, HR, SBP, BMI, and physical activity. A sex by ACEs interaction was tested to see if the relationship between ACEs and cfPWV differed between males and females. Statistical significance for a two-tailed test was set at $p \leq 0.05$ and all analysis were performed using SAS 9.4 (SAS Institute, Cary, NC).

CHAPTER 4: RESULTS

Descriptive characteristics of the participants at each assessment are reported in Table 4.1. A total of 76 young adults were recruited to participate in this study with slightly more than half of them being females (57.9%). The average age of participants at Time 1 was 12 (SD = 1) years and with an average follow up time of 9 years (SD = 0.18) the average age of participants was 21 (SD = 1) years at Time 2. There was an increase in systolic ($t = 4.44$, $p = <.0001$) and diastolic ($t = 3.28$, $p = 0.0013$) blood pressures, BMI ($t = 5.43$, $p = <.0001$), and a decrease in CCA compliance ($t = -7.22$, $p = <.0001$), distensibility ($t = -12.47$, $p = <.0001$), and HR ($t = - 4.66$, $p = <.0001$) over time. These changes are typical for most children as they age into young adulthood. Overall, a total of 71 respondents reported to have experienced at least 1 and up to a maximum of 15 ACEs (maltreatment, household dysfunction, and other) of which 34 (62% females) had experienced 4 or more ACEs. Considering the ACE categories, experiences of maltreatment (scored as 0 (No) and 1 (Yes)) including sexual, physical, and emotional abuse was reported to be 18%, 12%, and 25%, respectively. With regards to the prevalence of household dysfunctions, 20%, 7%, 36%, 15%, and 40% of the sample reported experiences of growing up in a household with someone with substance abuse, imprisoned, mentally ill, violent, and being separated from caregiver, respectively. All household dysfunction variables were scored as 0 (No) and 1 (Yes). Further, 20 participants experienced both maltreatment and household dysfunction, 9 experienced maltreatment but not household dysfunction, 31 experienced household dysfunction but not maltreatment, and 16 experienced neither maltreatment nor household dysfunction. Information regarding ACEs distribution can be found in Table 4.2.

Next, mixed-effects modelling was used to examine the longitudinal relationship between ACEs and measures of arterial stiffness. Due to technical issues and data quality (e.g. CCA image quality), participants included in the mixed-effects modelling for each arterial stiffness variable varied (refer to Tables 4.3-4.17). Since ACEs were conceptualized in 3 different ways, a set of 3 tables were created for each outcome variable (ECG-to-toe PWV, cIMT, compliance, and distensibility). For each outcome, the first table illustrates results of the analyses where ACEs was treated continuously. The second table for each outcome illustrates the results where ACEs was treated as <4 and ≥4, and the third table for each outcome illustrates the results of a 2x2 abuse by household dysfunction matrix. Tables 4.3-4.5 show the results obtained from the mixed-effects models predicting ECG-to-toe PWV over time. The two-way interaction between time and total ACE score (Table 4.3, Model 1, Figure 4.1) and between time and ACE <4 and ≥4 (Table 4.4, Model 1; Figure 4.2) were significant, suggesting that higher the ACE score, the greater the increase in ECG-to-toe PWV over time, and that individuals with 4 or more ACEs showed a more rapid increase in ECG-to-toe PWV over time compared to those less than 4 ACEs. Finally, the combined effect of experiencing both maltreatment and household dysfunction was tested (Table 4.5, Model 1, Figure 4.3). The results showed that in comparison to individuals who did not experience either of these ACEs, those who experienced both abuse and maltreatment showed a greater increase in ECG-to-toe PWV over time. Regardless of how ACEs were conceptualized, the findings did not differ by sex (Table 4.3-4.5, Model 3), and findings were independent of all covariates (Table 4.3-4.5, Model 4-7), suggesting an independent effect beyond lifestyle/behavioural measures. Finally, in addition to these results, SBP was the only significant covariate.

Tables 4.6-4.8 show the results from mixed effects analyses predicting cIMT over time. The results for the two-way interaction between time and total ACE score, and between time and ACE <4 and ≥4, when graphed look similar to those obtained when examining change in ECG-to-toe PWV. Those individuals who had a total ACE total one standard deviation above the mean experienced an accelerated increase in cIMT over time (Table 4.6, Model 1, Figure 4.4). Similarly, those who experienced 4 or more ACEs showed an accelerated increase in cIMT over time compared to those with less than 4 ACEs (Table 4.7, Model 1, Figure 4.5). As done with ECG-to-toe PWV, when the combined effect of maltreatment and household dysfunction was examined, the interaction graphs show that those who experienced both abuse and household dysfunction had a rapid increase in cIMT compared to the other groups. While cIMT remained unchanged over time for those who experienced dysfunction but not abuse, the graph shows a decline in cIMT over time for those who experienced abuse but not dysfunction, and those who experienced neither abuse nor household dysfunction (Table 4.8, Model 1, Figure 4.6). Once again, regardless of how ACEs were conceptualized, the findings did not differ by sex (Table 4.6-4.8, Model 3), and were independent of all covariates (Table 4.6-4.8, Model 4-7), suggesting an independent effect beyond lifestyle/behavioural measures.

Similar to the models tested for ECG-to-toe PWV and cIMT, models were also created and tested for examining change in compliance and distensibility over time (Tables 4.9-4.14). The two-way interaction term between ACEs and time was not significant when examining change in compliance and distensibility, irrespective of how the ACEs variable was conceptualized. These findings suggest that the exposure to ACEs on arterial compliance and distensibility did not differ over time. Further, these findings did not differ

by sex regardless of how ACEs were conceptualized, and the results remained non-significant after adjusting for all covariates with no substantial change in the magnitude of regression coefficient for the two-way interaction term between time and ACE. While HR was the only significant covariate for compliance, the results indicate that lifestyle/behavioural factors did not mediate the relationship between ACEs and all measures of arterial stiffness over time.

Finally, it should be noted that cfPWV is the gold standard for assessing arterial stiffness, however, this measure was only obtained at Time 2. Therefore, multiple linear regression was performed to cross-sectionally examine the relationship between cfPWV and ACEs (Tables 4.15-4.17). The unadjusted analyses revealed that the association between total ACEs score and cfPWV was not significant (Table 4.15, Model 1). It is important to note that the results, however, became significant after adjusting for HR, SBP, BMI, and physical activity, where one score increase in ACE was associated with greater cfPWV (Model 8) indicating a suppressor effect. Similar results were found when the combined effect of experiencing maltreatment and/or household dysfunction was tested. The unadjusted analysis showed that the association between individuals who experienced abuse and/or household dysfunction and cfPWV was not significant (4.17, Model 1). The results, however, became significant after adjusting for HR, SBP, BMI, and physical activity, where in comparison to individuals who did not experience either of these ACEs, those who experienced both abuse and household dysfunction were associated with greater cfPWV. However, the change in effect size was very small, suggesting that HR, SBP, BMI, and physical activity did not mediate the relationship between ACEs and cfPWV. In fact, there was a suppression effect for ACEs on cfPWV, that is, when the effect of the covariates

was partial out, ACEs showed a significant independent effect. SBP and physical activity were the only significant covariates. Meanwhile, the two-way interaction for cfPWV was not significant between ACE and sex, regardless of how the ACE variable was conceptualized.

Table 4.1: Demographic characteristics and cardiovascular measures at Time 1 and Time 2

	n	Time 1	Time 2	p-value
Sex, n (%)				
Male		32 (42.1)	32 (42.1)	
Female		44 (57.9)	44 (57.9)	
Age (yrs)	76	12 (1)	21 (1)	<.0001
ECG-to-toe PWV (m/sec)	46	4.0 (0.3)	4.1 (0.4)	0.1978
cIMT (mm)	72	0.4 (0.1)	0.4 (0.1)	0.5776
Compliance (mm^2/mmHg)	71	0.15 (0.05)	0.10 (0.04)	<.0001
Distensibility ($mmHg^{-1}x10^{-2}$)	71	0.8 (0.3)	0.4 (0.2)	<.0001
cfPWV (m/sec)	72		5.5 (0.7)	
Seated SBP (mmHg)	76	99 (11)	107 (10)	<.0001
Seated DBP (mmHg)	76	63.1 (10)	68.1 (8.9)	0.0002
Seated HR	76	85.1 (12)	76.4 (12)	<.0001
BMI (kg/m^2)	76	20.7 (4.9)	25.5 (5.9)	<.0001

Data reported as mean (SD) unless otherwise stated, PWV = pulse wave velocity, cIMT = carotid intima media thickness, cfPWV = carotid-femoral pulse wave velocity, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, BMI = body mass index.

Table 4.2: Distribution of ACEs (n = 76)

ACEs score, mean (SD)	3.8 (3.0)
ACEs score, n (%)	
0	5 (6.6)
1	11 (14.5)
2	14 (18.4)
3	12 (15.8)
4 or more	34 (44.7)
Abuse by Household Dysfunction Groups, n (%)	
Yes Abuse and Yes Household Dysfunction	20 (26.3)
No Abuse and Yes Household Dysfunction	31 (40.8)
Yes Abuse and No Household Dysfunction	9 (11.8)
No Abuse and No Household Dysfunction	16 (21.1)

ACEs = Adverse Childhood Experiences, n = number, SD = Standard Deviation

Table 4.3: Mixed-effects models predicting ECG-to-toe pulse wave velocity by cumulative ACEs score, time, sex, and all covariates (n = 46)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	4.0640	<.0001	3.9973	<.0001	4.0260	<.0001	3.1246	<.0001	3.9714	<.0001	4.0623	<.0001	4.1651	<.0001	3.1463	<.0001
Time (2)	-0.0567	0.4365	-0.0514	0.4786	-0.0667	0.4826	-0.1420	0.0656	-0.0726	0.3346	-0.0513	0.4810	-0.0732	0.3578	-0.1590	0.0632
ACEs	-0.0164	0.2322	-0.0146	0.2784	-0.0265	0.1134	-0.0291	0.0344	-0.0163	0.2341	-0.0159	0.2452	-0.0188	0.2227	-0.0318	0.0390
ACEs*time	0.0339	0.0237	0.0324	0.0300	0.0468	0.0122	0.0390	0.0095	0.0328	0.0286	0.0325	0.0306	0.0362	0.0306	0.0394	0.0185
Sex (Male)			0.1370	0.0412	0.0434	0.7464										
ACEs*sex					0.0392	0.1638										
Sex*time					0.0640	0.6518										
ACEs*sex*time					-0.0437	0.1387										
SBP							0.0098	0.0011							0.0105	0.0009
BMI									0.0044	0.4222					0.0008	0.8870
PA											0.0242	0.3793			0.0370	0.1731
HR													-0.0011	0.6523	-0.0011	0.6477

ACEs = adverse childhood experiences, SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

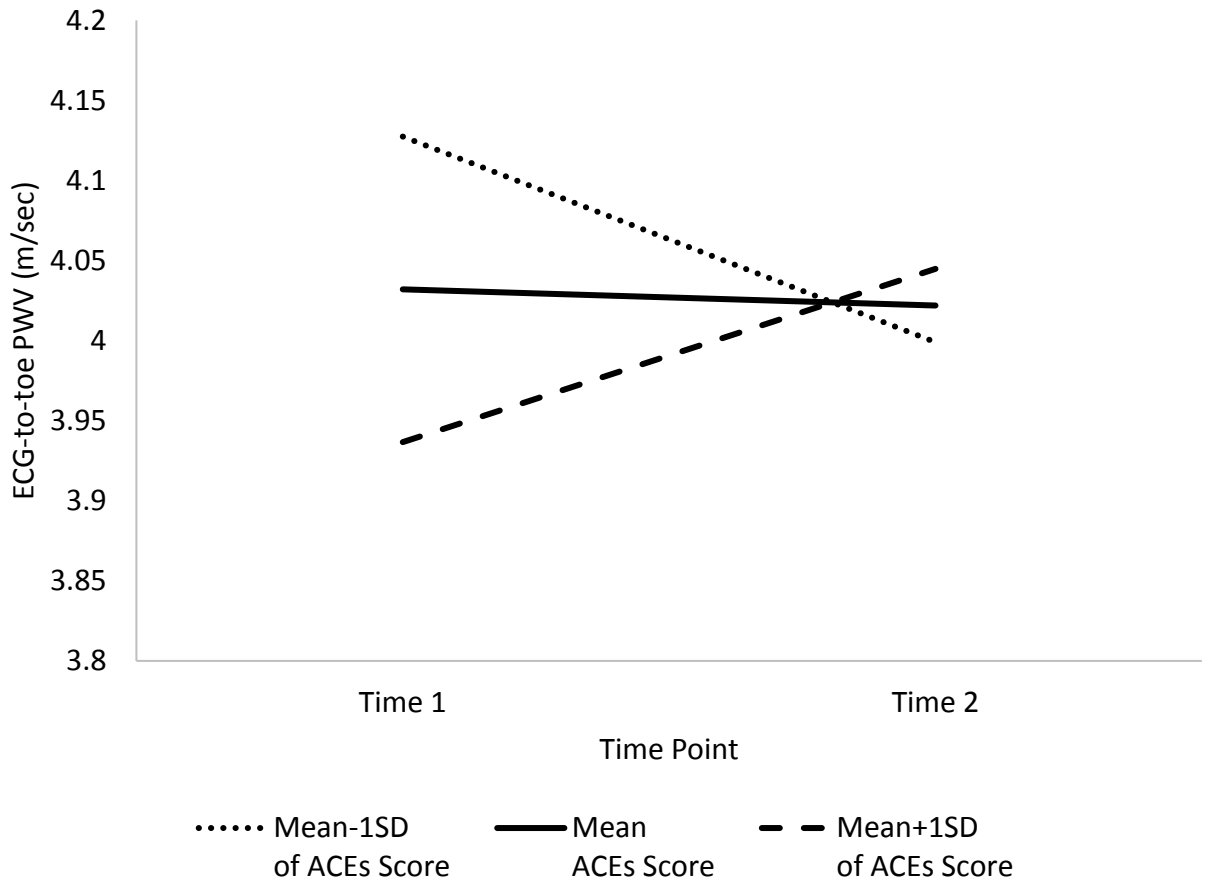

Figure 4.1 (Table 4.3, Model 8): Predicted ECG-to-toe PWV with increase in total ACEs score
PWV = Pulse Wave Velocity, ACEs = adverse childhood experiences, SD = Standard Deviation
Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.4: Mixed-effects models predicting ECG-to-toe pulse wave velocity by ACEs category (<4 and ≥4), time, sex, and all covariates (n = 46)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	4.0548	<.0001	3.9868	<.0001	3.9869	<.0001	3.0753	<.0001	3.9528	<.0001	4.0541	<.0001	4.1753	<.0001	3.1037	<.0001
Time (2)	-0.0173	0.7794	-0.0117	0.8507	0.0033	0.9701	-0.1077	0.1047	-0.0372	0.5706	-0.0159	0.7967	-0.0313	0.6388	-0.1253	0.0841
ACEs (≥4)	-0.1191	0.1615	-0.0988	0.2382	-0.1367	0.2144	-0.1831	0.0289	-0.1184	0.1628	-0.1167	0.1680	-0.1149	0.1811	-0.1777	0.0340
ACEs*time	0.1996	0.0334	0.1863	0.0465	0.2345	0.0589	0.2514	0.0075	0.1938	0.0379	0.1959	0.0360	0.1988	0.0366	0.2455	0.0097
Sex (Male)			0.1349	0.0466	0.1343	0.2361										
ACEs*sex					0.1164	0.4898										
Sex*time					-0.0307	0.8030										
ACEs*sex*time					-0.1399	0.4475										
SBP							0.0100	0.0007							0.0107	0.0005
BMI									0.0049	0.3762					0.0004	0.9431
PA											0.0289	0.2932			0.0423	0.1150
HR													-0.0014	0.5629	-0.0012	0.5957

ACEs = adverse childhood experiences (≥4 versus <4 (reference group)), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

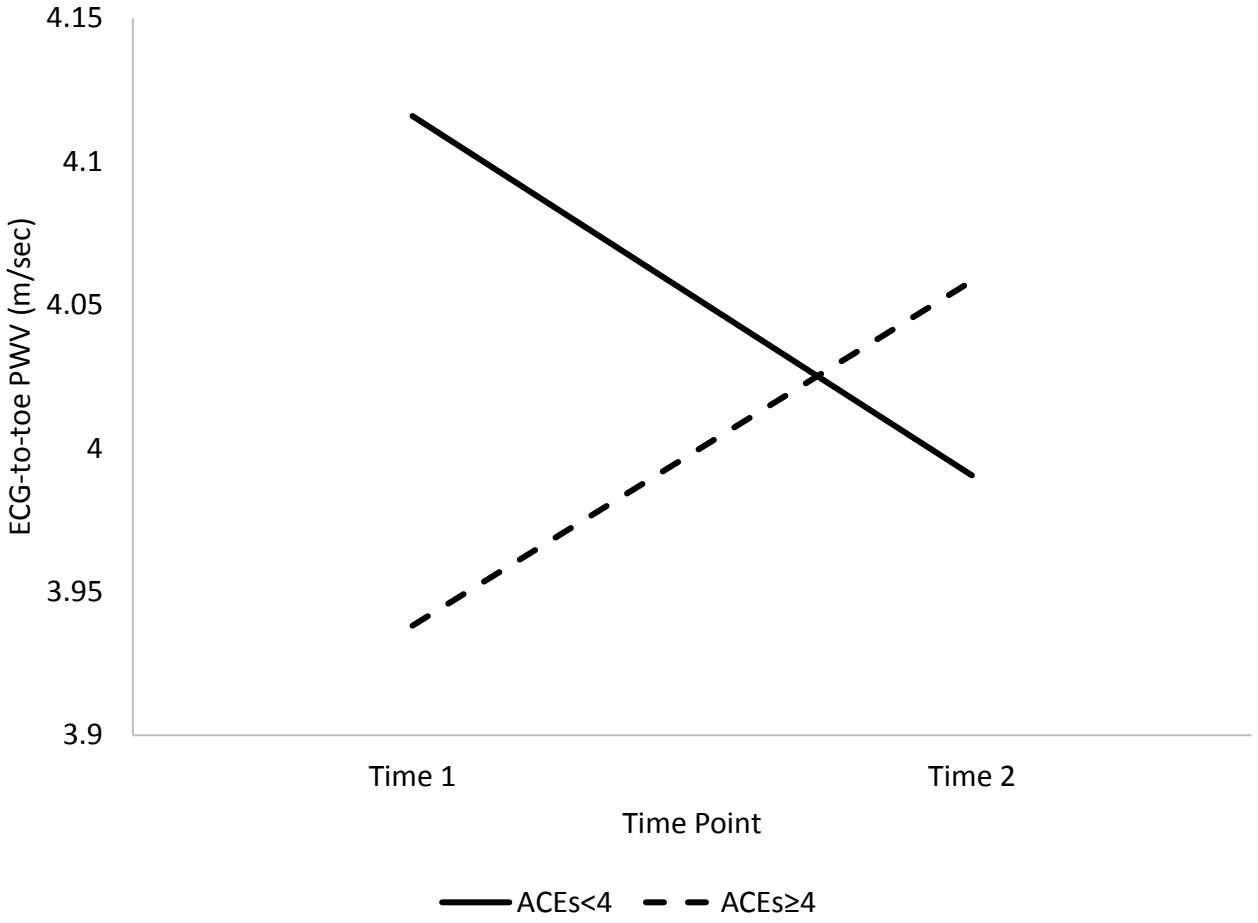

Figure 4.2 (Table 4.4, Model 8): Predicted ECG-to-toe PWV among those with <4 and ≥4 ACEs
PWV = Pulse Wave Velocity, ACEs = adverse childhood experiences
Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.5: Mixed-effects models predicting ECG-to-toe pulse wave velocity by maltreatment and household dysfunction groups, time, sex, and all covariates (n = 46)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	4.0930	<.0001	4.00	<.0001	4.0130	<.0001	3.2274	<.0001	4.0086	<.0001	4.1012	<.0001	4.2715	<.0001	3.3155	<.0001
Time (2)	-0.0814	0.4131	-0.08	0.4106	-0.0460	0.7450	-0.1449	0.1501	-0.1033	0.3217	-0.0870	0.3808	-0.1042	0.3141	-0.1830	0.0936
- / + m/d	-0.1334	0.2379	-0.11	0.3294	-0.0818	0.6015	-0.1160	0.2841	-0.1299	0.2506	-0.1482	0.1917	-0.1386	0.2222	-0.1385	0.2014
+ / - m/d	-0.0473	0.7505	-0.07	0.6545	-0.0227	0.9258	-0.0487	0.7326	-0.0740	0.6302	-0.0667	0.6546	-0.0677	0.6540	-0.1006	0.5036
+ / + m/d	-0.1420	0.2448	-0.09	0.4772	-0.1801	0.2600	-0.1700	0.1491	-0.1351	0.2694	-0.1407	0.2467	-0.1453	0.2435	-0.1665	0.1627
- / + m/d*time	0.1387	0.2598	0.14	0.2679	0.0666	0.6881	0.1489	0.2187	0.1474	0.2310	0.1513	0.2200	0.1389	0.2586	0.1691	0.1647
+ / - m/d*time	0.1349	0.4035	0.15	0.3425	-0.0123	0.9637	0.1135	0.4740	0.1406	0.3813	0.1459	0.3658	0.1473	0.3635	0.1400	0.3780
+ / + m/d*time	0.3199	0.0194	0.31	0.0223	0.4052	0.0208	0.3405	0.0119	0.3155	0.0205	0.3164	0.0204	0.3276	0.0193	0.3379	0.0141
Sex (Male)			0.15	0.0275	0.1408	0.4229										
- / + m/d*sex					-0.0685	0.7515										
+ / - m/d*sex					-0.0582	0.8438										
+ / + m/d*sex					0.4373	0.0939										
Sex*time					-0.0594	0.7466										
- / + m/d*sex*time					0.1365	0.5472										
+ / - m/d*sex*time					0.2479	0.4538										
+ / + m/d*sex*time					-0.4938	0.0667										
SBP							0.0086	0.0032							0.0092	0.0023
BMI									0.0040	0.5004					0.0010	0.8640
PA											0.0308	0.2663			0.0424	0.1227
HR													-0.0020	0.4171	-0.0018	0.4525

(m/d: m = maltreatment and d = household dysfunction), - / + m/d = No maltreatment and yes household dysfunction, + / - m/d = Yes maltreatment and no household dysfunction, + / + m/d = Yes maltreatment and yes household dysfunction, - / - m/d = No maltreatment and no household dysfunction (reference group), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

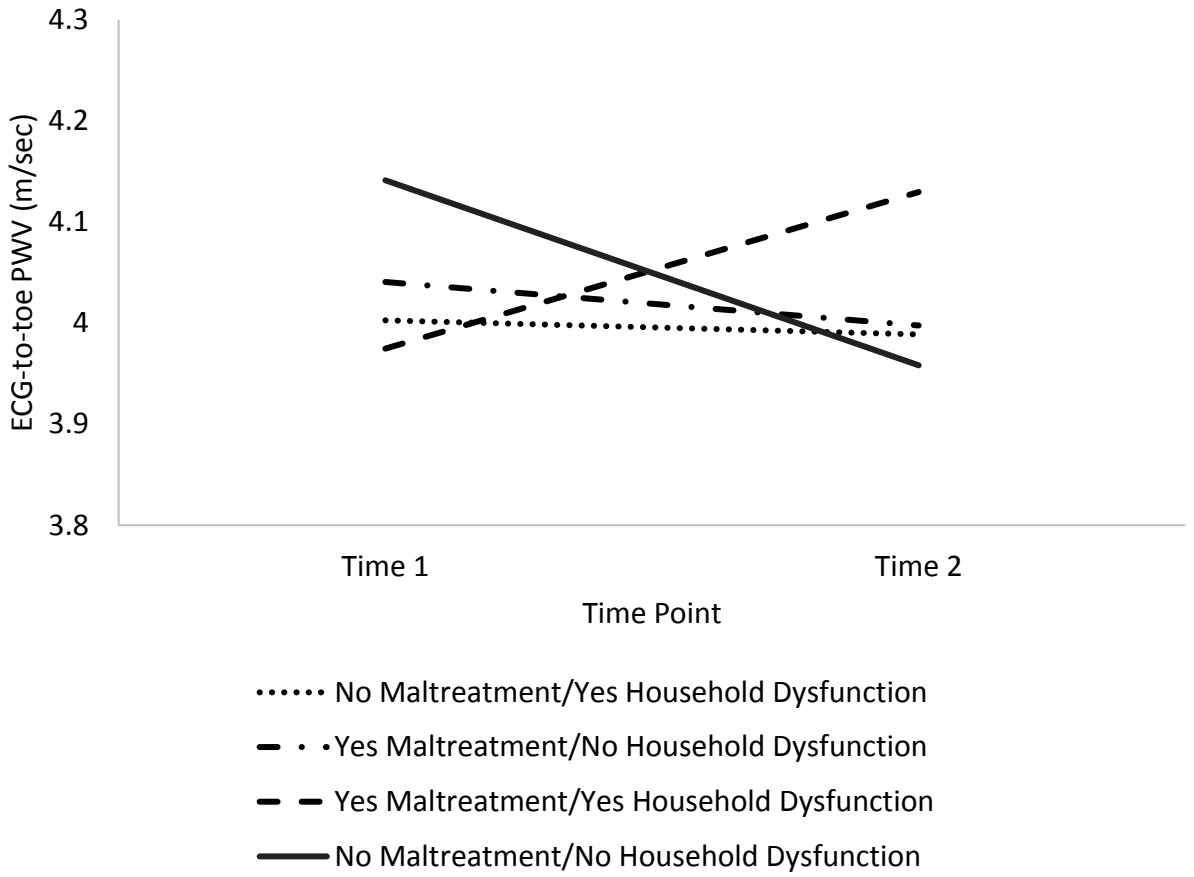

Figure 4.3 (Table 4.5, Model 8): Predicted ECG-to-toe PWV among those with: no abuse and yes household dysfunction, yes abuse and no household dysfunction, yes abuse and yes high household dysfunction, and no abuse and no household dysfunction

PWV = Pulse Wave Velocity

Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.6: Mixed-effects models predicting carotid intima-media thickness by cumulative ACEs score, time, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.4294	<.0001	0.4220	<.0001	0.4314	<.0001	0.4789	<.0001	0.4623	<.0001	0.4297	<.0001	0.4595	<.0001	0.5316	<.0001
Time (2)	-0.0433	0.0096	-0.0428	0.0102	-0.0564	0.0111	-0.0381	0.0301	-0.0361	0.0381	-0.0438	0.0089	-0.0453	0.0107	-0.0351	0.0652
ACEs	0.0005	0.8548	6.0×10^{-4}	0.8248	-0.0019	0.5895	0.0011	0.6954	0.0006	0.8243	0.0004	0.8798	0.0007	0.8179	0.0013	0.6785
ACEs*time	0.0108	0.0024	0.0108	0.0026	0.0145	0.0023	0.0105	0.0036	0.0108	0.0025	0.0110	0.0022	0.0106	0.0062	0.0102	0.0084
Sex (Male)			0.0159	0.2187	-0.0066	0.8003										
ACEs*sex					0.0062	0.2630										
Sex*time					0.0310	0.3415										
ACEs*sex*time					-0.0087	0.2123										
SBP							-0.00052	0.3760							-0.0004	0.4992
BMI									-0.00161	0.2010					-0.0015	0.2618
PA											-0.00298	0.6029			-0.0050	0.3966
HR													-0.00036	0.4737	-0.0004	0.4438

ACEs = adverse childhood experiences, SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

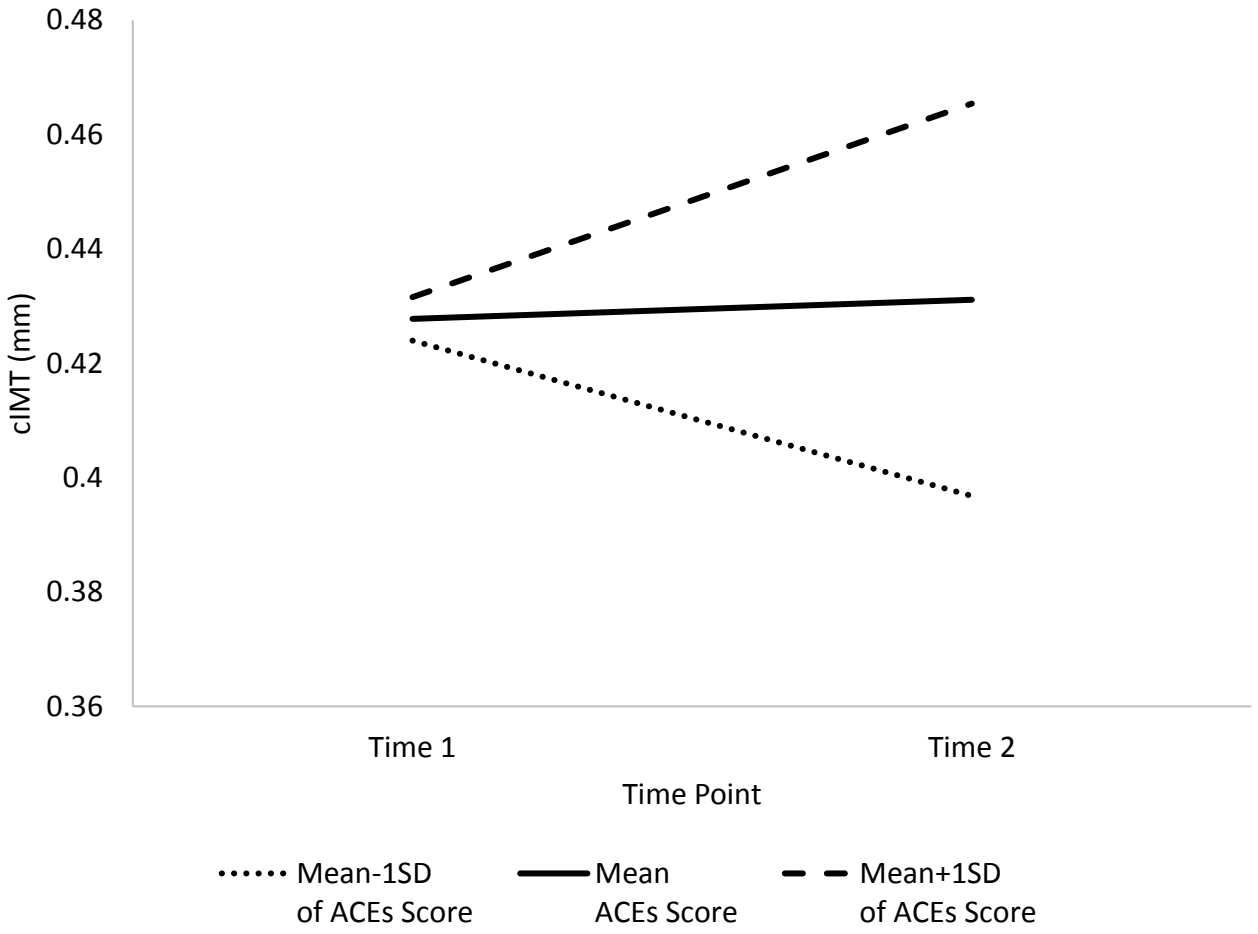

Figure 4.4 (Table 4.6, Model 8): Predicted cIMT with increase in total ACEs score
cIMT = Carotid Intima-Media Thickness, ACEs = adverse childhood experiences, SD = Standard Deviation
Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.7: Mixed-effects models predicting carotid intima-media thickness (cIMT) by ACEs category (<4 and ≥4), time, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.4313	<.0001	0.4225	<.0001	0.4283	<.0001	0.4570	<.0001	0.4612	<.0001	0.4314	<.0001	0.4855	<.0001	0.5284	<.0001
Time (2)	-0.0360	0.0073	-0.0355	0.0081	-0.0427	0.0206	-0.0335	0.0201	-0.0294	0.0410	-0.0360	0.0073	-0.0418	0.0037	-0.0343	0.0304
ACEs (≥4)	9.9×10^{-5}	0.9951	1.9×10^{-3}	0.9017	-0.0079	0.7078	0.0013	0.9344	0.0007	0.9673	-2×10^{-5}	0.9988	0.0013	0.9343	0.0024	0.8818
ACEs*time	0.0737	0.0003	0.0733	0.0004	0.0837	0.0019	0.0722	0.0005	0.0727	0.0004	0.0737	0.0003	0.0740	0.0004	0.0722	0.0006
Sex (Male)			0.0181	0.1593	0.0062	0.7729										
ACEs*sex					0.0226	0.4855										
Sex*time					0.0147	0.5750										
ACEs*sex*time					-0.0241	0.5434										
SBP							-0.00026	0.6436							-0.0001	0.8436
BMI									-0.00146	0.2401					-0.0015	0.2587
PA											-0.0018	0.7538			-0.0037	0.5248
HR													-0.0006	0.1955	-0.0007	0.1867

ACEs = adverse childhood experiences (≥4 versus <4 (reference group)), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

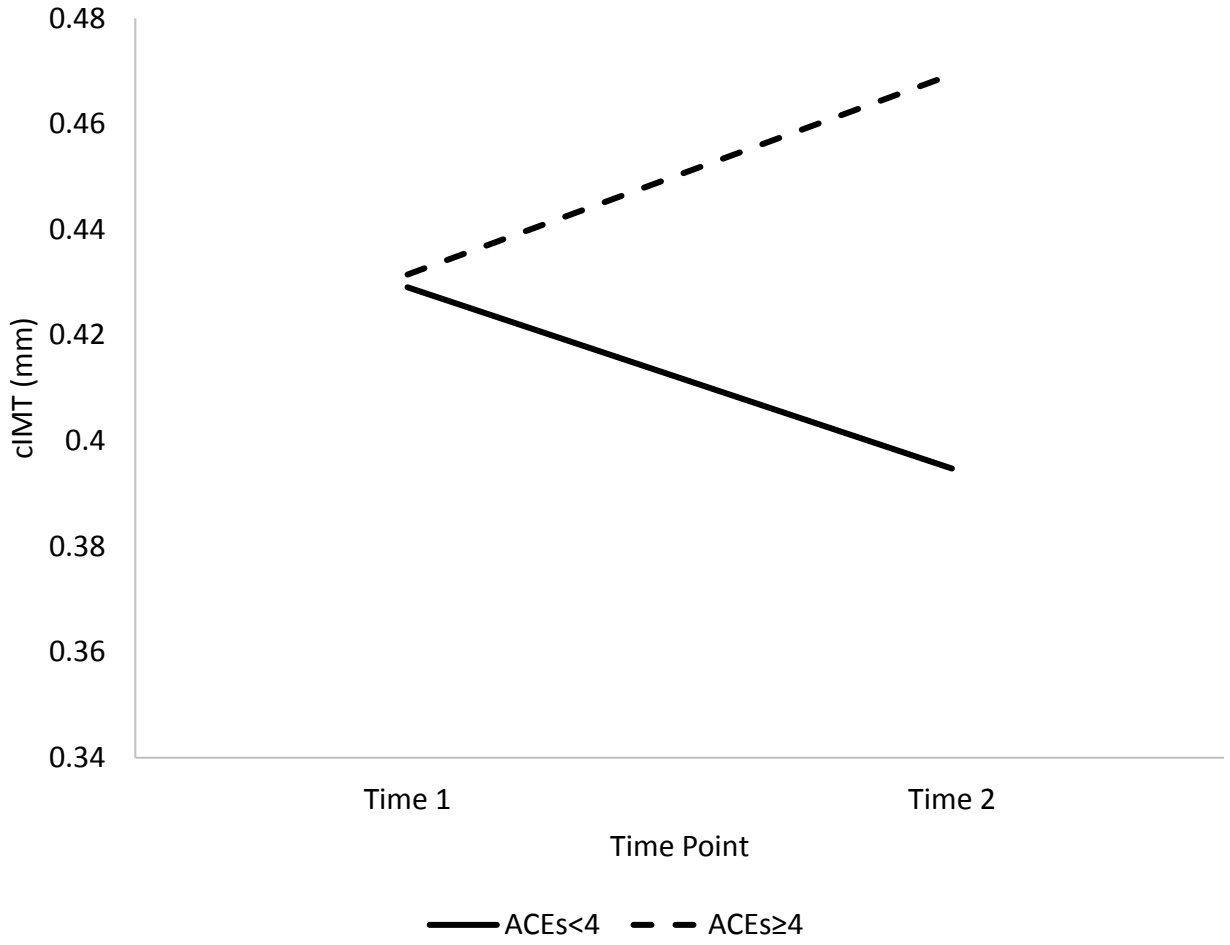

Figure 4.5 (Table 4.7, Model 8): Predicted cIMT among those with <4 and ≥4 ACEs
cIMT = Carotid Intima-Media Thickness, ACEs = adverse childhood experiences
Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.8: Mixed-effects models predicting carotid intima-media thickness by maltreatment and household dysfunction groups, time, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.4375	<.0001	0.4251	<.0001	0.4602	<.0001	0.4568	<.0001	0.4672	<.0001	0.4367	<.0001	0.4954	<.0001	0.5339	<.0001
Time (2)	-0.0339	0.1156	-0.0333	0.1221	-0.0699	0.0334	-0.0324	0.1406	-0.0259	0.2562	-0.0332	0.1239	-0.0414	0.0662	-0.03150	0.1932
- / + m/d	-0.0014	0.9492	0.0022	0.9231	-0.0326	0.3196	-0.0021	0.9253	-0.0036	0.8745	-0.0003	0.9880	-0.0022	0.9225	-0.00272	0.9042
+ / - m/d	0.0006	0.9832	-0.0009	0.9753	-0.0588	0.2300	0.0006	0.9844	0.0086	0.7827	0.0024	0.9361	-0.0044	0.8862	0.006679	0.8338
+ / + m/d	-0.0209	0.3956	-0.0137	0.5792	-0.0492	0.1447	-0.0208	0.3984	-0.0225	0.3585	-0.0206	0.4014	-0.0230	0.3538	-0.02395	0.3341
- / + m/d*time	0.0318	0.2273	0.0310	0.2391	0.0503	0.1848	0.0317	0.2284	0.0289	0.2729	0.0307	0.2469	0.0325	0.2205	0.02744	0.3028
+ / - m/d*time	-0.0239	0.5083	-0.0229	0.5263	0.0647	0.2742	-0.0234	0.5165	-0.0282	0.4365	-0.0255	0.4824	-0.0204	0.5754	-0.02715	0.4595
+ / + m/d*time	0.0750	0.0106	0.0742	0.0114	0.1160	0.0038	0.0743	0.0112	0.0739	0.0114	0.0748	0.0108	0.0790	0.0084	0.07704	0.0100
Sex (Male)			0.0209	0.1352	-0.0375	0.3071										
- / + m/d*sex					0.0576	0.1987										
+ / - m/d*sex					0.0925	0.1303										
+ / + m/d*sex					0.0598	0.2465										
Sex*time					0.0610	0.1507										
- / + m/d*sex*time					-0.0211	0.6825										
+ / - m/d*sex*time					-0.1390	0.0651										
+ / + m/d*sex*time					-0.0808	0.1779										
SBP							-0.0002	0.7445							-0.0001	0.8618
BMI									-0.0014	0.3182					-0.0014	0.3476
PA											-0.0027	0.6440			-0.0047	0.4295
HR													-0.0007	0.1996	-0.0007	0.2038

- / + m/d = No maltreatment and yes household dysfunction, + / - m/d = Yes maltreatment and no household dysfunction, + / + m/d = Yes maltreatment and yes household dysfunction, - / - m/d = No maltreatment and no household dysfunction (Reference group), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

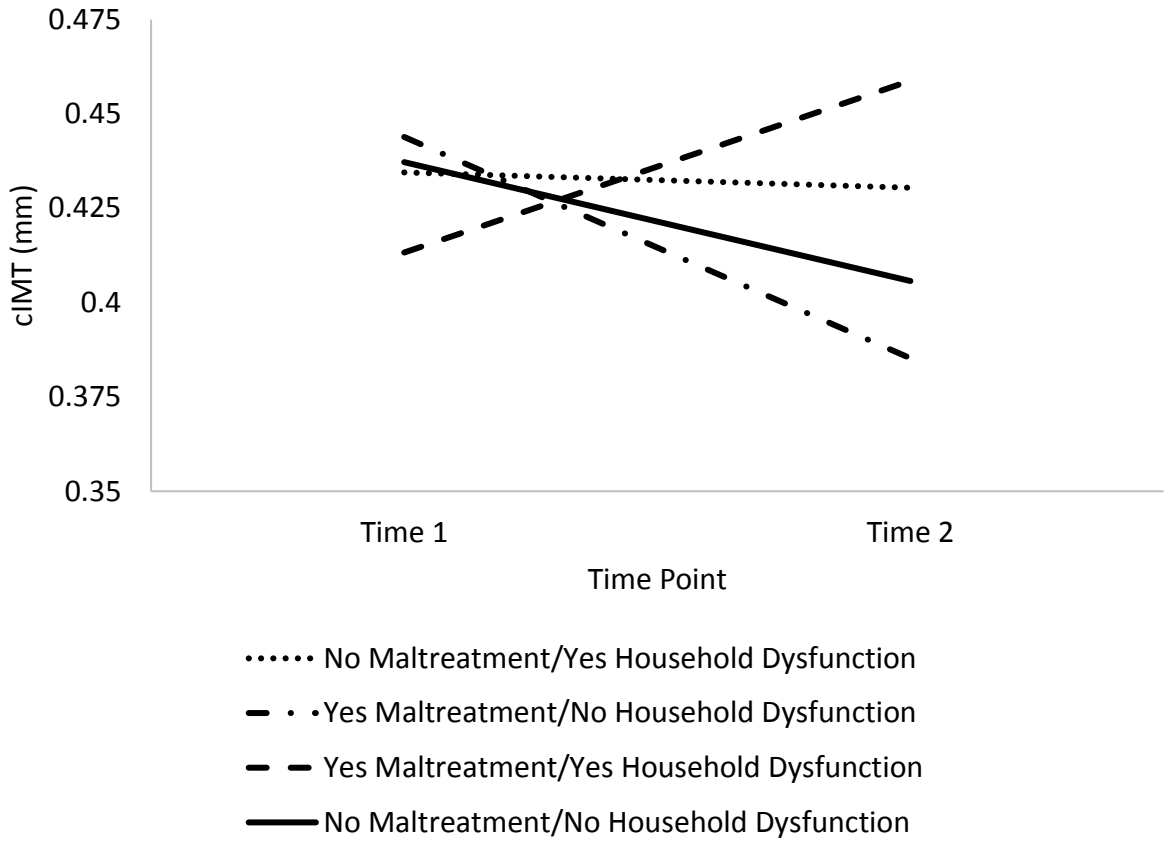

Figure 4.6 (Table 4.8, Model 8): Predicted cIMT among those with: no maltreatment and yes household dysfunction, yes maltreatment and no household dysfunction, yes maltreatment and yes high household dysfunction, and no maltreatment and no household dysfunction

cIMT = Carotid Intima-Media Thickness

Time 1 = mean age of 12 years, Time 2 = mean age of 21 years

Table 4.9: Mixed-effects models predicting compliance by cumulative ACEs score, time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.1443	<.0001	0.1406	<.0001	0.1401	<.0001	0.1486	0.0001	0.1248	<.0001	0.1447	<.0001	0.2155	<.0001	0.2225	<.0001
Time (2)	-0.0475	<.0001	-0.0472	<.0001	-0.0472	0.0016	-0.0470	<.0001	-0.0516	<.0001	-0.0480	<.0001	-0.0556	<.0001	-0.0596	<.0001
ACEs	0.0018	0.2902	0.0018	0.2743	0.0023	0.2824	0.0018	0.2916	0.0017	0.3034	0.0017	0.3170	0.0010	0.5727	0.0010	0.5879
ACEs*time	$-7.9x10^{-7}$	0.9997	-0.0001	0.9767	-0.0008	0.7816	-4×10^{-5}	0.9878	0.0001	0.9774	0.0001	0.9500	0.0005	0.8339	0.0007	0.7797
Sex (Male)			0.0081	0.2969	0.0097	0.5562										
ACEs*sex					-0.0013	0.7049										
Sex*time					-0.0003	0.9889										
ACEs*sex*time					0.0019	0.6857										
SBP							-0.0001	0.9038							-0.0003	0.5089
BMI									0.0010	0.2135					0.0011	0.1535
PA											-0.0035	0.3366			-0.0048	0.1780
HR													-0.0008	0.0102	-0.0009	0.0056

ACEs = adverse childhood experiences, SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.10: Mixed-effects models predicting compliance by ACEs category (<4 and ≥4), time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.1514	<.0001	0.1475	<.0001	0.1466	<.0001	0.1434	0.0002	0.1315	<.0001	0.1516	<.0001	0.2229	<.0001	0.2214	<.0001
Time (2)	-0.0510	<.0001	-0.0508	<.0001	-0.0508	<.0001	-0.0518	<.0001	-0.0553	<.0001	-0.0511	<.0001	-0.0588	<.0001	-0.0629	<.0001
ACEs (≥4)	-0.0008	0.9367	0.0002	0.9873	0.0052	0.6977	-0.0013	0.9051	-0.0012	0.9067	-0.0011	0.9140	-0.0021	0.8385	-0.0022	0.8304
ACEs*time	0.0075	0.5721	0.0070	0.6000	0.0004	0.9836	0.0080	0.5536	0.0083	0.5401	0.0077	0.5666	0.0108	0.4059	0.0111	0.4008
Sex (Male)			0.0081	0.3071	0.0099	0.4677										
ACEs*sex					-0.0134	0.5213										
Sex*time					0.0002	0.9928										
ACEs*sex*time					0.0175	0.5185										
SBP							0.0001	0.8237							-0.0002	0.6700
BMI									0.0010	0.2086					0.0011	0.1597
PA											-0.0035	0.3288			-0.0047	0.1890
HR													-0.0008	0.0077	-0.0009	0.0041

ACEs = adverse childhood experiences (≥4 versus <4 (reference group)), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.11: Mixed-effects models predicting compliance by maltreatment and household dysfunction groups, time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.1472	<.0001	0.1431	<.0001	0.1531	<.0001	0.1528	0.0002	0.1378	<.0001	0.1461	<.0001	0.2134	<.0001	0.2266	<.0001
Time (2)	-0.0424	0.0047	-0.0421	0.0050	-0.0591	0.0100	-0.0419	0.0059	-0.0449	0.0047	-0.0413	0.0060	-0.0509	0.0008	-0.0523	0.0013
- / + m/d	-0.0022	0.8735	-0.0010	0.9443	-0.0113	0.5786	-0.0024	0.8627	-0.0015	0.9118	-0.0005	0.9726	-0.0030	0.8210	-0.0007	0.9571
+ / - m/d	0.0256	0.1804	0.0254	0.1823	0.0149	0.6240	0.0257	0.1792	0.0227	0.2517	0.0284	0.1380	0.0189	0.3163	0.0182	0.3557
+ / + m/d	0.0073	0.6209	0.0097	0.5183	-0.0008	0.9706	0.0073	0.6194	0.0078	0.5967	0.0078	0.5989	0.0017	0.9089	0.0026	0.8584
- / + m/d*time	-0.0029	0.8719	-0.0032	0.8591	0.0137	0.5995	-0.0029	0.8698	-0.0019	0.9168	-0.0046	0.7961	-0.0021	0.9012	-0.0031	0.8579
+ / - m/d*time	-0.0084	0.7371	-0.0085	0.7351	0.0255	0.5252	-0.0084	0.7377	-0.0063	0.8027	-0.0107	0.6703	-0.0038	0.8756	-0.0033	0.8938
+ / + m/d*time	-0.0122	0.5297	-0.0126	0.5195	0.0019	0.9426	-0.0124	0.5240	-0.0119	0.5455	-0.0126	0.5208	-0.0043	0.8223	-0.0041	0.8299
Sex (Male)			0.0069	0.3835	-0.0096	0.6705										
- / + m/d*sex					0.0172	0.5308										
+ / - m/d*sex					0.0175	0.6502										
+ / + m/d*sex					0.0185	0.5604										
Sex*time					0.0289	0.3244										
- / + m/d*sex*time					-0.0289	0.4214										
+ / - m/d*sex*time					-0.0565	0.2742										
+ / + m/d*sex*time					-0.0196	0.6356										
SBP							-0.0001	0.8791							-0.0002	0.5528
BMI									0.0005	0.5954					0.0007	0.4497
PA											-0.0041	0.2533			-0.0053	0.1422
HR													-0.0008	0.0173	-0.0008	0.0097

(m/d: m = maltreatment and d = household dysfunction), - / + m/d = No maltreatment and yes household dysfunction, + / - m/d = Yes maltreatment and no household dysfunction, + / + m/d = Yes maltreatment and yes household dysfunction, - / - m/d = No maltreatment and no household dysfunction (reference group), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.12: Mixed-effects models predicting distensibility by cumulative ACEs score, time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.0077	<.0001	0.0076	<.0001	0.0072	<.0001	0.0091	<.0001	0.0081	<.0001	0.0077	<.0001	0.0098	<.0001	0.0120	<.0001
Time (2)	-0.0042	<.0001	-0.0042	<.0001	-0.0039	<.0001	-0.0041	<.0001	-0.0041	<.0001	-0.0042	<.0001	-0.0046	<.0001	-0.0045	<.0001
ACEs	0.0001	0.1216	0.0001	0.1214	0.0002	0.0267	0.0001	0.0886	0.0001	0.1174	0.0001	0.1363	0.0001	0.5373	0.0001	0.4548
ACEs*time	-2×10^{-5}	0.8446	-2×10^{-5}	0.9529	-0.0001	0.4313	-3×10^{-5}	0.7718	-2×10^{-5}	0.8314	-2×10^{-5}	0.8928	4.4×10^{-5}	0.7132	4.1×10^{-5}	0.7324
Sex (Male)			2.1×10^{-5}	0.8435	0.0010	0.2232										
ACEs*sex					-0.0003	0.1029										
Sex*time					-0.0008	0.4758										
ACEs*sex*time					0.0003	0.2913										
SBP							-1×10^{-5}	0.4044							-2×10^{-5}	0.3301
BMI									-2×10^{-5}	0.5606					$-8.8\text{x}10^{-6}$	0.8166
PA											-0.0002	0.3118			-0.0003	0.1532
HR													-2×10^{-5}	0.1272	-3×10^{-5}	0.0931

ACEs = adverse childhood experiences, SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.13: Mixed-effects models predicting distensibility by ACEs category (<4 and ≥4), time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.0082	<.0001	0.0081	<.0001	0.0079	<.0001	0.0087	<.0001	0.0086	<.0001	0.0082	<.0001	0.0103	<.0001	0.0119	<.0001
Time (2)	-0.0045	<.0001	-0.0045	<.0001	-0.0043	<.0001	-0.0045	<.0001	-0.0044	<.0001	-0.0045	<.0001	-0.0048	<.0001	-0.0046	<.0001
ACEs (≥4)	-4×10^{-5}	0.9415	-3×10^{-5}	0.9450	0.0001	0.3848	$-6.1\text{x}10^{-6}$	0.9905	-3×10^{-5}	0.9553	-0.0001	0.9189	-0.0002	0.7213	-0.0001	0.7975
ACEs*time	0.0005	0.4833	0.0005	0.4846	-0.0001	0.9028	0.0005	0.5187	0.0005	0.4981	0.0005	0.4805	0.0007	0.3014	0.0006	0.3526
Sex (Male)			1.7×10^{-5}	0.9631	0.0005	0.4141										
ACEs*sex					-0.0015	0.1462										
Sex*time					-0.0004	0.6507										
ACEs*sex*time					0.0015	0.2922										
SBP							$-5.9\text{x}10^{-6}$	0.7420							-1×10^{-5}	0.5014
BMI									-2×10^{-5}	0.5940					$-9.48\text{x}10^{-6}$	0.8035
PA											-0.0002	0.3023			-0.0002	0.1654
HR													-3×10^{-5}	0.0972	-3×10^{-5}	0.0702

ACEs = adverse childhood experiences (≥4 versus <4 (reference group)), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.14: Mixed-effects models predicting distensibility by maltreatment and household dysfunction groups, time, sex, and all covariates (n = 71)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	0.0077	<.0001	0.0076	<.0001	0.0085	<.0001	0.0085	<.0001	0.0085	<.0001	0.0076	<.0001	0.0096	<.0001	0.0117	<.0001
Time (2)	-0.0040	<.0001	-0.0040	<.0001	-0.0050	<.0001	-0.0040	<.0001	-0.0038	<.0001	-0.0040	<.0001	-0.0043	<.0001	-0.0040	<.0001
- / + m/d	0.0004	0.5639	0.0004	0.5567	-0.0008	0.4018	0.0004	0.5948	0.0003	0.6197	0.0005	0.4793	0.0004	0.5813	0.0004	0.5536
+ / - m/d	0.0011	0.2548	0.0011	0.2555	-3×10^{-5}	0.9815	0.0011	0.2489	0.0013	0.1780	0.0012	0.1962	0.0009	0.3519	0.0013	0.1947
+ / + m/d	0.0007	0.3492	0.0007	0.3445	0.0002	0.8437	0.0007	0.3460	0.0006	0.3791	0.0007	0.3315	0.0003	0.6289	0.0003	0.6333
- / + m/d*time	-0.0002	0.8023	-0.0002	0.8002	0.0011	0.4200	-0.0002	0.7959	-0.0003	0.7323	-0.0003	0.7299	-0.0002	0.8097	-0.0004	0.6429
+ / - m/d*time	-0.0007	0.6164	-0.0007	0.6156	0.0010	0.6295	-0.0006	0.6168	-0.0008	0.5247	-0.0008	0.5560	-0.0005	0.6778	-0.0008	0.5242
+ / + m/d*time	-0.0004	0.7130	-0.0004	0.7112	0.0003	0.8558	-0.0004	0.6936	-0.0004	0.6852	-0.0004	0.7017	-3×10^{-5}	0.9684	-3×10^{-5}	0.9720
Sex (Male)			0.0001	0.8919	-0.0013	0.2391										
- / + m/d*sex					0.0023	0.0851										
+ / - m/d*sex					0.0018	0.3385										
+ / + m/d*sex					0.0001	0.9478										
Sex*time					0.0016	0.2801										
- / + m/d*sex*time					-0.0025	0.1827										
+ / - m/d*sex*time					-0.0027	0.3035										
+ / + m/d*sex*time					-0.0003	0.9032										
SBP							$-8\text{x}10^{-6}$	0.6531							-1×10^{-5}	0.4625
BMI									-4×10^{-5}	0.3584					-3×10^{-5}	0.4901
PA											-0.0002	0.2298			-0.0003	0.1083
HR													-2×10^{-5}	0.1426	-2×10^{-5}	0.1158

(m/d: m = maltreatment and d = household dysfunction), - / + m/d = No maltreatment and yes household dysfunction, + / - m/d = Yes maltreatment and no household dysfunction, + / + m/d = Yes maltreatment and yes household dysfunction, - / - m/d = No maltreatment and no household dysfunction (reference group), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.15: Multiple regression models predicting carotid-femoral pulse wave velocity (cfPWV) by cumulative ACEs score, age, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	5.4144	0.0014	5.0018	0.0047	4.9336	0.0061	3.1330	0.0475	4.8585	0.0046	3.7865	0.0152	4.8119	0.0100	2.1931	0.1843
ACEs	0.0517	0.1251	0.0545	0.1087	0.0660	0.2180	0.0456	0.1309	0.0531	0.1121	0.0684	0.0270	0.0540	0.1119	0.0607	0.0402
Age	-0.0043	0.9550	0.0176	0.8271	0.0190	0.8154	-0.0658	0.3428	-0.0039	0.9583	0.0696	0.3245	0.0038	0.9600	0.0079	0.9106
Sex (Male)			-0.1433	0.4209	-0.0772	0.7951										
ACEs*sex					-0.0190	0.7805										
SBP							0.0341	<.0001							0.0239	0.0059
BMI									0.0217	0.1389					0.0106	0.4158
PA											-0.3182	0.0001			-0.2261	0.0059
HR													0.0055	0.4475	0.0018	0.7754

ACEs = adverse childhood experiences, SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

Table 4.16: Multiple regression models predicting carotid-femoral pulse wave velocity (cfPWV) by ACEs category (<4 and ≥4), age, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	5.3926	0.0015	5.1012	0.0039	5.0626	0.0044	2.9170	0.0642	4.9017	0.0043	3.9900	0.0114	5.0639	0.0063	2.4081	0.1429
ACEs (≥4)	0.2594	0.1290	0.2582	0.1325	0.3435	0.1325	0.2837	0.0623	0.2520	0.1376	0.2766	0.0771	0.2510	0.1464	0.2873	0.0536
Age	-7.5×10^{-5}	0.9992	0.0159	0.8437	0.0158	0.8453	-0.0596	0.3869	-7.8×10^{-4}	0.9918	0.0656	0.3598	0.0037	0.9621	-2.7×10^{-4}	0.9970
Sex (Male)			-0.1100	0.5349	-0.0247	0.9153										
ACEs*sex					-0.1956	0.5658										
SBP							0.0352	<.0001							0.0263	0.0026
BMI									0.0204	0.1661					0.0091	0.4857
PA											-0.2989	0.0003			-0.2051	0.0115
HR													0.0033	0.6498	-4.6×10^{-4}	0.9419

ACEs = adverse childhood experiences (≥4 versus <4 (reference group)), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity
E = regression estimate, p = p-value

Table 4.17: Multiple regression models predicting carotid-femoral pulse wave velocity (cfPWV) by maltreatment and household dysfunction groups, age, sex, and all covariates (n = 72)

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	E	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**	**E**	**p**
Intercept	5.6093	0.0016	5.4235	0.0031	4.6673	0.0128	2.6916	0.1043	4.6958	0.0106	4.1918	0.0106	5.1836	0.0075	1.9445	0.2643
- / + m/d	0.1320	0.5661	0.1240	0.5931	0.3305	0.3375	0.2549	0.2146	0.2044	0.3799	0.1358	0.5167	0.1370	0.5539	0.2728	0.1771
+ / - m/d	0.2771	0.3595	0.2743	0.3675	-0.1190	0.7942	0.2025	0.4476	0.1427	0.6462	0.2969	0.2815	0.2854	0.3485	0.1466	0.5854
+ / + m/d	0.3300	0.2005	0.3109	0.2370	0.2564	0.4744	0.4545	0.0489	0.3956	0.1272	0.3798	0.1074	0.3226	0.2137	0.5001	0.0276
Age	-0.0128	0.8704	-0.0020	0.9807	0.0322	0.6993	-0.0626	0.3716	-0.0016	0.9840	0.0533	0.4682	-0.0074	0.9256	2.9×10^{-4}	0.9968
Sex (Male)			-0.0801	0.6622	-0.0584	0.8754										
- / + m/d*sex					-0.4338	0.3474										
+ / - m/d*sex					0.7137	0.2393										
+ / + m/d*sex					0.2657	0.6181										
SBP							0.0369	<.0001							0.0277	0.0019
BMI									0.0258	0.1252					0.0166	0.2596
PA											-0.3035	0.0003			-0.2025	0.0135
HR													0.0041	0.5846	-5.9×10^{-4}	0.9269

(m/d: m = maltreatment and d = household dysfunction), - / + m/d = No maltreatment and yes household dysfunction, + / - m/d = Yes maltreatment and no household dysfunction, + / + m/d = Yes maltreatment and yes household dysfunction, - / - m/d = No maltreatment and no household dysfunction (reference group), SBP = systolic blood pressure, BMI = body mass index, PA = physical activity, HR = heart rate
E = regression estimate, p = p-value

To summarize, the results showed that individuals with exposure to ACEs experience a greater increase in arterial stiffness over time in comparison to those with no exposure to ACEs, and the increase in arterial stiffness was similar between males and females. Also, differences in HR, SBP, BMI, and physical activity did not mediate the relationship between ACEs and arterial stiffness over time indicating that the effect is independent of these more traditional factors.

CHAPTER 5: DISCUSSION

Although limited, evidence obtained from previous studies suggest that exposure to ACEs may be positively associated with arterial stiffness in childhood and in adulthood (Hakulinen et al., 2016; Klassen et al., 2016; Loucks et al., 2014; Su et al., 2014). However, two of these studies were cross-sectional in design (Klassen et al., 2016; Su et al., 2014), and while changes in structural composition of the arteries has been studied in relation to ACEs using a longitudinal design (Hakulinen et al., 2016; Loucks et al., 2014), participants in these studies were already adults at the start of the study and differences in IMT between groups (higher among those with ACEs) was already present at baseline. Based on the results of both the longitudinal and cross-sectional studies, it appears that changes in arterial stiffness in response to ACEs may occur at an early stage in life, likely sometime in childhood and adolescence. Therefore, in order to identify possible opportunities for early intervention and prevention, it is important to identify whether ACEs affects arterial stiffness early in life. This is the first longitudinal study to examine the relationship between ACEs and change in arterial stiffness in children as they transition into early adulthood, while addressing the limitations of previous research. Overall, the results suggest that individuals exposed to ACEs have a greater increase in arterial stiffness over time, and that this increase is similar for males and females and is independent of HR, SBP, BMI and physical activity.

One of the main findings of this study was that a greater exposure to ACEs demonstrated a greater increase in arterial stiffness from childhood into adulthood. The results showed that both ECG-to-toe PWV and cIMT increased significantly over the follow-up period with higher total ACEs score as well as among those who experienced 4

or more ACEs compared to less than 4 ACEs. The increase in ECG-to-toe PWV and cIMT over time was also observed when qualitative aspects of ACEs (maltreatment and/or household dysfunction) were considered. While the observed change in ECG-to-toe PWV is statistically greater among those with ACEs, the observed change (<0.5 m/s) is not clinically significant (Papaioannou et al., 2012). However, the interaction graph suggests that over the next decade, those with ACEs will have a clinically important increase in PWV compared to those with no ACEs. This is supported by the evidence for cIMT, where the increase is IMT was already clinically significant (>0.03) among those with ACEs. These results also suggest that the effect of ACEs on arterial stiffness is resilient regardless of how ACEs was conceptualized. These findings are consistent with the results obtained from previous studies. Some studies have found that the effect of cumulative childhood psychosocial risk factors is a better indicator of total psychosocial risk burden than any single risk factor (Anda et al., 2006; Chartier, Walker, & Naimark, 2010), whereas others have suggest that a threshold model (<2 and ≥2 ACEs and <4 and ≥4 ACEs) may better fit the relation between ACEs and health outcomes (Felitti et al., 1998; Pretty et al., 2013; Su et al., 2014). Further, a study found that the impact of ACEs depends on the type of ACEs (maltreatment versus household dysfunction) (MacDonald & Tough, 2014). In addition, the current study also used cross-sectional data to examine the association between ACEs and cfPWV, and found a positive association between ACEs and cfPWV after adjusting for covariates. cfPWV is considered to be the gold standard for assessing arterial stiffness. However, since cfPWV was only obtained at Time 2, a longitudinal examination of the relationship was not possible. However, the results obtained from cfPWV support those

obtained from the longitudinal examination of the relationship between ACEs and ECG-to-toe PWV.

In relation to the second hypothesis, this study examined the moderating effect of sex on the relationship between ACEs and changes in arterial stiffness over time. Overall, the results show that an increase in arterial stiffness in response to ACEs over time was similar for males and females. This finding is consistent with the findings reported by two other longitudinal studies conducted in adults (Hakulinen et al., 2016; Loucks et al., 2014), and further suggests that the change in arterial stiffness between males and females is similar even from childhood into young adulthood. However, this finding is in conflict with the results reported from a cross-sectional study conducted by Klassen and colleagues (2016) using the same cohort who found PWV to higher only in males with 4 or more ACEs. The inconsistency in findings may be because Klassen and colleagues (2016) examined the association between ACEs and arterial stiffness in children aged 10-14 years, while the current study examined the relationship over a 9 year follow-up period. Therefore, while differences between sexes may be present in childhood, the results of the current study suggest that females catch up with males and that both males and females experience a similar increase in arterial stiffness over time in relation to ACEs.

In addition, this study also examined the effect of HR, SBP, BMI, and physical activity on the relationship between ACEs and arterial stiffness over time. The results showed that differences in HR, SBP, BMI, and physical activity did not mediate the relationship between ACEs and arterial stiffness over time, regardless of how ACEs were conceptualized suggesting that an independent effect exists beyond traditional and lifestyle/behavioural factors. These results emphasize the need to examine alternative

pathways to explain the relationship between ACEs and arterial stiffness over time. For example, the mechanisms underlying the ACEs-arterial stiffness relationship may be related to the physiological functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in helping individuals adjust to internal and external stressors (Rhee & Pearce, 2011). Research shows that hormonal stress reactivity increases significantly throughout puberty, which is accompanied by an increase in activity of the HPA axis (Stroud et al., 2009). Typically, the HPA axis is not constantly activated and turns off through a negative feedback cycle resulting in cortisol levels to return to pre-stress levels after the stressor has passed. However, recurrence of stressful experiences may trigger an allostatic shift in the normal circadian rhythm of stress-induced cortisol secretion (Stephens, 2012). In presence of chronic or repeated exposure to psychological stress during the developmental years, the HPA axis becomes increasingly activated resulting in an overexposure to stress hormones (Guilliams & Edwards, 2010), which can make this system permanently unstable or dysfunctional (Faravelli et al., 2010). This may be the case among individuals with ACEs as they are more likely to experience prolonged stress and anxiety, which may compromise the functioning of this system over time. In individuals with ACEs, the glucocorticoid receptor (receptor to which the stress hormone cortisol binds) may become desensitized due to persistent exposure to high levels of cortisol, thus diminishing the negative feedback responsible for maintaining hormone homeostasis (Kalmakis et al., 2015). Disturbance in hormone homeostasis may possibly lead to chronic activation of the HPA axis resulting in increased cortisol production, in turn hindering the ability of cortisol to regulate inflammatory responses (Guilliams & Edwards, 2010). Clinical studies have shown that females who have experienced physical and sexual abuse

in childhood (Heim et al., 2000), and males who have experienced early life trauma exhibited a greater HPA axis response in adulthood (Heim et al., 2008). It is suggested that elevated cortisol production may promote stiffening of the arteries by suppressing the synthesis of nitric oxide, which is a vasodilator (Kelly et al., 1998). Therefore, it could be proposed that psychosocial stress increases the HPA axis activity and accompanying increase in cortisol secretion, which may in part explain the increase in arterial stiffness over time.

In addition to cumulative effect of ACEs (Felitti et al., 1998), studies are now proposing that different forms of stress elicit different patterns of hormonal response. For example, a threat to one's physical self (i.e., physical and sexual abuse) elicits a different pattern of HPA activity compared to a threat to the social self (i.e., parents getting divorced) as they both require different adaptation demands (Miller, Chen, & Zhou, 2007). In addition to duration, intensity of stress also plays an important role in the activation of the HPA axis. A meta-analysis found that cortisol response to acute but intense traumas elicited a more pronounced alteration in HPA function (Miller et al., 2007). Therefore, future studies should examine whether type and/or severity of abuse plays an important role in altering biological response, as well as increase our overall understanding of the consequences of ACEs on cardiovascular health.

Although HR and SBP did not mediate the relationship between ACEs and arterial stiffness over time, it may be too early to dismiss the role of these factors in the relationship. The results showed that HR and SBP were the only covariates that were independently associated with compliance and ECG-to-toe PWV, respectively. Increase in HR was associated with decrease in compliance, and increase in SBP was associated with increase

in ECG-to-toe PWV. These findings are consistent with a large body of evidence that suggest a relationship between HR, SBP and arterial stiffness (Chen et al., 2017; Ferreira et al., 2016; Li et al., 2004; Logan & Kim, 2016; Puato et al., 2008). It could also be proposed that ACEs may be associated with greater risk of arterial stiffness through alterations in autonomic regulation. A study showed that increased sympathetic activity promotes endothelial dysfunction and structural changes in the vessel wall (i.e. fibrosis) (Brook & Julius, 2000), and another study showed decreased parasympathetic activity to be associated with higher HR and BP (Floras & Ponikowski, 2015; Licht et al., 2010). Using the same sample as the current study, Pretty and colleagues (2013) found that children who had experienced 4 or more ACEs showed significantly higher HR compared to children with less than 4 ACEs. Further, a previous study done in children did not find differences in SBP in response to ACEs (Pretty et al., 2013), but studies done in adults found greater SBP among those with ACEs (Alastalo et al., 2013; Stein et al., 2009; Su et al., 2015), suggesting that higher SBP in response to ACEs may appear later in life. It may be possible that exposure to ACEs is associated with higher sympathetic nerve activity, and lower parasympathetic activity (Danese & McEwen, 2012), which can may result in elevated HR and vasoconstriction (Julius & Majahalme, 2000). Research shows an association between HR, SBP, and arterial stiffness (Chen et al., 2017; Ferreira et al., 2016; Li et al., 2004; Logan & Kim, 2016; Puato et al., 2008), and between physical inactivity, BMI, SBP, and arterial stiffness (DeSouza et al., 2000; Kim & Jee, 2017; Zebekakis et al., 2005) where physical inactivity and higher BMI maybe related to arterial stiffness through higher SBP (Farpour et al., 2009). Taken together, it is important to recognize the interdependencies between the psychosocial stressors and the physiological risk factors

which may occur simultaneously in adulthood, and in turn lead to an even greater risk for cardiovascular disease than previously thought. However, further longitudinal research is required to test these mechanisms underlying the relationship between ACEs and arterial stiffness.

In addition to ECG-to-toe PWV and cIMT, the effect of ACEs on arterial compliance and distensibility was also examined. The results showed a significant decrease in compliance and distensibility over time in the entire sample, which is consistent with previous work that have shown arterial compliance and distensibility to decrease with age (Benetos et al., 1993; Laogun & Gosling, 1982). However, the results found no statistically significant change in compliance or distensibility over time in relation to ACEs, irrespective of how the ACEs variable was conceptualized. Previous studies have found that although arterial compliance and distensibility mainly depends on the intrinsic properties of the arterial wall, it also partially depends on BP (Marchais et al., 1992). However, in this study SBP did not explain the relationship between ACEs and compliance and distensibility. As mentioned previously, this may be due to the possibility that participants in this study were still relatively young at the end of the study (average age of 21 years) and may not yet have experienced pathological increases in BP. This is supported by the results of a longitudinal study with a 23-year follow-up period (Su et al., 2014). Su and colleagues (2014) found that history of multiple traumatic events was associated with a rapid increase in BP but only after participants were over 30 years of age. Another study found SBP to be negatively associated with compliance but only after 30 years of age (Juonala et al., 2005). Therefore, a longer follow-up period may be required to see if changes in compliance and distensibility are observed or not.

5.1 Strengths & Limitations

The strengths of the current study include use of a longitudinal study design that allowed the exploration of trajectories of change in arterial stiffness over time in the same cohort of participants. Examining changes in arterial stiffness from childhood into early adulthood is important because it provides understanding of the causal relationship between ACEs and arterial stiffness, and more importantly, when changes in arterial stiffness begin to manifest. Further, unlike most previous studies that relied on long-term recall of ACE exposure among adults, this study minimized recall and reporting biases by obtaining the exposure information at an early age. Third, this study examined if changes in the traditionally recognized risk factors including HR, SBP, BMI, and physical activity mediated the relationship between ACEs and arterial stiffness over time, which has not been included in earlier studies. Finally, this study also examined separate and compound effects of both maltreatment and household dysfunction on arterial stiffness, which has not been examined previously.

Several limitations of this study need to be addressed in future work. First, this was a pilot study with a small sample. It was underpowered to identify more modest effect sizes. With that in mind, however, many of the marginal effects that trended towards statistical significance may prove to be statistically significant with a larger sample. Therefore, it can be proposed that the link between ACEs and arterial stiffness may be even greater than what was observed in the current study. Second, the impact of ACEs may depend on the timing, severity, and chronicity of ACEs (Miller, Chen, & Zhou, 2007), which was not assessed in this study. Third, this study did not measure possible resiliency to exposure to traumatic experiences such as whether some children had protective systems in place or

adults they could depend on and trust (e.g., positive caregiver influence) (Cicchetti, 2013), which may neutralize the impact of emotional stressors on arterial health. Finally, data analysis for arterial stiffness at time 1 and 2 was completed by two different people. However, both inter- and intra-class correlations of arterial stiffness (e.g., PWV, IMT, compliance, and distensibility) within our lab have been shown to range between 0.71-0.90.

5.2 Conclusion

Overall, the results suggest that exposure to ACEs is associated with increased arterial stiffness from childhood into early adulthood. This is of concern as arterial stiffness has been identified as an important preclinical risk factor for various important cardiovascular outcomes including atherosclerosis, stroke, coronary artery disease, and coronary heart disease among adults (Chae et al., 1999; Franklin et al., 1997; Herrington et al., 2004; Sutton-Tyrrell et al., 2005; Urbina et al., 2011). The finding that exposure to ACEs leads to a greater increase in arterial stiffness from childhood into young adulthood suggests that remodeling of the arterial walls begins at an early age, accelerating the emergence of heart disease in adulthood. The results emphasize the need for early identification and intervention as to alter the negative cardiovascular trajectory in order to prevent future detrimental cardiovascular outcomes in adult life. Further, the increase in arterial stiffness was similar between males and females suggesting that males and females are equally affected and interventions must be targeted to both sexes. However, it would be up to future research to identify whether similar or different interventions would be required for males and females possibly due to varying ACE exposure, use of coping mechanisms as well as other social and environmental factors. Finally, differences in HR,

SBP, BMI, and physical activity did not mediate the relationship between ACEs and arterial stiffness over time. This is an important finding because it suggests that focusing interventions designed around traditional risk and lifestyle factors may not address this link, and that a new and different approach is required to help individuals with ACEs. Also, given the potential long-term clinical consequences associated with arterial stiffness, there is a critical need to not only deliver the intervention in a timely manner, but to develop novel interventions. For example, studies have found ACEs to be associated with psychosocial or emotional factors (Alshawi & Lafta, 2015; Felitti et al., 1998, Reiser et al., 2014), while others have found psychosocial and emotional factors to be associated with arterial stiffness (Ross et al., 2015; Seldenrijk et al., 2011). Therefore, future studies should consider examining the effect of psychosocial factors, including mastery, self-esteem, depressive affect, anxiety and hostility on the relationship between ACEs and stiffness. Since the mechanism underlying the association between ACEs and arterial stiffness remains poorly understood, future research should test the psychosocial and emotional factors and their interaction with biological systems such as the HPA axis and adaptive stress responses and inflammation.

In conclusion, this study supports previous work on adults linking ACEs to chronic diseases and early mortality and identifies how this connection may transpire over the life course. In addition, it adds to the growing literature connecting ACEs with arterial stiffness as an intermediate, preclinical outcome linking ACEs to cardiovascular diseases identified in previous studies (Dong et al., 2004; Felitti et al, 1998), and extends it by demonstrating that these differences in arterial stiffness happens much earlier than previously thought.

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