University of Alberta

Sex Differences in the Relationship between Childhood Trauma and

Cardiovascular Disease Risk in Adulthood

by

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ABSTRACT

Childhood trauma is a chronic stressor that has been linked to cardiovascular disease (CVD). Evidence also shows that females may have a heightened reactivity to interpersonal and chronic stress than males.

The subjects for this study included 6881 members of Statistics Canada's National Population Health Survey. The main objectives were to assess whether women who report childhood trauma are more likely than men who report childhood trauma to have CVD, and possible mediating and moderating factors in the association between childhood trauma and CVD.

Our results suggested that the effect of childhood trauma on CVD is heightened among women when compared to men. Stressful life events in adulthood were found to heighten the impact of childhood trauma on CVD, particularly among women. Also, depression, smoking, and poor diet were found to partially mediate the relationship between childhood trauma and CVD. This has important implications for sex differences in CVD risk.

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"The research and analysis are based on data from Statistics Canada and the opinions expressed do not represent the views of Statistics Canada."

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CVD	Cardiovascular disease
CTE	Childhood traumatic event
ACE study	Adverse Childhood Experiences study
CDC	Centers for Disease Control and Prevention
ANS	Autonomic Nervous System
HPA	Hypothalamic-Pituitary-Adrenal Axis
SNS	Sympathetic Nervous System
PNS	Parasympathetic Nervous System
CRF	Corticotrophin-releasing factor
ACTH	Adrenocorticotropic hormone
PTSD	Post-traumatic stress disorder
NPHS	National Population Health Survey
SES	Socioeconomic status
CIDI	Composite International Diagnostic Interview
CIDI-SFMD	Composite International Diagnostic Interview Short Form for Major Depression
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

CHAPTER 1.0 INTRODUCTION

1.1. Epidemiology of CVD

Cardiovascular disease (CVD) accounts for 27% of deaths in industrialized countries and 21% of deaths in developing countries, making it the leading cause of death worldwide (Eysmann and Douglas 1992; Lopez, Mathers et al. 2006). In Canada, heart disease is the leading cause of death among women and among men it is the second leading cause of death (Manuel, Leung et al. 2003).

There has been a drastic decline in CVD morbidity and mortality in Canada since 1969 (Manuel, Leung et al. 2003; Tu, Nardi et al. 2009). The decrease in CVD morbidity and mortality is mainly due to improvements in the healthcare system and health promotion policies that have led to the betterment of Canadian population health such as reduced smoking rates, and control of high blood pressure (Health Canada 1995).

However, the rate of decline for heart disease has been more rapid among men than among women (Hayes 1996). Also, after a cardiovascular event, women are more likely to experience poor outcomes such as death than men (Worrall-Carter, Ski et al. 2011). Thus, although heart disease is generally viewed as mostly affecting middle-aged men, the burden of CVD morbidity and mortality among women is becoming a cause for concern.

An increase in CVD is expected due to the aging demographic and adverse lifestyle changes (Worrall-Carter, Ski et al. 2011). For example,

overweight has doubled among children and tripled among adolescents since 1970 in the United States, and this is projected to increase the prevalence of overweight in adults (Bibbins-Domingo, Coxson et al. 2007). This trend in Canada is similar to that of the United States, showing an increase in overweight and obesity among children and adolescents (Ball and McCargar 2003). Obesity is also associated with other CVD risk factors such diabetes and high blood pressure (Wilson, D'Agostino et al. 2002). Finally, although smoking prevalence has decreased with time over the past decade, this decline seems to be slowing (Reid JL 2012).

There are some risk factors for CVD that are not modifiable such as age, gender, family history of heart disease, birth weight and personal history of heart disease (Poulter 2003). However, there are also many risk factors that are modifiable. A major study that has outlined six main risk factors for CVD is the Framingham Heart Study. The Framingham Heart Study was initiated in 1948 and has a sample size of 5209 (Worrall-Carter, Ski et al. 2011). The six risk factors which were identified included high blood pressure, high body mass index (30 kg/m^2 or more), high blood cholesterol, diabetes, smoking, and physical inactivity (Dawber, Mann et al. 1956).

Evidence shows that lifestyle and psychological risk factors for CVD such as physical inactivity and depression are more common among women than men (Worrall-Carter, Ski et al. 2011). Since many CVD risk factors are modifiable, the identification and modification of risk factors is key to the

prevention of CVD. In order to reduce the burden of CVD among women it is necessary to explore sex differences in CVD risk factors.

At least one of the modifiable CVD risk factors outlined above have been reported by 63% of Canadians (Health Canada 1995). Also, research has shown that with each additional risk factor, the risk for CVD increases greatly (Health Canada 1995). For example, among those who have one other risk factor, the risk for heart disease doubles for smokers (Health Canada 1995). Thus, rather than focusing on one risk factor at a time, it is important to focus on reducing multiple risk factors. As a result, identifying criteria that may influence an increase in multiple risk factors for CVD may be particularly important for targeting its reduction.

1.2. Childhood Traumatic Events

Childhood trauma for the purposes of this thesis refers the physical or psychological threat to a child resulting from traumatic events. Childhood traumatic events have been found to have a prevalence of 31-60% in Canada using retrospective reports from respondents above the age of 20 (Thompson and Cui 2000). This prevalence seems to be becoming more common with time, since it is increasing as age cohorts decrease (Thompson and Cui 2000). Similarly, in the United States, a prevalence of 52.1% was found for exposure to childhood abuse and household dysfunction by the Adverse Childhood Experiences (ACE) study, which was conducted by Kaiser Permanente and the Centers for Disease Control and Prevention (CDC) and has a sample of 18, 175 Americans (Felitti, Anda et al. 1998).

Studies assessing childhood traumatic events have associated childhood trauma with many adverse psychological and physiological health outcomes such as such as depression (Hovens, Wiersma et al. ; Bernet and Stein 1999), post-traumatic stress disorder (Hovens, Wiersma et al. ; Widom 1999; Moffitt, Caspi et al. 2007), chronic pain (Jones, Power et al. 2009), fibromyalgia (Jones, Power et al. 2009) and ischemic heart disease (Dong, Giles et al. 2004). Also, multiple forms of childhood abuse have been found to frequently co-occur (Dong, Anda et al. 2004). It is rare that only one traumatic event is experienced by those that have a history of trauma (Kessler 2000). So, those with trauma history have often had many episodes of exposure to traumatic events. Thus, the cumulative influence of interrelated experiences may be a more appropriate method of assessing the effects of childhood trauma than looking at specific childhood traumatic events (Dong, Anda et al. 2004).

Accordingly, strong graded relationships have been found between the number of forms of childhood trauma reported and adverse health outcomes (Dong, Anda et al. 2004). Studies have shown that many forms of childhood trauma rather than a specific type of childhood trauma are what generally lead to adverse long-term effects (Dong, Anda et al. 2004). For example, strong graded relationships have been found between multiple forms of childhood trauma and smoking (Anda, Croft et al. 1999), drug abuse (Dube, Anda et al. 2002) liver disease (Dong, Dube et al. 2003) and suicide attempts (Dube, Anda et al. 2001), to name a few.

1.3. Overview of the Association between Childhood Trauma and CVD

Childhood traumatic events have been found to have an influence on many physical health factors such as cardiovascular disease (Hovens, Wiersma et al. ; Bernet and Stein 1999; Jones, Power et al. 2009). It has been well established that CVD is more prevalent in men than in premenopausal women (Wingard, Suarez et al. 1983; Lerner and Kannel 1986; Vitale, Miceli et al. 2007). However, evidence also shows that chronic stress is a risk factor for CVD morbidity and mortality (Iso, Date et al. 2002; Nielsen, Kristensen et al. 2008; Fujino, Tanabe et al. 2011) and that females may have a heightened reactivity to stress when compared to males (Weiss, Longhurst et al. 1999; McCormick, Linkroum et al. 2002). As a result, in the presence of chronic stress, pre-menopausal women may show a higher risk for CVD when compared to age-matched men (Iso, Date et al. 2002; Korkeila, Vahtera et al. 2010).

Childhood trauma is a chronic stressor, which has been linked to CVD (Dong, Giles et al. 2004; Sumanen, Koskenvuo et al. 2005; Alastalo, Raikkonen et al. 2009). Evidence suggests that early adverse childhood experiences lead to a hyperactive stress response (Alastalo, Raikkonen et al. 2009) which may in turn heighten the risk for CVD (Sumanen, Koskenvuo et al. 2005; Alastalo, Raikkonen et al. 2009). Thus, since women have been shown to have a higher reactivity to chronic stress, the experience of childhood traumatic events may heighten the risk for CVD among pre-menopausal women when compared to age-matched men

Since CVD is the leading cause of death among women in developed countries (Mehta 2011) it is important to investigate the risk factors which may perpetuate the disease among women. In addition, childhood trauma has shown an increasing trend over time, with this increase being more pronounced among women than among men (Thompson and Cui 2000). Thus, the impact of childhood trauma on CVD may be an association that is particularly important to investigate for women. Few prospective studies have explored the association between childhood traumatic events and CVD. In addition, there do not seem to be any studies to date that have assessed this association in the Canadian population or sex differences in the relationship between childhood traumatic events and CVD as a primary analysis.

1.4. Theoretical Framework: The Allostatic Load Hypothesis

The effect of exposure to early life stressors on adverse health outcomes can be explained through the allostatic load hypothesis. Allostasis is the response to stress which is short-term and adaptive (Mcewen and Stellar 1993). The allostatic load hypothesis refers to the long term negative physiological effects of chronic over-activity or under-activity of the adaptive systems in the body that result from repeated or chronic stress (Mcewen and Stellar 1993). There are two main systems that regulate the stress response. These include the Autonomic Nervous System (ANS) and the Hypothalamic-Pituitary-Adrenal Axis (HPA).

The ANS can be divided into two subsystems: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS

releases adrenaline into the system, initiating the response to stress (McEwen 1998). The SNS works in tandem with the PNS. The PNS acts to relax the stress response after its activation by the SNS. If the stressor is acute, our biological systems can return to homeostasis. However, if the stress is chronic, the body has trouble deactivating the SNS and remains in a state of hyper-arousal. Overexposure to adrenaline over time can lead to allostatic load and negatively affect the cardiovascular system through prolonged elevation of blood pressure (McEwen 1998; Lewington, Clarke et al. 2002).

The HPA axis is a response to stress in which the hypothalamus releases corticotrophin-releasing factor (CRF) as the initial reaction to stress (Heim and Nemeroff 2001). CRF binds to the pituitary gland which then releases adrenocorticotropic hormone (ACTH) into the bloodstream (McEwen 1998). ACTH is transported through the bloodstream to the adrenal gland, which then releases cortisol (a glucocorticoid) into the bloodstream. Atrophy of the hippocampus has been found to occur as a result of chronic psychosocial stress (Magarinos, McEwen et al. 1996). Since the hippocampus plays a role in shutting off the HPA stress response, its atrophy impairs negative feedback, which leads to an HPA axis response to stressful stimuli that is more prolonged (Jacobson and Sapolsky 1991; Herman and Cullinan 1997). Elevated cortisol levels for prolonged periods of time as a result of persistent HPA axis activation may then lead to a redistribution of body fat (resulting in abdominal obesity), hypertension, elevated lipoprotein levels, and type II diabetes, which are all risk factors for CVD (Howlett, Rees et al. 1985; Wong and Wong 2002).

1.5. Chronic Stress: Impact on Childhood Trauma and CVD

1.5.1. Chronic Stress and CVD

Psychological stress has been linked to CVD morbidity and mortality through the increases in heart rate and arterial pressure that it causes (Lucini, Norbiato et al. 2002). It has also been suggested that abdominal fat accumulation may occur as a result of chronic stress (Bjorntorp 1991). Chronic cortisolemia, a result of HPA axis activation (Saketos, Sharma et al. 1993) influences a redistribution of stored energy toward the intra-abdominal region. This is because higher blood flow, more cells per mass units, and more glucocorticoid receptors can be found in visceral adipose tissue (Vale 2005). Thus abdominal fat is influenced to a greater extent by glucocorticoids than subcutaneous adipose tissue (Vale 2005). Abdominal obesity is in turn a risk factor for CVD (Lapidus, Bengtsson et al. 1984; Rexrode, Carey et al. 1998; Yusuf, Hawken et al. 2004).

1.5.2. Childhood Trauma as a Chronic Stressor

Since childhood traumatic events rarely occur only once, and are often unpredictable, stress as a result of childhood trauma is often prolonged. In these situations, the child may feel that they cannot predict or control their surroundings. As a basic component of human survival, the need to protect oneself from harm may cause people to seek to control over their environments. The inability to control or predict possibly adverse events in ones immediate environment has been found to be very distressing in both human and animal studies (Abramson, Seligman et al. 1978; Mineka and

Kihlstrom 1978; Foa, Steketee et al. 1989). The stress of waiting for the unpredictable or uncontrollable event may make it difficult to turn off the stress response. Supporting this is evidence which shows that the HPA axis and autonomic nervous system overreact in animals that have experienced early unpredictable stress (Meaney, Tannenbaum et al. 1994). This chronic stress can lead to adverse effects on the psychological development of a child.

Experiences of trauma during childhood may lead to permanent changes in the stress response (Heim and Nemeroff 2001). These permanent changes may occur because high levels of catecholamines and cortisol in the developing brain could negatively affect brain development through the inhibition of neurogenesis, faster loss of neurons, and delays in myelination (De Bellis 2002). This means that childhood trauma is a chronic stressor that may have more persistent effects on stress reactivity in adulthood than chronic stressors that occur in adulthood. This is supported by research which suggests that once traumatized, children have been found to have a higher likelihood of being diagnosed with PTSD than adults (De Bellis 2002).

Research has shown that permanent changes to the stress response can occur as a result of experiencing stressful events during childhood. Evidence shows that childhood trauma is associated with persistent changes in HPA axis function (Heim, Newport et al. 2000; De Bellis 2002). For example, elevated cortisol levels have been found in children who have been institutionalized when compared to children who have not been institutionalized (Carlson and Earls 1997). This alteration of HPA axis functioning due to early trauma has

also been found in animal studies (Plotsky and Meaney 1993; Meaney, Tannenbaum et al. 1994; Suomi 1997; van Oers, de Kloet et al. 1998).

1.6. Link between Childhood Trauma and CVD

1.6.1. Effect of Childhood Trauma on CVD

Childhood trauma may thus lead to a higher risk of CVD by influencing a hyperactive stress response. In support of this possibility is evidence which shows that those who experience childhood trauma have higher blood pressure than those who do not (Luecken 1998; Alastalo, Raikkonen et al. 2009). High blood pressure is in turn a risk factor for CVD (Kannel 1995; Wong and Wong 2002). Obesity has also been found to be associated with childhood trauma (Felitti 1991; Felitti 1993; Williamson, Thompson et al. 2002). Overweight and obesity are also risk factors for CVD (Wong and Wong 2002; Wannamethee, Shaper et al. 2005).

Childhood trauma has been found to increase the likelihood towards CVD (Sumanen, Koskenvuo et al. 2005; Loucks, Almeida et al. 2011). In a study that used data from the Health and Social Support (HeSSup) study, which is a longitnudinal study that consists of 25901 respondents representative of the Finnish population, an increased risk of CVD was found among those who reported childhood adversities (Korkeila, Vahtera et al. 2010). Another study that looked at the association between childhood family psychosocial environment and the risk for coronary heart disease using a longitudinal study that consisted of 5115 Americans, found a positive association between these two factors (Loucks, Almeida et al. 2011) Also, in a

study using the ACE study data, a dose-response relationship between adverse childhood experiences and ischemic heart disease was found (Dong, Giles et al. 2004).

1.6.2. Sex Differences in the Link between Childhood Trauma and CVD

Stress reactivity may act as an underlying mechanism in the link between adverse childhood experiences and cardiovascular disease. Animal models show that women have a more hyperactive response to chronic stress than men (Handa 2007). Both human and animal data suggest that in females, the HPA axis is more reactive to stress than it is in males (Mccormick, Smythe et al. 1995; Weiss, Longhurst et al. 1999). However, the literature suggesting a more reactive stress response among females is more consistent for animal data than it is for human data (Kudielka and Kirschbaum 2005). Most studies that have assessed psychological stress in humans have found either no significant sex differences in HPA axis activity or higher cortisol responses among men to controlled lab stress tasks or acute real-life stressors such as academic exams (Kudielka and Kirschbaum 2005).

The variability in the literature concerning sex differences in HPA axis activity may be a result of the type of stressor being assessed. For example, animal models show that women have a more hyperactive response to chronic stress than men (Handa 2007). In addition, women have been found to show a greater stress response to interpersonal stressors. For example, marital conflict, and social interaction challenges have been found to elicit a greater HPA axis response among women than among men (Stroud, Tanofsky-Kraff et al. 2000;

Kudielka and Kirschbaum 2005; Whited 2009). On the other hand, men but not women have been found to have significant cortisol increases to situations involving intellectual inferiority and performance failures (Stroud, Tanofsky-Kraff et al. 2000).

One explanation for sex differences in the HPA axis stress response is differences in the cognitive processing of psychological stress. For example, activation of the amygdala has been found to differ by sex in response to emotionally arousing film clips (Cahill, Haier et al. 2001; Killgore and Yurgelun-Todd 2001).

It is suggested that sex differences in stress reactivity may also be influenced by hormones. Evidence suggests that estrogen may increase CRH gene expression in he hypothalamus (Vamvakopoulos and Chrousos 1993), and that glucocorticoid-dependent negative feedback on the HPA axis is impaired by estrogen (Weiser and Handa 2009). This is supported by evidence which shows that estrogen causes an increased cortisol response to stress (Handa, Burgess et al. 1994) and that more women than men develop PTSD when exposed to a traumatic event (Seeman 1997). Also, research shows that the HPA axis is activated by estrogen and inhibited by testosterone in rodents (Putnam, Chrousos et al. 2005). In line with these findings, the link between perceived mental stress and cardiovascular disease has been found to be particularly marked among women (Iso, Date et al. 2002).

Since chronic stress affects CVD (Low, Salomon et al. 2009), and women are more sensitive to chronic stress than men (Handa 2007), women who experience adverse childhood events may be more likely to develop CVD than men who experience adverse childhood events. There is evidence to suggest that this may be the case. For example, in a study assessing the relationship between childhood trauma and cardiovascular disease, it was found that the risk for cardiovascular disease was greater among women than among men (Korkeila, Vahtera et al. 2010). In addition, the risk for CVD among these women was more than three times higher than that of women who had not reported adverse childhood experiences. A dose-response relationship between childhood trauma and CVD was also found among women, and after adjusting for depression this risk persisted. This association also persisted after adjusting for age, suggesting that hormonal changes in women are unlikely to explain this effect.

The authors of this study suggest that this differential risk of CVD between women and men among those who have experienced early childhood trauma may be explained by gender-dependent differences in HPA axis performance and resulting differences in stress reactivity. Prospective studies assessing differences between women and men in CVD vulnerability due to long-term stress, as well as the link between childhood trauma and CVD are limited (Korkeila, Vahtera et al. 2010).

1.7. Measuring Childhood Trauma

1.7.1. Scales

Numerous scales have been used to measure childhood trauma. Some of these measures for childhood trauma include the Childhood Trauma Interview (CTI), the Adverse Childhood Experiences (ACE) score, the Retrospective Assessment of Traumatic Experiences (RATE), the Child Abuse and Trauma Scale (CATS), the parent-to-child version of the Conflict Tactics Scale (CTSPC), the Parental Bonding Instrument (PBI), the Childhood Experience of Care and Abuse (CECA.Q) and the Childhood Trauma Questionnaire (CTQ). Some of the most used instruments to assess childhood trauma appear to be the PBI, the CECA.Q and the CTQ (Pietrini, Lelli et al. 2010).

The Childhood Trauma Interview assesses childhood interpersonal trauma (Fink, Bernstein et al. 1995). The ACE score measures childhood trauma by assessing abuse (emotional, physical and sexual), neglect (emotional and physical), and household dysfunction (including substance abuse, domestic violence, mental illness, having a criminal household member, and parental divorce) (Dong, Giles et al. 2004). The RATE measures loss, physical abuse, sexual abuse and verbal abuse (Gallagher, Flye et al. 1992). The CAT scale is a 38-item scale which asks about sexual, physical, and psychological mistreatment, physical or emotional neglect and experiencing a negative home environment as a child or adolescent (Sanders and Beckerlausen 1995). The CTSPC asks parents about whether their child has experienced nonviolent discipline, psychological aggression, physical

assault, neglect and sexual abuse (Mackinnon, Henderson et al. 1991). The PBI includes a care scale which assesses affection and warmth or rejection and coldness or indifference as well as a protection scale which assesses overprotection, control, intrusion and encouragement of psychological dependence, or the allowance and promotion of independence and autonomy (Mackinnon, Henderson et al. 1991). The CECA questionnaire assesses physical abuse, sexual abuse, antipathy and neglect (Smith, Lam et al. 2002). Lastly, the CTQ measures emotional, physical, and sexual abuse, as well as emotional and physical neglect (Paivio and Cramer 2004).

1.7.1. General Issues

One problem concerning the instruments used to measure childhood trauma is that they are not designed to be age specific (Strand, Sarmiento et al. 2005). There has also been controversy with regards to the validity of information from retrospective reports (Widom and Morris 1997). The use of retrospective recall concerning childhood information has particularly been questioned due to the effects of mood on the memory of autobiographical information (Paris 1995). Fallibility of memory concerning traumatic experiences such as childhood maltreatment (Williams 1994; Widom and Morris 1997; Brennen, Hasanovic et al. 2010), measurement bias (Fergusson, Horwood et al. 2000), and intentionally false reporting (Widom and Morris 1997), are other suggested problems in establishing accuracy in the retrospective recall of childhood traumatic events. Despite these criticisms of the reliability and validity of retrospective reporting, many studies have found it to be accurate

for childhood maltreatment (Paivio 2001). Many of these questionnaires have acceptable psychometric properties (Roy and Perry 2004).

1.8. Factors Associated with Childhood Trauma and CVD

1.8.1. Demographic Factors

Socioeconomic status (Zielinski 2009) has been associated with childhood trauma. Aging has been associated with a loss of efficiency in the ability to retrieve autobiographical information (Borrini, Dallora et al. 1989). Socioeconomic status (McGrath, Matthews et al. 2006; Song, Ferrer et al. 2006; Tarasiuk, Greenberg-Dotan et al. 2006) and age (Booth, Kapral et al. 2006; Pinto 2007; Sniderman and Furberg 2008) have also been linked to CVD and CVD risk. Since menopausal women have a higher risk for CVD than pre-menopausal women, controlling for age may prevent hormonal changes in women from confounding the effect of childhood trauma on CVD among women when compared to men (Korkeila, Vahtera et al. 2010). Parental history of CVD also heightens the risk for CVD (Shear, Webber et al. 1985). Those who have parental history of heart disease have been found to be two to seven times more likely to have heart disease (Shear, Webber et al. 1985).

1.8.2. Health Risk Behaviors

Childhood trauma is linked with poor diet, low levels of physical activity, smoking, and alcohol abuse (Felitti, Anda et al. 1998; Anda, Croft et al. 1999). It is suggested that the decision to engage in these risk behaviors may be a coping mechanism to deal with the stress of having experienced childhood

trauma (Felitti, Anda et al. 1998; De Bellis 2002). Smoking and alcohol abuse further heighten cortisol levels, which may further perpetuate these risky health behaviors (De Bellis 2002; Campbell, Moffatt et al. 2008). Poor diet (Wilcox, Parra-Medina et al. 2001), low levels of physical activity (Wilcox, Parra-Medina et al. 2001; Maximova, O'Loughlin et al. 2009), smoking (Jee, Park et al. 2007; Campbell, Moffatt et al. 2008), and alcohol abuse (Murray, Connett et al. 2002) are also all associated with CVD.

1.8.3. Stressful Life Events

Experiencing abuse or neglect in childhood seems to lead to a greater emotional and psychological sensitivity to stress in adulthood (Heim, Newport et al. 2008; McLaughlin, Green et al. 2010). This is supported by evidence showing that adults who have experienced childhood traumas are more likely than those who have not experienced these traumas to develop psychiatric disorders when confronted with subsequent life stressors (McLaughlin, Green et al. 2010).

Childhood traumatic events may affect hippocampal structure, leading to this sensitivity to recent stressful life events. The hippocampus acts to inhibit the HPA axis response to stress (McEwen 1998). It has high levels of cortisol receptors (McEwen, Dekloet et al. 1986) and is thus particularly sensitive to the effect of chronic stressful experiences (Fuchs and Flugge 1998; McEwen 1999; Sapolsky 1999; Lee, Ogle et al. 2002; Miller and O'Callaghan 2005). This atrophy of the hippocampus caused by stress further perpetuates over-activity of the stress response (Sapolsky 2001). In support of

this evidence, it has been found that among individuals with post-traumatic stress disorder, traumatic events that occurred earlier in life and for a longer period of time are predictive of decreased hippocampal volume (Gurvits, Shenton et al. 1996; Vythilingam, Heim et al. 2002; Bremner, Vythilingam et al. 2003; Kitayama, Vaccarino et al. 2005). This hypersensitivity to stress as a result of decreased hippocampal volume may in turn worsen the affect of stressful stimuli on the risk for CVD among those who have experienced childhood trauma.

Stressful life events have been linked to the development of CVD. For example, work stress has been associated with about a 50% higher risk for coronary heart disease (Kivimaki, Vahtera et al. 2008). Also, neighbourhood stress has been associated with a higher likelihood for CVD mortality (Fujino, Tanabe et al. 2011). Those with coronary heart disease have been found to have significantly more stressful life events than those who do not have coronary heart disease (Rafanelli, Roncuzzi et al. 2005).

1.8.4. Depression

Childhood trauma has been associated with depression (Felitti, Anda et al. 1998; Bradley, Binder et al. 2008; Gilbert, Widom et al. 2009). There is evidence to suggest that for women, the experience of childhood sexual abuse is associated with 60% of lifetime depression, and for men it is associated with 39% of lifetime depression (Cutler and Nolenhoeksema 1991).

The stress sensitization, stress amplification, and stress inoculation hypotheses expand on the association between childhood trauma and depression in adulthood. The stress sensitization hypothesis states that those who experience childhood trauma may have an increased vulnerability to the effects that stressful life events in adulthood have on the development of depression (Hammen, Henry et al. 2000). Research suggests that childhood trauma lowers ones threshold for withstanding stress later in life, leading to a higher risk of psychopathology after experiencing mild stressful life events among those who have experienced childhood traumatic events when compared to those that have not experienced childhood traumatic events (Hammen, Henry et al. 2000; Dougherty, Klein et al. 2004; Kendler, Kuhn et al. 2004; Harkness, Bruce et al. 2006; Espejo, Hammen et al. 2007; Rudolph and Flynn 2007; McLaughlin, Conron et al. 2010). Studies have found evidence for the stress sensitization hypothesis concerning the impact of stressful life events on heightening the influence of childhood trauma on depression (Hammen, Henry et al. 2000; McLaughlin, Conron et al. 2010; Colman, Garad et al. 2012) PTSD (McLaughlin, Conron et al. 2010), anxiety disorders (McLaughlin, Conron et al. 2010) perceived stress (McLaughlin, Conron et al. 2010) and recurrence of bipolar disorder (Dienes, Hammen et al. 2006).

The stress amplification model suggests that those who have experienced adversities in childhood would have a higher risk for psychopathology after severe stressful life events later in life, but not mild stressors when compared to those who have not experienced childhood

adversities (Rudolph and Flynn 2007). There is also evidence for this possibility in the literature (Abela 2001; Hankin and Abramson 2001; Eley, Sugden et al. 2004; Rudolph and Flynn 2007).

However, the stress inoculation hypothesis suggests that depression may be less likely to develop among those who experience stressful life events and have also experienced adversity in childhood (Rudolph and Flynn 2007). This hypothesis suggests that experiencing adversity in childhood may act as a buffer against the adverse effect of stressful life events on depression (Rudolph and Flynn 2007). There is also some evidence to support this possibility (Boyce and Ellis 2005).

Depression has also been linked to cardiovascular disease. It has been suggested that this link between depression and CVD is due to a heightening of the inflammatory response caused by depression (Lesperance, Frasure-Smith et al. 2004; Empana, Sykes et al. 2005). Even mild elevations in inflammation have been found to influence cardiovascular disease risk (Ridker, Cushman et al. 1997). Adolescent-onset depression has also been associated with a higher BMI in adulthood (Gaysina, Hotopf et al. 2011), which is in turn a risk factor for CVD (Kannel 1995; Wong and Wong 2002).

Research also shows an increase in both coronary heart disease (CHD) development (Ferketich, Schwartzbaum et al. 2000) and mortality (de Leon, Krumholz et al. 1998; Wassertheil-Smoller, Shumaker et al. 2004) among depressed patients. In addition, studies show that the risk of having a cardiac

event in depressed patients is 2-5 times higher than that of non-depressed patients (Nicholson, Kuper et al. 2006; Rutledge, Reis et al. 2006).

1.8.5. High Blood Pressure

There is evidence which shows that those who experience childhood trauma have higher blood pressure than those who do not experience childhood trauma (Luecken 1998; Alastalo, Raikkonen et al. 2009). High blood pressure is also a known risk factor for cardiovascular disease (Kannel 1995; Wong and Wong 2002).

1.8.6. Overweight/Obesity

Obesity has also been found to be associated with childhood trauma (Felitti 1991; Felitti 1993; Williamson, Thompson et al. 2002)It has also been associated with cardiovascular disease after adjustment for cholesterol levels and blood pressure (Wong and Wong 2002; Wannamethee, Shaper et al. 2005).

1.9. Conceptual Framework

To illustrate the findings from the literature outlined above which will serve as the basis for the analyses undertaken in this study, a summary of the effect that SES, age, family history of heart disease, gender, stressful life events, depression, and health risk behaviours may have on the relationship between childhood trauma and CVD have been included in a diagram (below).

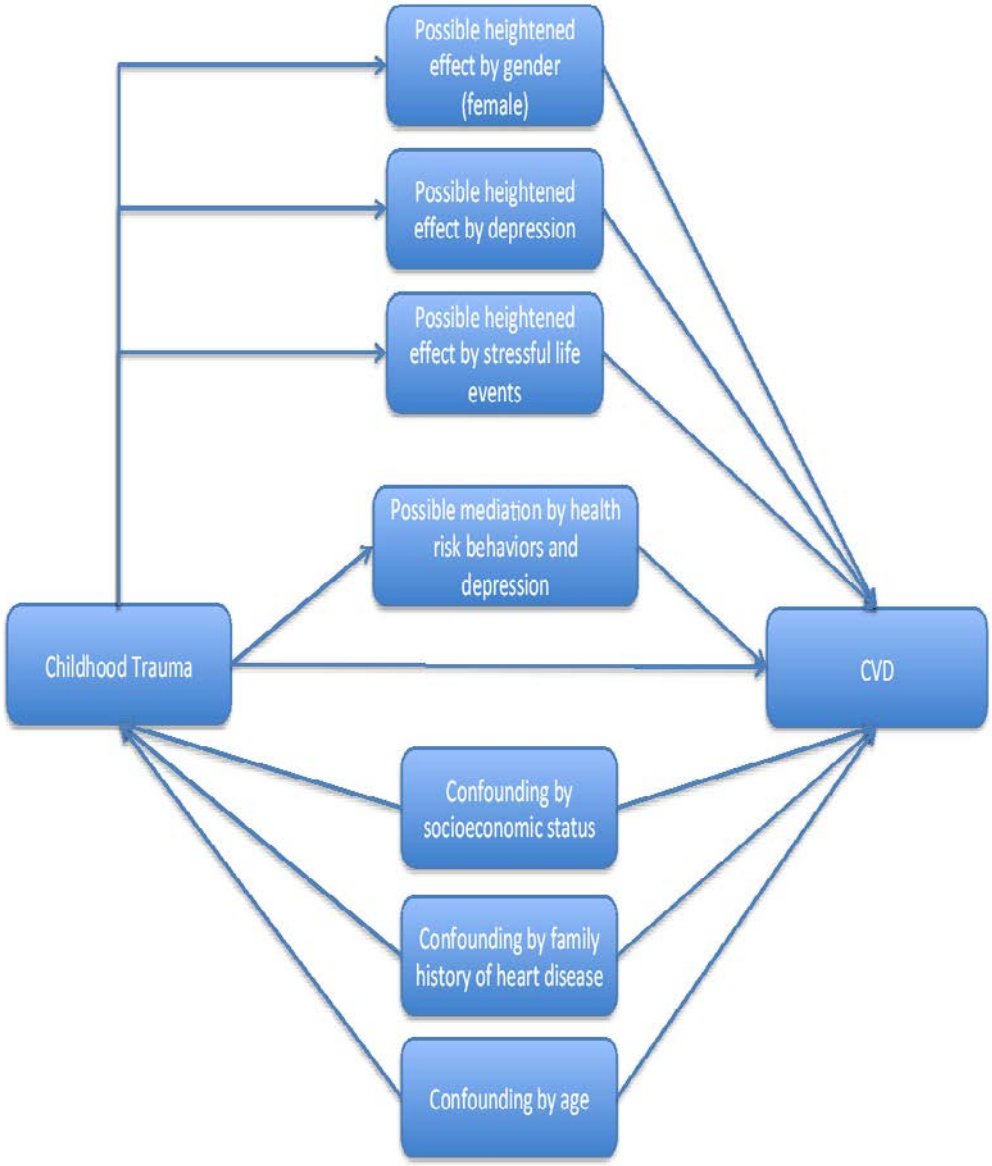

Figure 1: Conceptual Framework for Relationship between Childhood Trauma and CVD

1.10. Gaps in Research

Although a relationship between childhood trauma and CVD has been established in the literature, there have been no studies to date that have addressed this association in the Canadian population. There is also a paucity of research addressing sex differences in this relationship and possible explanations for these differences. Particularly, no studies to date have explored the effect of sex in moderating the relationship between childhood trauma and CVD. A previous study has shown a larger association between childhood trauma and CVD among women than among men, but did not test this difference between sexes statistically (Korkeila, Vahtera et al. 2010).

There is evidence that childhood trauma may lead to a hypersensitivity to stress (Meaney, Tannenbaum et al. 1994; Carlson and Earls 1997; Heim, Newport et al. 2000; Heim and Nemeroff 2001; De Bellis 2002). Evidence also suggests that vulnerability to stress observed among those who have experienced childhood trauma may be heightened by stressful life events (McLaughlin, Green et al. 2010). Also, it is possible that depression may lead to HPA axis dysfunction (Neigh and Nemeroff 2006). The allostatic load hypothesis further suggests that HPA axis dysfunction may increase the risk for CVD (McEwen 1998). This suggests that stressful life events and depression may heighten the influence of childhood trauma on CVD. Since estrogen is suggested to impact HPA axis dysfunction, this effect may be higher among women than among men (Handa, Burgess et al. 1994; Weiser and Handa 2009). However, this possibility has not previously been explored.

In addition, health risk behaviors and depression may be intermediate factors in the relationship between childhood trauma and CVD. It is suggested that those who experience childhood trauma are more likely to engage in health risk behaviors (Felitti, Anda et al. 1998; Campbell, Moffatt et al. 2008) and are also more likely to be depressed (Bradley, Binder et al. 2008). Also, many health risk behaviors have been associated with CVD (Wilcox, Parra-Medina et al. 2001; Murray, Connett et al. 2002; Jee, Park et al. 2007; Maximova, O'Loughlin et al. 2009). Depression has also been associated with CVD (Nicholson, Kuper et al. 2006; Rutledge, Reis et al. 2006). The effect of health risk behaviors and depression in mediating the relationship between childhood trauma and CVD has also not been previously addressed in the literature.

1.11. Statement of Problem

Childhood trauma is highly prevalent in the Canadian population and is becoming more common as time goes by (Thompson and Cui 2000). The allostatic load hypothesis suggests that chronic stressors lead to adverse physical health consequences (Mcewen and Stellar 1993). Corroborating with the allostatic load hypothesis is research that suggests that childhood trauma is a risk factor for CVD (van Oers, de Kloet et al. 1998; Dong, Giles et al. 2004; Korkeila, Vahtera et al. 2010). Since estrogen is suggested to perpetuate HPA axis dysregulation leading to a hypersensitivity to stress (Handa, Burgess et al. 1994; Weiser and Handa 2009), the association between childhood trauma and CVD may be particularly heightened among women.

1.12. Purpose of Study

The purpose of this study is to address sex differences in the relationship between childhood trauma and CVD and possible pathways and mechanisms for these differences.

1.13. Public Health Implications and Significance of Study

The significance of this research is to develop a greater understanding of the influence of early life traumatic experiences on CVD. It is also to inform public health policy so that possible emerging risk groups such as women who experience childhood trauma can be considered to a greater extent in both clinical and public health practice.

There have been no studies to date that have explored the association between childhood trauma and CVD in the Canadian population. In addition, there are few studies that have examined sex differences in the association between childhood trauma and CVD, and none that have assessed this as a primary analysis.

1.14. Research Objectives

1.14.1. Primary Objective

The proposed research will assess whether women who experience childhood trauma are more likely than men who experience childhood trauma to have CVD when controlling for age and socioeconomic status (SES).

It is expected that the effect of childhood trauma on CVD will be stronger among women than among men because females have been found to have a more hyperactive response to stress than males (Mccormick, Smythe et al. 1995; Weiss, Longhurst et al. 1999; Handa 2007). Chronic stress has been linked to CVD due to its perpetuation of CVD risk factors such as prolonged elevation of blood pressure and abdominal obesity (Howlett, Rees et al. 1985; McEwen 1998; Lewington, Clarke et al. 2002; Wong and Wong 2002). Thus, chronic stressors such as childhood trauma may have a stronger influence on CVD among women when compared to men after controlling for possible confounders.

1.14.2. Secondary Objectives

One of the secondary objectives was to investigate whether women who experience childhood trauma are more likely than men who experience childhood trauma to have CVD if they have recently experienced stressful life events or depression when controlling for age, and SES. Since evidence suggests that traumatic events may heighten the stress response to a greater extent among women than men (Seeman 1997), it was hypothesized that the impact of childhood trauma on CVD after the experience of recent life stressors and depression will be greater among women than among men after controlling for possible confounders.

The other secondary objective was to address whether health risk behaviours or depression mediate the relationship between childhood trauma and CVD and whether this is heightened among women when compared to

men. It was hypothesized that since health risk behaviours may be used as a coping mechanism to deal with stress due childhood trauma (Felitti, Anda et al. 1998; De Bellis 2002), and depression has been associated with childhood trauma to a greater extent among women than among men (Cutler and Nolenhoeksema 1991), the mediation effects of health risk behaviours and depression on the relationship between childhood trauma and CVD would be heightened among women when compared to men.

1.14.3. Hypotheses

Hypothesis 1: Those who report childhood trauma will be more likely than those who do not report childhood trauma to have CVD or be at higher risk for CVD (due to high blood pressure or overweight/obesity).

Hypothesis 2: Women who report childhood trauma will be more likely than men who report childhood trauma to have CVD or be at higher risk for CVD (due high blood pressure or overweight/obesity).

Hypothesis 3: Childhood trauma will be more likely to lead to CVD and higher risk for CVD (high blood pressure or overweight/obesity) among those who report recent stressful life events when compared to those who do not report recent stressful life events. This effect will be higher among women than among men.

Hypothesis 4: Depression will heighten the impact of childhood trauma on CVD and higher risk for CVD (high blood pressure or overweight/obesity), with this effect being higher among women than among men.

Hypothesis 5: Depression may mediate the relationship between childhood trauma and CVD, with this effect being stronger among women when compared to men.

Hypothesis 6: Health risk behaviors may mediate the relationship between childhood trauma and CVD, with this effect being stronger among women when compared to men.

1.15. Structure of this Thesis

To address the research questions outlined above, a study was conducted using data from the National Population Health Survey (NPHS) which is a prospective study conducted by Statistics Canada. In the second chapter of this thesis, the methodology used for this study will be discussed including information concerning the sample for this study, the measures used for this study and the statistical analyses that were conducted. The third chapter will address the results of this study. The last chapter will integrate the findings of this study with previous research, outline the general implications of the findings, outline the strengths and limitations of this study and discuss future directions.

CHAPTER 2.0 METHODS

2.1. Data Source: National Population Health Survey

This research used data from the National Population Health Survey (NPHS), which is a prospective study conducted by Statistics Canada to collect longitudinal information regarding the health and socio-demographic characteristics of the Canadian population. The first cycle of data collection was in 1994/1995, and participants were followed up every two years. During the first three cycles of the NPHS (1994/95 to 1998/99), the survey was conducted both cross-sectionally and longitudinally. However, beginning in cycle four (2000/2001) the NPHS Household component became longitudinal only, with the cross-sectional component being taken over by the Canadian Community Health Survey (CCHS).

The NPHS Household component has followed a nationally representative sample of 17,276 Canadians since 1994. This sample has been contacted every two years, with the most recent data collection in 2008/09. The attrition rate in the first cycle (1994/95) of the NPHS was 9.3% (Statistics Canada 2010a). The cumulative attrition rate by cycle eight (2008/09) was 42% (Statistics Canada 2010a).

Although the target population of the NPHS included household residents in the ten Canadian provinces in 1994/1995, residents of some remote areas in Ontario and Quebec were excluded (Statistics Canada 2010a). Residents of health institutions, those living on Native reserves and Crown

lands, and full-time Canadian Forces members who lived on Canadian Forces bases were also excluded from the sample (Statistics Canada 2010a).

The NPHS uses a stratified multi-stage survey design (Statistics Canada 2010a). In the first stage, geographic and/or socio-economic strata were formed and within each stratum, approximately six clusters were selected (Statistics Canada 2010a). These clusters were usually Census Enumeration Areas and were selected with Probability Proportional to Size (Statistics Canada 2010a). In the second stage, a sample of dwellings was chosen within each cluster (Statistics Canada 2010a). Due to this complex multi-stage survey design, the bootstrap method was required for the purposes of this study to calculate variance estimates.

2.2. Study Design

This study used data from the NPHS to assess the impact of childhood trauma on CVD in a retrospective cohort design.

2.3. Study Population and Exclusion Criteria

The subjects for this study included 6881 members of Statistics Canada's National Population Health Survey (NPHS) between the ages of 18 and 49 who reported on seven childhood traumatic events at baseline (1994/1995) including parental divorce, physical abuse, parental substance abuse, long hospital stay, being sent away from home for wrongdoing, parental unemployment, and frightening experiences that were thought about for years after.

Those who were above the age of 49 at baseline were excluded from the sample because childhood trauma is retrospectively assessed in the NPHS, and older participants may have more trouble accurately remembering childhood traumatic events. Age has been associated with impairment of recall (Erngrund, Mantyla et al. 1996).

Those above the age of 49 were also excluded to reduce the possibility of survivor bias. The effect of early life exposures such as smoking on heart disease has been found to decline with age (The American Heart Association 1978; Kannel and Larson 1993; Tate, Manfreda et al. 1998). For example, although at younger ages disadvantaged groups show greater mortality, there is a reversal in this pattern in old age (Corti, Guralnik et al. 1999; Thornton 2004). Such attenuated associations in old age are suggested to be the result of selective survival rather than truly diminished effects (Vaupel and Yashin 1985; Mohtashemi and Levins 2002). Also, in the Framingham study, the impact of smoking on risk for coronary heart disease was significant for men who were between the ages of 35 and 64 but not for men between the ages of 65 and 94 (Kannel and Larson 1993). In 2008/09 our sample is between the ages of 32 and 63.

Those who had inconsistent reports of childhood traumatic events when comparing reports from 1994/95 (cycle 1) and 2008/09 (cycle 8) were also excluded from the analyses. Those who consistently reported childhood traumatic events were those who reported either “yes” or “no” for having

experienced childhood trauma in both cycle 1 and cycle 8. Thus, those who initially reported childhood traumatic events (cycle 1) but did not report their occurrence 2008/09 (cycle 8) and those who did not initially report any childhood traumatic events (cycle 1) but reported their occurrence 2008/09 (cycle 8) were excluded from the sample.

Members of the NPHS who were inconsistent in their reporting of childhood traumatic events were excluded in order to reduce possible bias due to selective reporting of childhood trauma influenced by current mental state. For example, amplification of recall for perceived life threats have been found among those with a lack of post-traumatic stress syndrome (PTSD) symptom improvement when compared to those who did show PTSD symptom improvement (Heir, Piatigorsky et al. 2009).

2.4. Measures

The following describes measures from the NPHS that were used for this study and the cycles in which they were used.

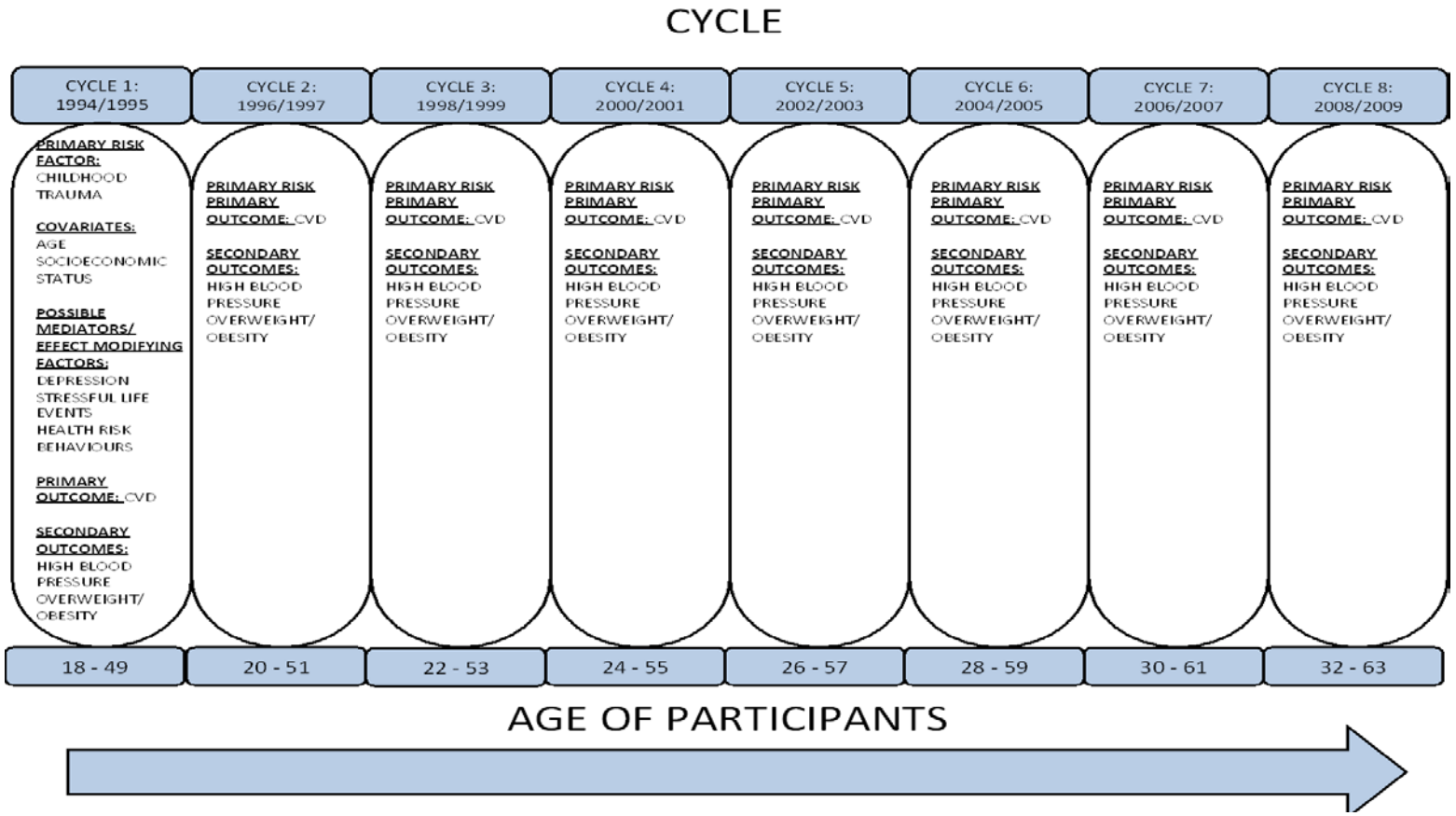

Figure 2: Flow Diagram for NPHS Data Use

2.4.1. Exposure of Interest: Childhood Traumatic Events

Childhood trauma at baseline was the primary risk factor for this study. It was assessed in the NPHS using the "Trauma Index" (Thompson and Cui 2000). Participants were asked whether they had experienced seven traumatic events as a child or teenager, before they moved out of the house. Members of the NPHS were asked to answer the following questions to assess childhood traumatic events: (1) "did you spend 2 weeks or more in the hospital?" (2) "did your parents get a divorce?" (3) "did your father or mother not have a job for a long time when they wanted to be working?" (4) "did something happen that scared you so much you thought about it for years after?" (5) "were you sent away from home because you did something wrong?" (6) "did either of your parents drink or use drugs so often that it caused problems for the family?" and (7) "were you ever physically abused by someone close to you?" (Statistics Canada 2010b).

For the purposes of this study a categorical variable for childhood trauma was created with the following categories: (1) those who reported no childhood traumatic events, (2) those who reported one or two childhood traumatic events and (3) those who reported three or more childhood traumatic events. Childhood trauma was categorized in this way because previous studies have found strong graded relationships between childhood trauma and adverse psychological and physical health outcomes (Anda, Croft et al. 1999; Dube, Anda et al. 2002; Dong, Dube et al. 2003). In addition, many forms of childhood maltreatment co-occur (Dong, Anda et al. 2004), and assessing the cumulative influence of these interrelated events rather than one childhood

traumatic event is suggested to be a more appropriate method for investigating the effects of childhood trauma (Dong, Anda et al. 2004).

2.4.2. Primary Outcome of Interest: Cardiovascular Disease

The cumulative incidence of CVD between 1994/95 and 2008/09 was used as the primary outcome. Self-reports of heart disease, self-reported use of heart medication, and deaths due to CVD were combined to assess CVD. Heart disease was measured every two years for all members of the NPHS with the question "do you have heart disease?" (Statistics Canada 2010b). This was asked of all NPHS respondents (Statistics Canada 2010b). The use of heart disease medication was assessed in the NPHS by asking "in the past month, did you take medicine for the heart?" (Statistics Canada 2010b). This question was asked of all respondents in the NPHS above the age of 12 (Statistics Canada 2010b). The possible responses for both of these questions were "yes", "no" and "don't know" (Statistics Canada 2010b).

The causes of death of members from the NPHS are coded using the International Statistical Classification of Diseases and Related Problems (ICD-10) (Statistics Canada 2010a). The death of NPHS members is coded after attaining confirmation with regards to both the dates and causes of death using the Canadian Vital Statistics Database (Statistics Canada 2010a). ICD-10 codes for ischemic heart disease (I20-I25) or heart failure (I50-150.9) were used to classify participants as having died due to CVD.

2.4.3. Secondary Outcomes of Interest: High Blood Pressure and Overweight/obesity

High Blood Pressure

High blood pressure was measured in the NPHS every two years by self-reported diagnosis for all respondents 12 years of age or older (Statistics Canada 2010b). Those who were included as having high blood pressure in the study were those who reported "yes" to the question "do you have high blood pressure?" (Statistics Canada 2010b). The cumulative incidence of high blood pressure was used for the purposes of this study.

Overweight/Obesity

The NPHS also assesses overweight and obesity in every cycle (Statistics Canada 2010b). Body Mass Index was derived in the NPHS based on self-reported height, weight and sex (Statistics Canada 2010c). BMI was assessed for all members of the NPHS, with the exception of pregnant women (Statistics Canada 2010b). The body mass index (BMI) groups included underweight (BMI less than 18.4kg/m^2) normal weight (BMI between 18.5kg/m^2 and 25kg/m^2), overweight (BMI between 25kg/m^2 and 29.9kg/m^2), and obese (30kg/m^2 or more) (Statistics Canada 2010b).

For the purposes of this study the cumulative incidence of overweight/obesity was used. Overweight and obesity were combined into one category, with underweight/normal weight as the reference category.

2.4.4. Covariates

Age at baseline was controlled for, and used as a continuous variable. Socioeconomic status (SES) at baseline was also controlled for. To assess SES, educational attainment and income adequacy were combined into one dichotomous variable. Although income is a common marker of social standing, health studies have started to use educational level instead as a marker of socioeconomic status (Elo and Preston 1996).

Some reasons for the use of educational attainment as a marker of socioeconomic status are that not all people have an income, and health impairments in adulthood probably affects educational attainment less than employment and income (Elo and Preston 1996). The stability of educational attainment however can also mask changes in the life circumstances of participants (Elo and Preston 1996). Thus, both educational attainment and income adequacy were used to assess SES for the purposes of this study. A combined measure for SES using both income and education has been found to predict risk of death from coronary heart disease better than income or education separately (Bucher and Ragland 1995).

Highest level of education was asked of all respondents and was a derived variable in the NPHS based on answers to the following three questions (1) “excluding kindergarten, how many years of elementary and high school have you successfully completed?” (2) “have you graduated from high school?” and (3) “what is the highest level of education that you have attained?” (Statistics Canada 2010b).

The categories for this variable included (1) less than secondary school education (2) secondary school graduation (3) some post-secondary and (4) post-secondary graduation. This variable was dichotomized for the purposes of this study with those who reported some post-secondary education and post-secondary graduation labeled as “high education” and those who reported less than secondary school education and secondary education as “low education” (Statistics Canada 2010b).

Income adequacy was also asked of all participants and derived in the NPHS using the following question: “what is your best estimate of the total income, before taxes and deductions, of all household members from all sources in the past 12 months?” (Statistics Canada 2010b). Respondents then classified their household income as one of the following: (1) less than $20,000, $20,000 or more, or no income (2) less than $10,000 or $10,000 or more (3) less than $5,000 or $5,000 or more (4) less than $15,000 or $15,000 or more (5) less than $40,000, or $40,000 or more (6) less than $30,000, or $30,000 or more (7) < $50,000, $50,000 to <$60,000, $60,000 to < $80,000, or >$80,000 (Statistics Canada 2010b). These questions were used by the NPHS to create two categories for income adequacy: low income, and middle/high income (Statistics Canada 2010b).

The two variables for educational status and income adequacy were then combined, with those who reported both “low education” and “low income” classified as “low SES”. The reference category was “middle-high

SES" and included those who reported "middle/high income" and "high education" as well as those who reported one of the two, since education (Gardarsdottir, Hardarson et al. 1998) and high income (Andersen, Osler et al. 2003) have both been found to be protective for cardiovascular disease morbidity and mortality.

Family history of heart disease was only assessed in cycle 3 (1998/99) for participants that reported having some knowledge of their birth family's health history (Statistics Canada 2010b). Participants in the NPHS were asked: "did your birth mother ever have heart disease?" and "did your birth father ever have heart disease?" (Statistics Canada 2010b). For the purposes of this study, family history of heart disease was assessed as a dichotomous variable with those who had one or two parents with heart disease coded as having family history of heart disease.

2.4.5. Possible Mediators: Depression and Health Risk Behaviours

Depression

The NPHS assessed depression using an 8-point scale measure: the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD), which has been validated and was developed from the full Composite International Diagnostic Interview (CIDI) (Kessler RC 1998). The larger CIDI is a standardized diagnostic interview, which was designed by the World Health Organization to assess mental health disorders (Wittchen 1994). When compared to the full CIDI, 90% sensitivity and 94%

specificity has been found for classifying major depressive disorder using the CIDI-SF (Kessler RC 1998).

Depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994) is assessed by the CIDI-SFMD by asking about symptoms of depression during the preceding twelve months (Kessler RC 1998). According to the DSM-IV criteria, a major depressive episode is classified by having either depressed mood or loss of interest, in addition to at least 4 other depressive symptoms for a two-week period in the preceding year (American Psychiatric Association 1994). The other 5 depressive symptoms can include (1) change in appetite or weight (2) sleep disturbances (either hypersomnia or insomnia) (3) psychomotor changes such as agitation (e.g. pacing, or inability to sit still) or retardation (e.g. slowed speech, or slowed body movements) (4) fatigue and (5) a sense of worthlessness or guilt (6) diminished ability to think or concentrate (7) recurrent thoughts of death (suicidal ideation or attempt) (American Psychiatric Association 1994). Corresponding to the DSM-IV criteria of 5-9 symptoms to classify a major depressive episode (American Psychiatric Association 1994), a score of 5 or higher on a 0-8 scale using the CIDI-SFMD was considered as having major depression (Kessler RC 1998). Depression was assessed at baseline for the purposes of this study.

Health Risk Behavior: Smoking

Smoking was also assessed at baseline. Categories for self-reported smoking status in the NPHS included smoking “everyday”, “occasionally”, or “not at

all" (Statistics Canada 2010b). This variable was recoded for the purposes of this study as a dichotomous variable combining those who reported smoking daily and occasionally, with those who reported not smoking at all as the reference category.

Health Risk Behavior: Low Physical Activity

The physical activity index is a derived variable in the NPHS based on questions asking whether participants have engaged in 26 different physical activities in the past 3 months including walking for exercise, gardening or yard work, and swimming, as well as the number of times they engaged in these activities and the time spent participating in these activities (Statistics Canada 2010c).

The physical activity index was separated in the NPHS into three categories: active, moderately active, and inactive (Statistics Canada 2010c). Being active is defined as those that average 3.0+ kcal/kg/day of energy expenditure (Statistics Canada 2010c). Being moderately active is defined as those who average 1.5-2.9 kcal/kg/day (Statistics Canada 2010c). Being inactive is defined as those who expend less than 1.5 kcal/kg of energy per day (Statistics Canada 2010c). This variable was assessed at baseline, and was dichotomized for the purposes of this study, with those who reported being active or moderately active combined and used as the reference category.

Health Risk Behavior: Heavy Drinking

Average daily alcohol consumption was a derived variable in the NPHS, which took the reported weekly total of alcohol consumed and divided it by seven (Statistics Canada 2010c). Heavy drinking was classified for the purposes of this study as an average of more than two drinks per day for men and an average of more than one drink per day for women (Jensen, Andersen et al. 2002; United States Department of Health and Human Services 2005). A dichotomous variable was created for heavy drinking with those who did not fit these criteria as the reference category. Heavy drinking was assessed at baseline.

Health Risk Behavior: Poor Diet

Self-perceived eating habits were assessed in the NPHS by asking: in general, would you say that your eating habits are: “excellent”, “very good”, “good”, “fair” or “poor” (Statistics Canada 2010b). A dichotomous variable was created for poor diet with those who reported "excellent”, “very good”, “good”, and “fair” eating habits as the reference category. Poor diet was assessed at baseline for the purposes of this study.

2.4.6. Possible Effect Modifying Factor: Stressful life events

A categorical variable with three categories was created for stressful life events by combining self-reports of divorce, self-reports of unemployment, high work stress and high chronic stress at baseline. The three categories consisted of those who (1) did not report any stressful life events (2) reported one stressful life event (3) reported two or more stressful life events. The variable for stressful life events was categorized in this way to

observe the cumulative effect of stressful life events on heightening the impact of childhood trauma. This also follows what other studies addressing similar associations have done (Colman, Garad et al. 2012).

Current labor force status was a derived variable in the NPHS using reports of working status in the last 12 months (Statistics Canada 2010c). The two categories consisted of “employed” and “unemployed” (Statistics Canada 2010b). Marital status was assessed by the NPHS by asking “what is your current marital status?”. The categories consisted of (1) now married (2) common-law (3) living with a partner (4) single (never married) (5) widowed (6) separated (7) divorced (Statistics Canada 2010b). This variabe was recoded with those who reported being married, common-law, living with a partner and single (never married) as the reference category. Those who were widowed, separated and divorced were combined since marital dissolution has been linked with higher cardiovascular mortality (Lynch, Kaplan et al. 1996; Matthews and Gump 2002).

Work stress is measured in the NPHS using the work stress index (Statistics Canada 2010b). This index combines responses to the following questions: “please tell me if you strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree” (1) your job requires you to learn new things, (2) your job requires a high level of skill (3) your job allows you freedom to decide how you do your job (4) your job requires that you do things over and over (5) your job is very hectic (6) you are free from conflicting demands that others make (7) your job security is good (8) your

job requires a lot of physical effort (9) you have a lot to say about what happens in your job (10) you are exposed to hostility or conflict from the people you work with (11) your supervisor is helpful in getting the job done and (12) the people you work with are helpful in getting the job done (Statistics Canada 2010b). High work stress was defined as those who are above the 90th percentile on this scale. The 90th percentile has been used to classify high stress in previous studies (Pope, Tillman et al. 2005; Colman, Garad et al. 2012).

Chronic stress is measured by the following questions for which members of the NPHS either responded "true", "false", "yes", or "no": (1) you are trying to take on too many things at once (2) there is too much pressure to be like other people (3) too much is expected of you by others (4) you don't have enough money to buy the things you need (5) your friends are a bad influence (6) you would like to move but you cannot (7) your neighborhood or community is too noisy or too polluted (8) you have a parent, a child or partner who is in very bad health and may die (9) someone in your family has an alcohol or drug problem (10) people are too critical of you or what you do and (11) "do you have any children?" (Statistics Canada 2010b). This study used the general chronic stress index in the NPHS, which combines these items (Statistics Canada 2010b). High chronic stress was defined as those who are above the 90th percentile on this scale (Pope, Tillman et al. 2005; Colman, Garad et al. 2012)

2.5. Statistical Analysis

The associations between childhood traumatic events, sex and the cumulative incidence of CVD were assessed from 1994/95 to 2008/09 using logistic regression adjusting for age, and socioeconomic status. High blood pressure and overweight/obesity may be intermediate factors in the relationship between childhood trauma and CVD. Also high blood pressure and overweight/obesity are very strongly related to CVD in the literature and are often used to assess cardiovascular disease risk. Thus, high blood pressure and overweight/obesity were assessed as secondary outcomes. The cumulative incidence of both high blood pressure and overweight/obesity were used for the purposes of this study.

Cumulative incidence is the proportion of an initially disease free population that develops an outcome after a specified period of time. The cumulative incidences of CVD, high blood pressure and overweight/obesity over 15 years (1994/95 to 2008/09) were used for the purposes of this study. Since CVD is a rare outcome, the odds ratios that were attained using CVD as the outcome approximate the relative risk. An odds ratio for the purposes of this study refers to the ratio between the odds of an outcome for those who report exposure to childhood traumatic events and the odds of an outcome for those who do not report exposure to childhood traumatic events.

The effect of childhood trauma was first assessed for CVD. An interaction term between childhood trauma and sex was assessed with CVD as the dependent variable to determine whether the effect of childhood trauma on CVD is heightened among women when compared to men. This interaction

was also evaluated using high blood pressure and overweight/obesity as outcomes. Significant interaction terms between childhood trauma and sex were then stratified by sex (male or female) to understand interaction effects.

The second stage of the analysis was to address possible mediators and modifying factors. Whether recent stressful life events modify the relationship between childhood trauma and CVD was first investigated. Thus, an interaction term between childhood trauma and stressful life events was explored for CVD. Significant interaction terms were then stratified by the categories for stressful life events to understand the interaction effects and by sex (male or female) to investigate whether these associations were stronger among women than men. The effect of depression in heightening the effect of childhood trauma on CVD was also assessed. Significant interactions were to be stratified by depression to understand interaction effects and by sex as well.

It is unclear in the literature for whether depression is a modifying or mediating factor in the relationship between childhood trauma and CVD. As a result, depression was also assessed as a possible mediator. Evidence shows that health risk behaviors may also mediate the relationship between childhood traumatic events and CVD in adulthood. Thus, health risk behaviors were investigated as mediators as well. The health risk behaviors assessed for the purposes of this study included reports of being physically inactive, poor diet, heavy drinking and smoking. The variable for childhood traumatic events was dichotomized to assess mediation (Baron and Kenny 1986; Muller, Judd et al.

2005). The causal steps strategy and the product of coefficients approach were both used to assess mediation.

The causal steps strategy was delineated by Baron and Kenny in 1986 and consists of a series of analyses to determine mediation (Baron and Kenny 1986). In order to demonstrate mediation using this approach the following three models were used:

(1) LOGIT [P (CVD| Childhood Trauma)] = $\alpha + \beta_{10}$Childhood Trauma

(2) LOGIT [P (Mediator| Childhood Trauma)] = $\alpha + \beta_{20}$Childhood Trauma

(3) LOGIT [P (CVD| Childhood Trauma, Mediator)] = $\alpha + \beta_{30}$Childhood Trauma + β_{31}Mediator

According to this approach, four conditions must be met in order to establish mediation. First, in equation 1 there must be an overall effect of the independent variable (childhood traumatic events) on the dependent variable (CVD) ($\beta_{10} \neq 0$). In equation 2 the effect of the independent variable on the mediator must also be significant ($\beta_{20} \neq 0$). In equation 3, there must be a significant effect of the mediator on the outcome while controlling for the independent variable ($\beta_{31} \neq 0$). Lastly, the residual direct effect of the independent variable on the outcome in equation 3 (β_{30}) should be smaller in absolute value than the overall effect of the independent variable on the outcome in equation 1 (β_{10}). The individual effects of four health risk behaviours (smoking, heavy drinking, poor diet, physical inactivity) and depression on mediating the relationship between childhood trauma and CVD

were to be assessed, if a relationship was first found to exist between childhood trauma and CVD.

This approach however, has been criticized for having low power, and also for not quantifying the indirect effect (Hayes 2009). Instead of quantifying this effect, it must be logically inferred by the hypothesis tests. For this reason, the product of coefficients approach was also used to assess mediation.

The user written command for Stata 11, binary_mediation, was used to assess mediation through the product of coefficients approach. The program standardizes all the coefficients for both ordinary least squares and logit models, allowing for the use of binary outcomes to assess mediation using this approach.

In order to establish mediation, the relationship between the independent variable and the outcome (c) must first be significant (see Figure 2.1). In a simple mediation model a is the coefficient in the model in which the independent variable (childhood trauma) predicts the mediator, and b is the coefficient which predicts the outcome (CVD) from the mediator, controlling for the independent variable (Hayes 2009).

The coefficient that predicts the outcome from the independent variable controlling for the mediator (c') is the direct effect. The indirect effect of the independent variable on the outcome through the mediator is the

product of a, and b. The indirect effect is the extent to which a change in the outcome occurs when the independent variable is held constant, but the effect of the mediator on the outcome has the same impact that would have occurred if the independent variable had increased. If the indirect effect is significant but the direct effect is non-significant, this suggests full mediation. If both the indirect and direct effects are significant, this suggests partial mediation.

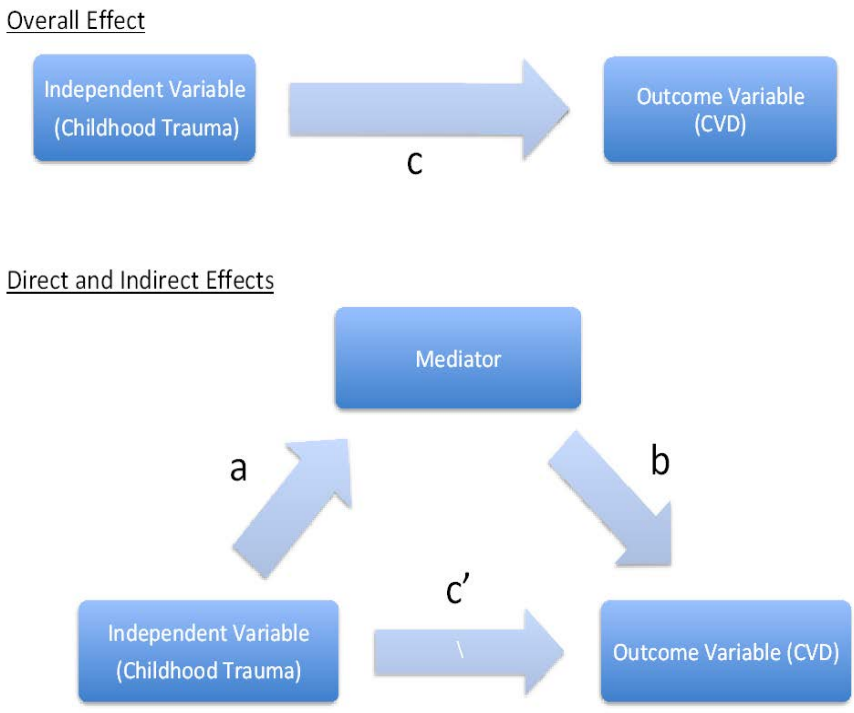

Figure 2.1: Simple Mediation Model

Mediated moderation was then assessed to investigate whether the mediators explain the heightened effect of childhood trauma among women when compared to men. It was assessed using the approach outlined by Muller et al (2005) (Muller, Judd et al. 2005). According to this approach, the

following three models were used for the purposes of this study to assess mediated moderation:

(4) LOGIT [P (CVD| Childhood Trauma, Sex, Childhood Trauma*Sex)] = α + β_{41}Childhood Trauma + β_{42}Sex + β_{43} Childhood Trauma*Sex

(5) LOGIT [P (Mediator| Childhood Trauma, Sex, Childhood Trauma*Sex)] = α + β_{51}Childhood Trauma + β_{52}Sex + β_{53}Childhood Trauma*Sex

(6) LOGIT [P (CVD| Childhood Trauma, Sex, Childhood Trauma*Sex, Mediator, Mediator*Sex)] = α + β_{61}Childhood Trauma + β_{62}Sex + β_{63}Childhood Trauma*Sex + β_{64}Mediator + β_{65}Mediator*Sex

These models are also illustrated in Figure 2.2. According to Muller et al (2005), in order to have evidence of mediated moderation, there must first be moderation. Thus, the magnitude of the overall effect of childhood trauma (the independent variable) on CVD (the outcome variable) must depend on sex (equation 4). After this effect is established, at least one of the two indirect paths from childhood trauma and CVD must be moderated.

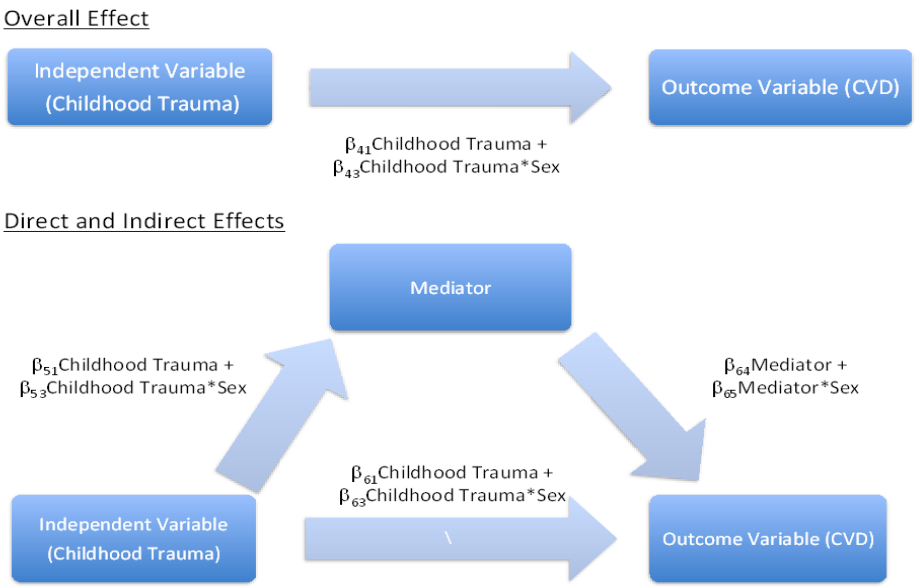

Figure 2.2: Models illustrating mediated moderation

In the first path the effect of childhood trauma on the mediator depends on sex. Thus, significance must be found for (1) the interaction effect between childhood trauma and sex on the mediator ($\beta_{53} \neq 0$) and (2) the direct effect of the mediator on CVD in equation 6 ($\beta_{64} \neq 0$). In the second path, the effect of the mediator on CVD depends on sex. Thus significance must be found for (1) the interaction effect between the mediator and sex for CVD ($\beta_{65} \neq 0$) and (2) the direct effect of childhood trauma on the mediator equation 5 ($\beta_{51} \neq 0$). So either one or both of these two patterns must exist in order to conclude mediated moderation: (1) both β_{53} and β_{64} are significant and/or (2) both β_{51} and β_{65} are significant. Lastly, when compared to the overall interaction effect between childhood trauma and sex for CVD, the residual interaction effect (β_{63}) should be reduced in magnitude.

STATA 11 was used to conduct the analyses.

2.6 Sensitivity Analyses

Sensitivity analyses were conducted in order to determine whether the exclusion of certain variables or groups of people would have an effect on the results of the study. A sensitivity analysis was administered for the Trauma Index, with the item "two weeks or longer in hospital" removed to address possible misclassification of the exposure since members of the NPHS who have spent two weeks or longer in a hospital as children may have been hospitalized due to early cardiovascular conditions, possibly introducing bias.

When excluding this item, the interaction effect between childhood trauma and stressful life events disappeared. However, all of the other results assessing CVD, high blood pressure and overweight/obesity as dependent variables remained consistent with results including the item "two weeks or longer in hospital" in the assessment for childhood trauma. Since the exclusion of this item from the overall index did not have much of an impact on the results, the decision was made for it to remain in the childhood trauma variable for the purposes of this study.

A sensitivity analysis was also conducted to assess whether family history of heart disease should be added as a covariate when looking at CVD as the outcome variable. The only change that occurred when controlling for family history of heart disease was that the impact of one or two childhood traumatic events on CVD was no longer significant. Results with this variable

included in the model and not included in the model were thus very similar. For this reason, it was not included as a covariate for the purposes of this study.

Results were also compared using a variable for income adequacy available in the NPHS with four categories, rather than the dichotomous variable created for SES. The use of the income adequacy variable as a covariate had little effect on the results and thus the SES variable created for the purposes of this study was used.

A sensitivity analysis was also conducted to assess whether the exclusion of inconsistent reporters had a significant impact on results for the primary outcome (see Tables 3.5 and 3.6). Similar to the results found with inconsistent reporters excluded, a significant dose-response relationship was found between childhood trauma and CVD. However, the interaction effect between childhood trauma and sex for CVD was not found to be significant. All of the other associations including the interaction effect between childhood trauma and stressful life events on CVD were similar to those found with inconsistent reporters excluded. The exclusion of inconsistent reporters was thus not found to have a dramatic effect on the results.

3.0 RESULTS

There were 17, 276 NPHS members in the sample at the beginning of the study. After the exclusion of (1) those that did not report on childhood traumatic events (2) those who were younger than 18 years of age or over 49 years of age at baseline and (3) those who inconsistently reported childhood traumatic events, the final sample consisted of 6881 members of the NPHS.

The incidence of CVD between 1994 and 2009 was 9%. Overweight or obesity was reported by 68.40% of the sample while high blood pressure was reported by 17.25% of the sample between 1994 and 2009. The prevalence of males in the sample was 48.10% while the prevalence of women was 50.90%. For those who reported on childhood traumatic events, 37.39% of the sample reported 1 or 2 childhood traumatic events while 13.52% reported more than 3 childhood traumatic events.

For the health risk behaviors, prevalence's of 36.59%, 3.98%, 19.66% and 60.07% were found for smoking, poor diet, heavy drinking and physical inactivity, respectively. At baseline 6.79% of the sample reported being depressed. At least one stressful life event was reported by 48% of the sample.

Table 3.0 Baseline characteristics of study participants

% Prevalence						
	Total (n=6881)	Inconsistent (*n*= 1163)	CVD (*n*= 589)	No CVD (*n*= 3459)	Completed for CVD (*n*= 3999)	Missing for CVD (*n*= 2882)
Age						
18-25	20.42%	21.90%	7.61%	19.13%	17.45%	24.53%
26-31	19.29%	18.89%	9.95%	18.97%	17.66%	21.55%
32-37	24.37%	23.27%	23.85%	25.15%	24.96%	23.54%
38-43	19.51%	19.22%	26.86%	21.03%	21.88%	16.23%
44-49	16.42%	16.72%	31.73%	15.72%	18.05%	14.15%
Sex						
Male	48.10%	47.28%	56.95%	47.84%	49.17%	49.02%
Female	50.90%	52.72%	43.05%	52.16%	50.83%	50.98%
Low SES						
No	93.72%	96.80%	92.54%	95.90%	95.41%	91.30%
Yes	6.28%	3.20%	7.46%	4.10%	4.59%	8.70%
Smoker						
No	63.41%	69.63%	56.93%	67.36%	65.84%	60.04%
Yes	36.59%	30.37%	43.07%	32.64%	34.16%	39.96%
Poor Diet						
No	96.02%	97.89%	95.34%	96.51%	96.35%	95.06%
Yes	3.98%	2.11%	4.66%	3.49%	3.65%	4.94%
Heavy Drinker						
No	80.34%	79.19%	83.11%	80.43%	80.82%	79.63%
Yes	19.66%	20.81%	16.89%	19.57%	19.18%	20.37%
Physically inactive						
No	39.93%	43.99%	35.90%	40.63%	39.94%	39.91%
Yes	60.07%	56.01%	64.10%	59.37%	60.06%	60.09%
Depressed						
No	93.21%	94.43%	90.80%	93.59%	93.18%	93.25%
Yes	6.79%	5.57%	9.20%	6.41%	6.82%	6.75%
Stressful life events						
0	51.97%	55.61%	46.43%	56.07%	54.67%	48.19%
1	20.41%	21.08%	24.00%	19.87%	20.47%	20.34%
>=2	27.62%	23.30%	29.56%	24.07%	24.86%	31.47%
Overweight/ obese						
No	56.99%	55.67%	37.70%	55.57%	52.95%	62.58%
Yes	43.01%	44.33%	62.30%	44.43%	47.05%	37.42%
High Blood Pressure						
No	96.75%	97.08%	87.48%	97.59%	96.12%	97.63%
Yes	3.25%	2.92%	12.52%	2.41%	3.88%	2.37%
Childhood Trauma						
0	49.09%	46.07%	41.34%	51.36%	49.91%	47.95%
1 or 2	37.39%	51.52%	39.75%	35.54%	36.15%	39.11%
>=3	13.52%	2.41%	18.91%	13.10%	13.95%	12.94%

Table 3.0.1 Baseline characteristics of study participants by gender

% Prevalence			
	Total (n=6881)	Males (*n*= 3379)	Females (*n*= 3502)
Age			
18-25	20.42%	21.56%	19.32%
26-31	19.29%	18.48%	20.07%
32-37	24.37%	24.03%	24.69%
38-43	19.51%	19.35%	19.67%
44-49	16.42%	16.58%	16.26%
Low SES			
No	93.72%	94.65%	92.82%
Yes	6.28%	5.35%	7.18%
Smoker			
No	63.41%	62.06%	64.71%
Yes	36.59%	37.94%	35.29%
Poor Diet			
No	96.02%	95.77%	96.26%
Yes	3.98%	4.23%	3.74%
Heavy Drinker			
No	80.34%	82.46%	78.09%
Yes	19.66%	17.54%	21.91%
Physically inactive			
No	39.93%	44.71%	35.32%
Yes	60.07%	55.29%	64.68%
Depressed			
No	93.21%	95.73%	90.78%
Yes	6.79%	4.27%	9.22%
Stressful life events			
0	51.97%	59.16%	45.06%
1	20.41%	21.15%	19.71%
>=2	27.62%	19.70%	35.24%
Overweight/obese			
No	56.99%	47.74%	66.40%
Yes	43.01%	52.26%	33.60%
High Blood Pressure			
No	96.75%	96.82%	96.68%
Yes	3.25%	3.18%	3.32%
Childhood Trauma			
0	49.09%	52.68%	45.61%
1 or 2	37.39%	36.92%	37.84%
>=3	13.52%	10.40%	16.54%

3.1. Effect of Childhood Traumatic Events on Cardiovascular Disease

Results showed that childhood traumatic events were significantly associated with CVD, particularly among those who reported three or more childhood traumatic events, indicating a dose-response relationship (see Table 3.1). Those who reported one or two childhood traumatic events were found to be 1.5 times more likely to also report CVD than those who did not report childhood traumatic events. Those who reported three or more childhood traumatic events were found to be 2.14 times more likely to report CVD. A significant interaction between childhood trauma and depression was not found.

Table 3.1. Odds ratios (OR) with 95% confidence intervals for the impact of childhood trauma on cardiovascular disease and cardiovascular disease risk

		CVD	High BP	Overweight
CTE's	1 or 2 CTE's	**1.50 [1.13, 1.99]	*1.26 [1.03, 1.53]	**1.32 [1.08, 1.60]
	3+ CTE's	**2.14 [1.56, 2.94]	**1.53 [1.19, 1.98]	**1.76 [1.27, 2.45]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.1.1. Childhood Trauma and Sex Interaction

A significant interaction between childhood trauma and sex was also found when CVD was assessed as the dependent variable. When stratified by sex, a significant relationship between childhood trauma and CVD was only found among women (see Table 3.2). For women, a significant relationship between childhood trauma and CVD was found for both those who reported one or two childhood traumatic events (OR=1.96, 95% CI: 1.26, 3.06) and those who reported three or more childhood traumatic events (OR=3.02, 95% CI: 1.87, 4.88). For men, the association between a history of one or two childhood traumatic events and CVD (OR=1.26, 95% CI: 0.86, 1.86), as well as the association between a history of three or more childhood traumatic events and CVD (OR=1.50, 95% CI: 0.92, 2.44) were non-significant. This indicates that effect of childhood traumatic events on having CVD may be heightened among women when compared to men.

The association between sex (with men as the comparison group) and CVD for those who did not report childhood traumatic events was found to be significant (OR=0.48, 95% CI: 0.32, 0.74, p=<0.01). The association between sex and CVD was not significant among those who reported childhood traumatic events.

The combined effect of one or two childhood traumatic events and women on CVD in comparison to no childhood traumatic events and men was not significant. The odds ratio for the combined effect of three or more childhood traumatic events and women on CVD when compared to those who

did not report childhood traumatic events and men was 1.47 and showed borderline significance (95% CI: 0.97, 2.26, *p*=0.07).

Table 3.2. Odds ratios (OR) with 95% confidence intervals for the impact of childhood traumatic events on cardiovascular disease and cardiovascular disease risk by sex

		CVD	High BP	Overweight
CTE's for women	1 or 2 CTE's	**1.96 [1.26, 3.06]	1.32 [0.99, 1.75]	**1.41 [1.09, 1.82]
	3+ CTE's	**3.02 [1.87, 4.88]	*1.43 [1.00, 2.05]	**2.21 [1.54, 3.16]
	No CTE's	---	---	---
CTE's for men	1 or 2 CTE's	1.26 [0.86, 1.86]	1.20 [0.89, 1.64]	1.18 [0.82, 1.71]
	3+ CTE's	1.50 [0.92, 2.44]	*1.69 [1.13, 2.53]	1.02 [0.56, 1.84]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.1.2. Childhood Trauma and Recent Stressful Life Events Interaction

A significant interaction was also found between childhood trauma and stressful life events for CVD. When stratifying the association between childhood trauma and CVD by the categories for stressful life events used for the purposes of this study (see Table 3.3), significance was only found for those who reported three or more childhood traumatic events and two or more stressful life events (OR=3.00, 95% CI: 1.74, 5.20).

The association between one stressful life event and CVD was not found to be significant for those who did not report childhood traumatic events, or those that reported one or two childhood traumatic events. However, the relationship between one stressful life event and CVD was found to be significant for those who reported three or more childhood traumatic events (OR=2.48, 95% CI: 1.19, 5.17, p=<0.05). The association between two or more stressful life events and CVD was not found to be significant for those who did not report childhood traumatic events or for those who reported one or two childhood traumatic events. However it was significant for those who reported three or more childhood traumatic events (OR=3.42, 95% CI: 1.62, 7.22, p=<0.01).

When stratifying the association between childhood trauma and CVD further by sex after stratifying this association by the categories for stressful life events, significance was only found among women (see Table 3.3). The significant associations that were found for women included the impact of three or more childhood traumatic events on CVD among those who reported one stressful life event (OR=4.09, 95% CI: 1.50, 11.20), as well as the impact of one or two childhood traumatic events (OR=2.95, 95% CI: 1.40, 6.41) and three or more childhood traumas (OR=4.40, 95% CI: 1.98, 9.76) on CVD among those who reported two or more stressful life events. No significant associations were found for men when the relationship between childhood trauma and CVD was stratified by stressful life events.

The combined effect of one or two childhood traumatic events and one stressful life event on CVD in comparison to no childhood traumatic events and no stressful life events was not found to be significant. However, a significant odds ratio of 2.2 was found for the combined effect of one or two childhood traumatic events and two or more stressful life events on CVD when compared to those who did not report childhood traumatic events and did not report stressful life events (95% CI: 1.39, 3.55, p=<0.01). For three or more childhood traumatic events the association with CVD was significant when combined with both one stressful life event (OR=2.76, 95% CI: 1.63, 4.67, p=<0.01) and two or more stressful life events (OR=3.80, 95% CI: 2.31, 6.25, p=<0.01), compared to no childhood traumatic events and no stressful life events.

Table 3.3. Odds ratios (OR) with 95% confidence intervals for the impact of childhood traumatic events on cardiovascular disease stratified by recent stressful life events

		SLE's = 0	SLE's = 1	SLE's = 2+
Overall	1 or 2 CTE's	1.45 [0.99, 2.11]	0.98 [0.49, 1.95]	1.77 [0.99, 3.15]
	3+ CTE's	1.12 [0.56, 2.26]	0.98 [0.90, 3.61]	**3.00 [1.74, 5.20]
	No CTE's	---	---	---
Women	1 or 2 CTE's	1.42 [0.73, 2.76]	2.03 [0.73, 5.60]	**2.95 [1.40, 6.41]
	3+ CTE's	1.56 [0.54, 4.50]	**4.09 [1.50, 11.20]	**4.40 [1.98, 9.76]
	No CTE's	---	---	---
Men	1 or 2 CTE's	1.47 [0.90, 2.40]	0.70 [0.29, 1.71]	0.92 [0.31, 2.73]
	3+ CTE's	0.71 [0.23, 2.19]	0.88 [0.31, 2.56]	1.79 [0.66, 4.86]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.1.3. Sensitivity Analysis for the effect of childhood trauma on CVD

When assessing the relationship between childhood trauma and CVD with the inclusion of those who inconsistently reported childhood traumatic events (see Table 3.4), the results were similar to those found when this group of individuals was excluded. A dose response relationship was found for the relationship between childhood trauma and CVD with those who reported one or two childhood traumas being 1.46 times more likely to have CVD and those who reported three or more childhood traumatic events being 2.31 times more likely to have CVD when compared to those who did not report childhood trauma. A significant interaction between childhood trauma and depression was not found.

Although the interaction effect between childhood trauma and sex was not found to be significant for CVD, the interaction effect between childhood traumatic events and stressful life events was still found to be significant. When stratifying by stressful life events, significance was still only found among women (see Table 3.5). The impact of three or more childhood traumatic events on CVD among women for those who reported one stressful life event was found to be significant (OR=3.59, 95%: 1.51, 8.54). The impact of both one or two childhood traumatic events (OR=2.17, 95%: 1.12, 4.19) and three or more childhood traumatic events (OR=3.94, 95% CI: 1.96, 7.93) on CVD for those who reported two or more stressful life events was also found to be significant among women.

Significance was not found for the association between one stressful life event and CVD for those who did not report childhood traumatic events, or those that reported one or two childhood traumatic events. The association between one stressful life event and CVD was found to be significant for those who reported three or more childhood traumatic events (OR=2.19, 95% CI: 1.11, 4.32, p=<0.05). The relationship between two or more stressful life events and CVD was not found to be significant for those who did not report childhood traumatic events or for those who reported one or two childhood traumatic events. However it was significant for those who reported three or more childhood traumatic events (OR=3.24, 95% CI: 1.63, 6.43, p=<0.01).

The combined effect of one or two childhood traumatic events and one stressful life event on CVD in comparison to no childhood traumatic events and no stressful life events was not found to be significant. However, the odds ratio for the combined effect of one or two childhood traumatic events and two or more stressful life events on CVD when compared to those who did not report childhood traumatic events and did not report stressful life events was significant (OR=2.01, 95% CI: 1.34, 3.02, p=<0.01). For three or more childhood traumatic events the association with CVD was significant when combined with both one stressful life event (OR=2.75, 95% CI: 1.66, 4.58, p=<0.01) and two or more stressful life events (OR=4.07, 95% CI: 2.53, 6.55, p=<0.01), compared to no childhood traumatic events and no stressful life events.

Table 3.4. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on CVD with inconsistent reporters included

		Overall	Men	Women
CTE's	1 or 2 CTE's	**1.46 [1.11, 1.91]	1.35 [0.92, 1.97]	**1.64 [1.13, 2.38]
	3+ CTE's	**2.31 [1.70, 3.13]	*1.83 [1.13, 2.95]	**2.81 [1.83, 4.32]
	No CTE's	---	---	---

*p<0.05
**p<0.01

Table 3.5. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on CVD with inconsistent reporters included stratified by recent stressful life events

		SLE's = 0	SLE's = 1	SLE's = 2+
Overall	1 or 2 CTE's	*1.52 [1.06, 2.19]	0.94 [0.50, 1.77]	1.61 [0.96, 2.70]
	3+ CTE's	1.25 [0.68, 2.32]	*1.99 [1.03, 3.86]	**3.26 [1.96, 5.42]
	No CTE's	---	---	---
Women	1 or 2 CTE's	1.51 [0.87, 2.62]	1.31 [0.57, 3.00]	*2.17 [1.12, 4.19]
	3+ CTE's	1.64 [0.67, 4.01]	**3.59 [1.51, 8.54]	**3.94 [1.96, 7.93]
	No CTE's	---	---	---
Men	1 or 2 CTE's	1.53 [0.93, 2.50]	0.79 [0.34, 1.83]	1.07 [0.42, 2.74]
	3+ CTE's	0.86 [0.33, 2.25]	1.02 [0.36, 2.88]	2.53 [0.99, 6.51]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.2. Effect of Childhood Traumatic Events on High Blood Pressure

Childhood trauma was also significantly associated with high blood pressure (see Table 3.1). There was a significant relationship between those who reported one or two childhood traumatic events and reports of high blood pressure (OR=1.50, 95% CI: 1.13, 1.99). There was also a significant relationship between three or more childhood traumatic events and high blood pressure (OR=2.14, 95% CI: 1.56, 2.94). However, the interaction between childhood trauma and sex was not found to be significant for high blood pressure. The interaction between childhood trauma and recent stressful life events was also not found to be significant. A significant interaction between childhood trauma and depression was not found.

3.3. Effect of Childhood Traumatic Events on Overweight/Obesity

Results also showed a significant relationship between childhood traumatic events and overweight or obesity (see Table 3.1). Those who reported one or two childhood traumatic events were 1.32 times more likely to be overweight or obese than those who did not report childhood traumatic events (95% CI: 1.27, 2.45). Those who reported three or more childhood traumatic events were also found to have an increased likelihood of being overweight or obese (OR=1.76, 95% CI: 1.27, 2.45). However, the interaction between childhood trauma and sex when assessing overweight/obesity as the dependent variable was not found to be significant. A significant interaction between childhood trauma and depression was not found.

3.3.1. Childhood Trauma and Stressful Life Events Interaction

There was a significant interaction between childhood traumatic events and recent stressful life events when assessing overweight/obesity as the dependent variable. Similar to the results found when using CVD as the dependent variable, when stratifying the relationship between childhood trauma and overweight or obesity by the categories of recent stressful life events, significance was only found for those who reported two or more recent stressful life events (see Table 3.6).

Table 3.6. Odds ratios (OR) with 95% confidence intervals for the impact of childhood traumatic events on overweight or obesity stratified by recent stressful life events

		SLE's = 0	SLE's = 1	SLE's = 2+
Overall	1 or 2 CTE's	1.10 [0.83, 1.47]	0.97 [0.61, 1.55]	**2.04 [1.42, 2.91]
	3+ CTE's	1.36 [0.80, 2.32]	1.43 [0.72, 2.86]	**2.40 [1.47, 3.92]
	No CTE's	---	---	---
Women	1 or 2 CTE's	1.08 [0.75, 1.55]	1.01 [0.57, 1.78]	**2.35 [1.53, 3.59]
	3+ CTE's	1.67 [0.90, 3.07]	1.82 [0.89, 3.71]	**2.70 [1.49, 4.89]
	No CTE's	---	---	---
Men	1 or 2 CTE's	1.15 [0.69, 1.92]	1.00 [0.48, 2.10]	1.47 [0.66, 3.26]
	3+ CTE's	0.76 [0.29, 1.97]	0.87 [0.17, 4.38]	1.84 [0.59, 5.74]
	No CTE's	---	---	---

*p<0.05
**p<0.01

Among those who reported two or more recent stressful life events, a reported history of one or two childhood traumatic events (OR=2.04, 95% CI: 1.42, 2.91) and a reported history of three or more childhood traumatic events (OR=2.40, 95% CI: 1.47, 3.92) significantly predicted overweight or obesity.

The association between one stressful life event and overweight/obesity was not found to be significant for those who did not report childhood traumatic events, those that reported one or two childhood traumatic events, or for those who reported three or more childhood traumatic events. The association between two or more stressful life events and overweight/obesity was also not found to be significant for those who did not report childhood traumatic events. However, it was found to be significant for those who reported one or two childhood traumatic events (OR=1.56, 95% CI: 1.06, 2.30, p=<0.01). The association between two or more stressful life events and overweight/obese was not significant for those who reported three or more childhood traumatic events

After stratifying the association between childhood trauma and CVD by the categories for stressful life events, these associations were further stratified by sex (see Table 3.6). Significance was again only found among women. Women who reported one or two childhood traumatic events (OR=2.35, 95% CI: 1.42, 2.91) as well as women who reported three or more childhood traumatic events (OR=2.70, 95% CI: 1.49, 4.89) were significantly more likely than women who did not report childhood traumatic events to be

overweight or obese if they also reported experiencing two or more recent life stressors.

The combined effect of one or two childhood traumatic events and one stressful life event on overweight/obesity in comparison to no childhood traumatic events and no stressful life events was not significant. The combined effect of one or two childhood traumatic events and two or more stressful life events significantly predicted overweight/obesity when compared to those who did not report childhood traumatic events and did not report stressful life events (OR=1.71, 95% CI: 1.21, 2.41, p=<0.01). The effect of three or more childhood traumatic events on overweight/obesity was not significant when combined with one stressful life event. However, the combined effect of three or more childhood traumatic events and two or more stressful life events was found to be significant when compared to no childhood traumatic events and no stressful life events (OR=2.03, 95% CI: 1.25, 3.27, p=<0.01).

3.4. Significant mediators as secondary outcomes

3.4.1. Smoking as a secondary outcome

Significantly higher odds of smoking were found for both those who reported one or two childhood traumatic events (OR=1.55, 95% CI: 1.34, 1.79) and those who reported three or more childhood traumatic events (OR=3.06, 95% CI: 2.50, 3.73). A significant interaction was also found between childhood traumatic events and sex when using smoking as the dependent variable. When stratifying the relationship between childhood trauma and smoking by sex, significance was found for both men and women. However, women who

reported childhood trauma showed higher odds of smoking than men who reported childhood trauma.

Table 3.7. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on smoking

		Overall	Men	Women
CTE's	1 or 2 CTE's	**1.55 [1.34, 1.79]	**1.34 [1.09, 1.66]	**1.80 [1.47, 1.20]
	3+ CTE's	**3.06 [2.50, 3.73]	**2.55 [1.90, 3.43]	**3.53 [2.72, 4.57]
	No CTE's	---	---	---

*p<0.05
**p<0.01

The association between sex (with men as the comparison group) and smoking for those who did not report childhood traumatic events was found to be significant (OR=0.70, 95% CI: 0.57, 0.85, *p*=<0.01). The association between sex and smoking was not significant among those who reported childhood traumatic events.

The combined effect of one or two childhood trauma and women on smoking in comparison to no childhood traumatic events and men was found to be significant (OR=1.27, 95% CI: 1.04, 1.53, *p*=<0.05). The odds ratio for the combined effect of three or more childhood traumatic events and women when compared to those who did not report childhood traumatic events and men was also significant (OR=2.52, 95% CI: 1.94, 3.26 *p*=<0.01).

A significant interaction was also found between childhood traumatic events and recent stressful life events. When stratifying the relationship between childhood trauma and smoking by the categories for recent stressful life events (see Table 3.8), all of the associations between childhood trauma and smoking were significant. However, the highest odds were found for those who reported three or more childhood traumatic events and two or more recent stressful life events (OR=4.28, 95% CI: 3.43, 6.88).

The association between one stressful life event and smoking was not found to be significant for those who did not report childhood traumatic events, or those that reported childhood traumatic events. The association between two or more stressful life events and smoking was not found to be significant for those who did not report childhood traumatic events, however it was significant for those who reported one or two childhood traumatic events (OR=1.57, 95% CI: 1.23, 1.99, p=<0.01) and those who reported three or more childhood traumatic events (OR=2.86, 95% CI: 1.95, 4.19, p=<0.01).

A significant interaction term between childhood trauma and stressful life events was found for women but not for men when looking at smoking as the dependent variable. The stratified association between childhood trauma and smoking by the categories of recent stressful life events was then further stratified by sex. The associations between childhood trauma and smoking for each stressful life events category were all significant for women (see Table 3.8). Women who reported three or more childhood traumatic events were

found to be 4.84 times more likely to smoke than women who did not report childhood trauma if they also reported two or more recent stressful life events.

The effect of one or two childhood traumatic events on smoking was found to be significant when combined with the effect of one stressful life event (OR=1.77, 95% CI: 1.32, 2.38, p=<0.01), as well as when combined with the effect of two or more stressful life events (OR=2.15, 95% CI: 1.72, 2.70, p=<0.01) when compared to those who did not report childhood traumatic events and did not report stressful life events. For three or more childhood traumatic events, the association with smoking was significant when combined with both one stressful life event (OR = 2.48, 95% CI: 1.68, 3.65, p=<0.01) and two or more stressful life events (OR=5.91, 95% CI: 4.42, 7.91, p=<0.01) when compared to no childhood traumatic events and no stressful life events.

Table 3.8. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on smoking stratified by recent stressful life events

		SLE's = 0	SLE's = 1	SLE's = 2+
Overall	1 or 2 CTE's	**1.38 [1.13, 1.68]	*1.49 [1.07, 2.07]	**1.75 [1.29, 2.37]
	3+ CTE's	**2.08 [1.51, 1.88]	**2.02 [1.34, 3.04]	**4.86 [3.43, 6.88]
	No CTE's	---	---	---
Women	1 or 2 CTE's	**1.66 [1.19, 2.32]	**1.97 [1.21, 3.21]	**1.75 [1.24, 2.45]
	3+ CTE's	**2.17 [1.36, 3.47]	**2.93 [1.65, 5.19]	**4.84 [3.25, 7.20]
	No CTE's	---	---	---
Men	1 or 2 CTE's	1.20 [0.92, 1.58]	1.17 [0.71, 1.94]	1.69 [1.00, 2.86]
	3+ CTE's	**2.16 [1.40, 3.35]	1.26 [0.67, 2.38]	**4.28 [2.38, 7.69]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.4.2. Diet as a secondary outcome

Childhood trauma was found to be significantly associated with poor diet (see Table 3.9) with those who reported three or more childhood traumatic events being 3.18 times more likely than those who did not report childhood trauma to report poor diet. A significant interaction between childhood trauma and sex was also found when using poor diet as the dependent variable. When stratifying the relationship between childhood trauma and sex, women who

reported childhood traumatic events were found to have higher odds of poor diet than men who reported childhood traumatic events.

The association between childhood trauma and poor diet was higher for women who reported three or more childhood traumatic events (OR=5.47, 95%: 2.66, 11.26) than it was for women who reported one or two childhood traumatic events (OR=3.63, 95%: 1.91, 6.90). Significance was found for both childhood trauma groups among women. However for men significance was only found for those who reported three or more childhood traumatic events (OR = 2.32, 95%: 1.03, 5.22).

The association between sex (with men as the comparison group) and poor diet for those who did not report childhood traumatic events was found to be significant (OR=0.38, 95% CI: 0.17, 0.83, p=<0.05). The association between sex and poor diet was not significant among those who reported childhood traumatic events.

The combined effect of one or two childhood traumatic events and women on poor diet in comparison to no childhood traumatic events and men was not significant. However, significance was found for the combined effect of three or more childhood traumatic events and women on poor diet when compared to those who did not report childhood traumatic events and men (OR=2.11, 95% CI: 1.01, 4.41, p=<0.05).

Table 3.9. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on diet

		Overall	Men	Women
CTE's	1 or 2 CTE's	1.72 [1.00, 2.97]	1.00 [0.46, 2.18]	**3.63 [1.91, 6.90]
	3+ CTE's	**3.18 [1.83, 5.52]	*2.32 [1.03, 5.22]	**5.47 [2.66, 11.26]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.4.3. Depression as a secondary outcome

Childhood trauma also significantly predicted depression (see Table 3.10). Both those who reported one or two childhood traumatic events (OR=1.79, 95% CI: 1.34, 2.40) and those that reported three or more childhood traumatic events (OR=4.95, 95% CI: 3.72, 6.59) had increased odds of depression. Also, there was a significant interaction effect between childhood trauma and stressful life events when looking at depression as the outcome.

When stratifying the association between childhood trauma and depression by stressful life events, most of the associations were found to be significant (see Table 3.11). However, the highest odds were found for those who did not report stressful life events with those who reported one or two childhood traumas being 2.76 times more likely to be depressed and those who reported three or more childhood traumatic events being 5.77 times more likely to be depressed when compared to those who did not report childhood trauma.

The association between one stressful life event and depression was significant for those who did not report a childhood traumatic event (OR=4.41, 95% CI: 2.37, 8.21, *p*=<0.01), those who reported one or two childhood traumatic events (OR=1.93, 95% CI: 1.18, 3.16, *p*=<0.01) and those who reported three or more childhood traumatic events (OR = 1.98, 95% CI: 1.05, 3.71, *p*=<0.01).

Significance was also found for the association between two or more stressful life events and depression for those who did not report a childhood traumatic event (OR = 2.87, 95% CI: 1.52, 5.40, *p*=<0.01), those who reported one or two childhood traumatic events (OR =2.17, 95% CI: 1.37, 3.44, *p*=<0.01) and those who reported three or more childhood traumatic events (OR = 2.76, 95% CI: 1.56, 4.90, *p*=<0.01).

The combined effects of one or two childhood traumatic events with one stressful life event (OR=5.34, 95% CI: 2.94, 9.70, *p*=<0.01) and two or more stressful life events (OR=6.01, 95% CI: 3.52, 10.22, *p*=<0.01) significantly predicted depression when compared to no childhood traumatic events and no stressful life events. Significance was also found for the effect of three or more childhood traumatic events combined with both one stressful life event (OR=11.42, 95% CI: 6.41, 20.35, *p*=<0.01) and two or more stressful life events (OR =15.97, 95% CI: 9.71, 26.25, *p*=<0.01) when compared to no childhood traumatic events and no stressful life events.

Table 3.10. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on depression

		Overall	Men	Women
CTE's	1 or 2 CTE's	**1.79 [1.34, 2.40]	1.59 [0.94, 2.68]	**2.36 [1.60, 3.50]
	3+ CTE's	**4.95 [3.72, 6.59]	**5.83 [3.49, 9.74]	**5.46 [3.70, 8.06]
	No CTE's	---	---	---

*p<0.05
**p<0.01

Table 3.11. Odds ratios (OR) with 95% confidence intervals for the effect of childhood trauma on depression stratified by recent stressful life events

		SLE's = 0	SLE's = 1	SLE's = 2+
Overall	1 or 2 CTE's	**2.76 [1.65, 4.62]	1.18 [0.63, 2.20]	**2.08 [1.20, 3.62]
	3+ CTE's	**5.77 [3.08, 10.84]	**2.45 [1.31, 4.57]	**5.57 [3.28, 9.45]
	No CTE's	---	---	---
Women	1 or 2 CTE's	**3.48 [1.71, 7.10]	1.09 [0.52, 2.29]	**2.43 [1.33, 4.45]
	3+ CTE's	**6.44 [2.82, 14.71]	*2.46 [1.12 5.40]	**5.65 [3.06, 10.44]
	No CTE's	---	---	---
Men	1 or 2 CTE's	1.93 [0.78, 4.76]	1.41 [0.41, 4.85]	1.57 [0.47, 5.30]
	3+ CTE's	*5.85 [1.53, 22.34]	1.26 [0.73, 7.96]	**6.55 [2.18, 19.67]
	No CTE's	---	---	---

*p<0.05
**p<0.01

3.5. Assessment of Mediation Effect of Health Risk Behaviors on the Relationship between Childhood Trauma and CVD

Since a significant overall association between childhood trauma and CVD was found (see Table 3.1) possible mediation was assessed for health risk behaviors and depression. For the purposes of the mediation analyses childhood trauma was treated as a dichotomous variable(Muller, Judd et al. 2005). The effect of childhood trauma as a dichotomous variable on CVD was significant (OR=1.66, 95% CI: 1.29, 2.13).

3.5.1. Poor Diet

When assessing poor diet as a possible mediator in the overall relationship between childhood trauma and CVD, childhood trauma was significantly related to poor diet (see Table 3.12.). Those who reported childhood traumatic events were 2.10 times more likely to have poor diet than those who did not report childhood traumatic events. The residual direct effect of childhood trauma on CVD after controlling for poor diet was also smaller than the initial effect found between childhood trauma and CVD (OR=1.63, 95% CI: 1.25, 2.13). However, the effect of poor diet on CVD after controlling for childhood traumatic events was not found to be significant. Thus, according to the causal steps approach to mediation, poor diet does not significantly mediate the relationship between childhood trauma and CVD.

When using the product of coefficients approach to mediation however, poor diet was found to significantly partially mediate the effect of childhood trauma on CVD (see Table 3.13). The indirect effect was found to

be significant (β=0.015, 95% CI: 0.001, 0.029). This indicates that poor diet significantly mediates 9% of the total effect between childhood trauma and CVD. However, significance was also found for the direct effect suggesting that poor diet explains part of the effect that childhood trauma has on CVD.

Table 3.12. Odds ratios (OR) with 95% confidence intervals for effect of diet on mediating the association between childhood trauma and CVD

β_{10}: Overall	CTE's	**1.66 [1.29, 2.13]
β_{30}: CTE's (CVD as outcome)	CTE's	**1.63 [1.25, 2.13] (⇓)
	No CTE's	---
β_{31}: Poor diet (CVD as outcome)	Poor Diet	1.52 [0.86, 2.69]
	Proper Diet	---
β_{20}: CTE's (Poor diet as outcome)	CTE's	**2.10 [1.27, 3.48]
	No CTE's	---

*p<0.05
**p<0.01

Table 3.13. Beta values with 95% confidence intervals for effect of health risk behaviors and depression on mediating the association between childhood trauma and CVD using the product of coefficients approach

	Indirect Effect	Direct Effect	Total Effect
Depression	**0.024 [0.009, 0.040]	**0.145 [0.094, 0.197]	**0.170 [0.117, 0.223]
Physical Inactivity	-0.0007 [-0.002, 0.001]	**0.157 [0.107, 0.207]	**0.156 [0.106, 0.207]
Poor Diet	*0.015 [0.001, 0.029]	**0.152 [0.097, 0.207]	**0.167 [0.111, 0.223]
Smoking	**0.015 [0.006, 0.024]	**0.144 [0.093, 0.196]	**0.159 [0.108, 0.211]
Heavy Drinking	- 0.001 [-0.005, 0.002]	**0.154 [0.098, 0.210]	**0.153 [0.100, 0.208]

*p<0.05
**p<0.01

3.5.2. Heavy Drinking

The impact of childhood trauma on heavy drinking was significant (see Table 3.14) with those who reported childhood traumatic events having higher odds of drinking heavily (OR=1.23, 95% CI: 1.04, 1.45) than those who did not report childhood traumatic events. Although the direct effect between childhood trauma and CVD was reduced when including heavy drinking as a covariate (OR = 1.67, 95% CI=1.28, 2.18), the effect of heavy drinking on CVD when controlling for childhood trauma was not significant (OR = 0.88, 95% CI: 0.62, 1.22), suggesting that heavy drinking does not mediate the relationship between childhood trauma and CVD. This is in line with the results using the product of coefficients approach in which the indirect effect was non-significant (see Table 3.13).

Table 3.14. Odds ratios (OR) with 95% confidence intervals for effect of heavy drinking on mediating the association between childhood trauma and CVD

β_{10}: Overall	CTE's	**1.66 [1.29, 2.13]
β_{30}: CTE's (CVD as outcome)	CTE's	**1.67 [1.28, 2.18] (⇑)
	No CTE's	---
β_{31}: Heavy drinking (CVD as outcome)	Heavy Drinking	0.884 [0.62, 1.22]
	No Heavy Drinking	---
β_{20}: CTE's (Heavy drinking as outcome)	CTE's	*1.23 [1.04, 1.45]
	No CTE's	---

*p<0.05
**p<0.01

3.5.3. Physical Activity

Although childhood trauma was found to significantly predict physical activity (see Table 3.15), the other conditions for the causal steps strategy to mediation analysis were not met. Thus, physical activity was not found to significantly mediate the relationship between childhood trauma and CVD. This corroborates with findings for the mediation effect of physical activity using the product of coefficients approach (see Table 3.13).

Table 3.15. Odds ratios (OR) with 95% confidence intervals for effect of physical activity on mediating the association between childhood trauma and CVD

β_{10}: Overall	CTE's	**1.66 [1.29, 2.13]
β_{30}: CTE's (CVD as outcome)	CTE's	**1.68 [1.31, 2.15]
	No CTE's	---
β_{31}: Physical inactivity (CVD as outcome)	Inactive	1.22 [0.95, 1.56]
	Active	---
β_{20}: CTE's (Physical inactivity as outcome)	CTE's	**0.76 [0.67, 0.86]
	No CTE's	---

*p<0.05
**p<0.01

3.5.4. Smoking

A partially significant mediation effect was found for smoking on the relationship between childhood trauma and CVD using the causal steps approach (see Table 3.16). Those who reported childhood traumatic events were found to be significantly more likely to report smoking (OR = 1.85, 95% CI: 1.62, 2.12). Smoking was also found to significantly predict CVD after controlling for childhood trauma (OR = 1.48, 95% CI: 1.14, 1.92). Lastly, the residual effect of childhood trauma on CVD after controlling for smoking was

reduced (OR = 1.58, 95% CI: 1.23, 2.02). Smoking was also found to partially mediate the relationship between childhood trauma and CVD using the product of coefficients approach (β=0.015, 95% CI: 0.006, 0.024) (see Table 3.13). This indicates that smoking significantly mediates 9% of the total effect between childhood trauma and CVD.

Table 3.16. Odds ratios (OR) with 95% confidence intervals for effect of smoking on mediating the association between childhood trauma and CVD

β_{10}: Overall	CTE's	**1.66 [1.29, 2.13]
β_{30}: CTE's (CVD as outcome)	CTE's	**1.58 [1.23, 2.02] (⇓)
	No CTE's	---
β_{31}: Smoking (CVD as outcome)	Smoker	**1.48 [1.14, 1.92]
	Non-Smoker	---
β_{20}: CTE's (Smoking as outcome)	CTE's	**1.85 [1.62, 2.12]
	No CTE's	---

*p<0.05
**p<0.01

3.6. Assessment of depression as a possible mediator and as a possible modifier in the relationship between childhood trauma and CVD

Depression was tested as both a possible effect-modifying factor and as a possible mediator in the relationship between childhood trauma and CVD.

3.6.1. Assessment of Effect Modification

An interaction term between childhood trauma and depression was assessed using CVD, high blood pressure and overweight/obesity as dependent

variables (see Table 3.2). None of these interactions were found to be significant.

3.6.2. Assessment of Mediation

When conducting the mediation analysis for depression, those who reported childhood traumatic events were found to be significantly more likely than those who did not report childhood traumatic events, to have depression (OR = 2.90, 95% CI: 2.17, 3.86) (see Table 3.17). Also, the residual direct effect of childhood trauma on CVD after controlling for depression was reduced (OR = 1.64, 95% CI: 1.27, 2.12). Borderline significance was found for the effect of depression on CVD after controlling for childhood trauma (OR = 1.46, 95% CI: 0.95, 2.25, p=0.085). A significant partial mediation effect for depression was found when using the product of coefficients approach to mediation analysis (β = 0.024, 95% CI: 0.009, 0.040) (see Table 3.13.). This indicates that depression significantly mediates 15% of the total effect between childhood trauma and CVD.

Table 3.17. Odds ratios (OR) with 95% confidence intervals for effect of depression on mediating the association between childhood trauma and CVD

β_{10}: Overall	CTE's	**1.66 [1.29, 2.13]
β_{30}: CTE's (CVD as outcome)	CTE's	**1.64 [1.27, 2.12] (⇓)
	No CTE's	---
β_{31}: Poor Diet (CVD as outcome)	Depressed	1.46 [0.95, 2.25]
	Not Depressed	---
β_{20}: CTE's (Mediator as outcome)	CTE's	**2.90 [2.17, 3.86]
	No CTE's	---

*p<0.05
**p<0.01

3.7. Mediated Moderation

Mediated moderation was assessed for all variables that were found to significantly mediate the relationship between childhood trauma and CVD. The interaction effect between childhood trauma and sex using CVD as the dependent variable was first assessed and was found to be significant.

3.7.1. Mediated moderation: smoking

Significance was found for the effect of childhood trauma on smoking (OR = 1.54, 95% CI: 1.26, 1.87) and the interaction effect between childhood trauma and sex using smoking as the dependent variable (OR = 1.46, 95% CI: 1.12, 1.90). However, the effect of smoking on CVD and interaction effect between smoking and sex using CVD as the dependent variable were not found to be significant. Thus neither paths necessary to conclude mediated moderation (β_{53} and β_{64}, or β_{51} and β_{65}) were found (see Table 3.18).

Table 3.18. Odds ratios (OR) with 95% confidence intervals for mediated moderation

	Smoking	Diet	Depression
β51: CTE's (Mediator as outcome)	**1.54 [1.26, 1.87]	1.28 [0.63, 2.59]	**2.46 [1.58, 3.85]
β53: CTE's and sex (Mediator as outcome)	**1.46 [1.12, 1.90]	*3.32 [1.33, 8.30]	1.29 [0.75, 2.21]
β64: Mediator (CVD as outcome)	1.84 [0.84, 4.05]	1.51 [0.23, 9.89]	1.27 [0.19, 8.38]
β65: Mediator and Sex (CVD as outcome)	0.85 [0.52, 1.39]	0.99 [0.31, 3.20]	1.07 [0.39, 2.95]

*p<0.05
**p<0.01

3.7.2. Mediated moderation: diet

Although a significant interaction term between childhood trauma and sex was found using diet as the dependent variable (OR = 3.32, 95% CI = 1.33, 8.30), none of the other possible conditions for mediated moderation were found to be significant. Thus, the results do not suggest that diet mediates the interaction effect between childhood trauma and sex when using CVD as the dependent variable (see Table 3.18).

3.7.3. Mediated moderation: depression

Childhood trauma was found to significantly predict depression (OR = 2.46, 95% CI: 1.58, 3.85). However none of the other conditions necessary to conclude mediated moderation were found to be significant. Thus, depression was also not found to mediate the interaction effect between childhood trauma and sex for CVD (see Table 3.18).

CHAPTER 4.0 GENERAL CONCLUSIONS AND DISCUSSION

4.1. Summary

In the present thesis, sex differences in the impact of childhood trauma on CVD were addressed using longitudinal data representative of the Canadian population. The effect of stressful life events and depression on heightening the impact of childhood trauma on CVD was assessed. The effect of depression and four health risk behaviors (poor diet, physical inactivity, smoking, and heavy drinking) on mediating the relationship between childhood trauma and CVD was also assessed. Significant mediating variables were then investigated for mediated moderation. Since significant mediators

are intermediate factors in the relationship between childhood trauma and CVD they were also used as secondary outcomes.

4.2. Principal Findings of this Thesis

The results of this thesis show a dose-response relationship between childhood trauma and CVD, which corroborates with the hypothesis that those who report childhood trauma will be more likely than those who do not report childhood trauma to experience CVD.

The second hypothesis for this study was that women who reported childhood trauma would be more likely than men who report childhood trauma to experience CVD. The findings were consistent with this hypothesis as well. The effect of childhood trauma on CVD was significantly heightened among women when compared to men when looking at interaction effects.

The third hypothesis was that childhood trauma will be more likely to lead to CVD among those who report recent stressful life events when compared to those who do not report recent stressful life events, and that these effects would be greater among women than among men. In this study, stressful life events were found to heighten the relationship between childhood trauma and CVD, and this effect only occurred among women. However, evidence was not found for the fourth hypothesis that depression would heighten the impact of childhood trauma on CVD. Rather, depression significantly decreased the impact of childhood trauma on CVD.

The same hypotheses that were postulated for CVD were also tested using high blood pressure and overweight/obesity as secondary outcomes. Childhood trauma was also significantly associated with both high blood pressure and overweight/obesity. Sex and recent stressful life events were not found to heighten the impact of childhood trauma on high blood pressure. When looking at overweight/obesity as the outcome, the effect of childhood trauma was not heightened among women when compared to men. However, recent stressful life events were found to heighten the impact of childhood trauma on overweight/obesity. This association was only found among women. Depression was not found to significantly heighten the effect of childhood trauma on these secondary outcomes.

The fifth hypothesis was that depression would mediate the relationship between childhood trauma and CVD, with this effect being stronger among women when compared to men. Depression was found to partially mediate the relationship between childhood trauma and CVD, which supports this hypothesis. However, depression was not found to mediate the moderation effect of sex on the relationship between childhood trauma and CVD.

Evidence was also found for the sixth hypothesis, that health risk behaviours may mediate the relationship between childhood trauma and CVD. Poor diet and smoking were found to partially mediate the relationship between childhood trauma and CVD. However these variables were also not

found to mediate the moderation effect of sex on the relationship between childhood trauma and CVD.

When looking at significant mediators as secondary outcomes, the effect of childhood trauma was heightened among women for poor diet and for smoking. However, the interaction effect between childhood trauma and sex was not found to be significant for depression. A significant interaction between childhood trauma and recent stressful life events was found for smoking, and for depression.

4.3. Discussion

The distribution in our sample of the factors assessed for the purposes of this study seems to reflect that of previous data assessing the Canadian population. Women were more likely than men to report stressful life events and to report three or more childhood traumatic events, and were about twice as likely as men to report depression. This is consistent with what previous literature has shown with regards to sex differences in the prevalence of depression (Lehtinen and Joukamaa 1994), stressful life events (Kendler, Thornton et al. 2001) and childhood trauma (Korkeila, Vahtera et al. 2010).

The prevalence of overweight/obesity at baseline in our sample was 43% overall, with 52% of men and 34% of women reporting being overweight or obese. This is also consistent with other Canadian data, which has shown a prevalence for overweight of 57% among men and a prevalence of 35-39% for women (Tremblay, Katzmarzyk et al. 2002).

The prevalence of high blood pressure in our sample was 3.3% overall, with 3.2% of men and 3.3% of women reporting high blood pressure. However other Canadian data has shown a prevalence of 21.1% (Joffres, Hamet et al. 2001). The prevalence of high blood pressure in Canada has been found to increase with age, with those between the ages of 18 and 54 showing prevalences between 2.1% and 4.6% for men and prevalences between 0.2 and 6.1 for women, while those between the ages of 55 and 74 showed prevalences between 21.9% and 33.8% for men and prevalences between 16% and 38.4% for women (Joffres, Hamet et al. 2001). Thus, our lower prevalences may be the result of having a younger sample, since members of the NPHS who were above the age at 49 at baseline were excluded. This may have led to an underestimate of our results for high blood pressure.

In our sample, 60% reported being physically inactive which corresponds with previous Canadian data on the prevalence of physical activity (Katzmarzyk, Gledhill et al. 2000). Our prevalences for smoking (Gilmore 2002) and heavy drinking (Health Canada 2011) at baseline are also similar to previous Canadian data. However, only 4% of our sample reported poor diet, while data from the Canadian Community Health Survey (CCHS) shows that 32% of males and 21% of females have carbohydrate intakes above the recommended intake (Health Canada 2012). In addition the CCHS shows that 25% of men and 23% of women have fat intakes above the recommended intake (Health Canada 2012). Evidence suggests that survey respondents tend to underestimate their energy intake (Black, Prentice et al. 1993). Thus, the

reports of poor diet in our sample may underestimate the actual prevalence of poor diet.

Those who were inconsistent in their reports of childhood traumatic events did not seem to differ from the sample that was used for the purposes of this study by age, sex, SES, health risk behaviours, depression, stressful life events, or obesity. However, they were less likely to report more than two childhood traumatic events. In a study assessing the reliability of self-reported childhood physical abuse, reporting only one rather than two or more types of childhood physical abuse was predictive of inconsistency (McKinney, Harris et al. 2009).

For the most part, the baseline characteristics for those who dropped out of the study when compared to those who remained in the study were very similar. However, those who dropped out were about two times more likely to report low SES, and were less likely to report being overweight or obese. Lower SES is associated with many of the health outcomes assessed in this study and thus our results may not reflect the extent to which many of these health outcomes may have occurred in the general population.

Association between Childhood Trauma and Cardiovascular Disease

The results of this thesis show a dose-response relationship between childhood trauma and CVD. This is in line with previous findings from the literature concerning the relationship between childhood trauma and CVD (Dong, Giles et al. 2004; Korkeila, Vahtera et al. 2010).

The findings of this study may be evidence of the accumulation model of life course epidemiology. The accumulation model of life course epidemiology is the idea that disadvantages experienced during childhood lead to a health-relevant disadvantage later in life and that factors which increase the risk for disease gradually accumulate over ones lifetime (Heikkinen 2011). The findings concerning the association of childhood trauma with other risk factors for CVD such as obesity, high blood pressure, smoking and depression support the accumulation model.

In the literature, many of these factors have also been associated with an increased risk for one another. For example, depression has been associated with the development of alcohol abuse and/or dependence, and nicotine dependence (Colman and Ataullahjan 2010; Mendelsohn 2012). Also, depression in adolescence has been associated with faster rates of increase in BMI in adulthood among women but not men (Gaysina, Hotopf et al. 2011). In addition, smoking has been found to increase the risk for high blood pressure (Halperin, Gaziano et al. 2008; Dochi, Sakata et al. 2009).

When addressing the difference between women and men in this association, the findings showed that women who report childhood traumatic events are significantly more likely to have CVD when compared to men who report childhood traumatic events. Although a previous study has shown that when stratified by sex the impact childhood trauma on CVD is greater among

women than among men (Korkeila, Vahtera et al. 2010), an interaction effect between childhood trauma and sex for CVD has not been previously explored.

This is the first study to our knowledge that has assessed the moderation effect of stressful life events on the relationship between childhood trauma and CVD. The allostatic load hypothesis suggests that early life stressors lead to adverse physical health consequences. Childhood trauma has also been linked with increased cortisol levels (Luecken 1998), particularly among women (Handa, Burgess et al. 1994). Increased cortisol may in turn affect the development of CVD (Whitworth, Mangos et al. 2000).

Cardiovascular mortality has also been associated with life stressors such as marital dissolution and chronic work stress (Matthews and Gump 2002). In addition, reports of stressful life events were significantly more likely to occur among those who have coronary heart disease (Rafanelli, Roncuzzi et al. 2005). Those who experience childhood traumatic events may be particularly vulnerable to life stressors in adulthood (McLaughlin, Conron et al. 2010). The findings of this study were in line with the hypothesis that the impact of childhood trauma on CVD would be heightened among those who have experienced recent stressful life events.

The effect of stressful life events on heightening the relationship between childhood trauma and CVD was only found among women when compared to men. This is also in line with the hypotheses. This may be due to a higher sensitivity to stress among women, which has been found in both

human and animal studies (Mccormick, Smythe et al. 1995; Luecken 1998). This higher sensitivity among women is suggested in the literature to be influenced by estrogen (Handa, Burgess et al. 1994; Weiser and Handa 2009).

Literature has shown that depression may lead also to dysregualtion of the HPA axis (Sheline 2003). This is supported by evidence which suggests that depression may lead to a reduction in hippocampal volume (MacQueen, Campbell et al. 2003). Thus, depression may exacerbate dysregulation of the HPA axis among those who experience childhood traumatic events. As a result, we hypothesized that the effect of childhood trauma on CVD would be heightened among those who are depressed when compared to those who are not depressed. A moderation effect of depression in the relationship between childhood trauma and CVD has not been previously addressed in the literature. However, this study did not find evidence that depression heightens the impact of childhood trauma on CVD.

Mediation of the association between childhood trauma and CVD

It was found that poor diet, smoking, and depression, partially mediate the relationship between childhood trauma and CVD. However, these factors were not found to mediate the moderation effect of sex on the relationship between childhood trauma and CVD. Previous studies have not seemed to address mediating factors in the relationship between psychological stress and CVD.

Secondary Outcomes

Childhood trauma was also significantly associated with high blood pressure and overweight/obesity. This is in line with evidence that has shown that exposure to trauma in early life has been associated with obesity in adulthood (Gunstad, Paul et al. 2006; Noll, Zeller et al. 2007), and with high blood pressure (Luecken 1998). However, when looking at overweight or obesity and high blood pressure as outcomes, the effect of childhood trauma was not heightened among women when compared to men.

When looking at the significant mediators as secondary outcomes, the effect of childhood trauma was heightened among women for poor diet and for smoking. However, the interaction effect between childhood trauma and sex was not found to be significant for depression, which is in line with the results of a recent study that has addressed this possible association (Arnow, Blasey et al. 2011).

Recent stressful life events were not found to heighten the impact of childhood trauma on high blood pressure or depression. There was no evidence for the stress sensitization hypothesis or the stress amplification hypothesis, which suggest an increased vulnerability to depression among those who have experienced childhood traumatic events if they experience stressful life events in adulthood (Hammen, Henry et al. 2000; Rudolph and Flynn 2007).

However, the reduced impact of childhood trauma on depression among those who reported stressful life events in adulthood when compared to those who did not report stressful life events provides support for the stress inoculation hypothesis which suggests that depression may be less likely to develop among those who experience stressful life events and have also experienced adversity in childhood (Rudolph and Flynn 2007). This hypothesis suggests that experiencing adversity in childhood may act as a buffer against the adverse effect of stressful life events on depression (Rudolph and Flynn 2007).

However, the interaction between childhood trauma and recent stressful life events was found to be significant when looking at smoking and overweight/obesity as outcomes, and these effects were found for women but not men. The results for overweight/obesity are similar to findings from another study that looked at the impact of stressful life events on Body Mass Index and found higher associations among women when compared to men (Barry and Petry 2008). The findings for smoking are in line with a study which found that women who experienced stressful life events were more likely to continue smoking and less likely to quit smoking when compared to men who experienced stressful life events (McKee, Maciejewski et al. 2003).

The findings for the moderation effect of stressful life events in the relationships between childhood trauma and CVD as well as CVD risk suggest that the stress amplification hypothesis may be expanded to include adverse physical health factors such as CVD rather than mental illness alone.

The impact of childhood trauma was higher among women when compared to men for CVD risk factors that were behavioral (poor diet and smoking) rather than depression, overweight/obesity, or high blood pressure. This suggests that heightened stress may result in more of a difference between women and men for cardiovascular disease risk through health risk behaviors rather than direct biological mechanisms.

A study looking at sex differences in health risk behavior suggested that men engage in more active health risk behaviors such as smoking or alcohol consumption whereas for women they were more passive such as physical inactivity (de Barros and Nahas 2001). A heightened stress response among women who experience childhood traumatic events may lead to engagement in more active forms of health risk behavior than is generally observed. This possibility is supported by findings from a recent study in which stress cues were found to elicit more subjective stress and cravings for smoking for women when compared to men (Saladin, Gray et al. 2012).

The literature shows that cigarette smoking may be particularly harmful for women in terms of the development of CVD. Smoking is suggested to predispose women to atherosclerosis (Worrall-Carter, Ski et al. 2011). In the Nurses' Health Study, the risk for atherosclerosis was increased by six times among women who smoked 20 cigarettes per day (Sarna, Bialous et al. 2008). Cardiovascular disease risk was found to almost double for those who smoked 4-5 cigarettes per day.

In another study, it was found that the occurrence of the first acute myocardial infarction (AMI) was more premature among women that smoked when compared to male smokers (Grundtvig, Hagen et al. 2009). This study also showed that years lost due to AMI was two times higher among women when compared to men. It is suggested that these sex differences in the relationship between smoking and CVD may be the result of women having smaller coronary arteries and vessel size than men (Ashby, Mehran et al. 2003).

4.4. General Implications

This thesis focused on sex differences in the influence of childhood trauma on CVD and CVD risk. Since childhood trauma is both highly prevalent in Canada and is becoming more common as time goes by, it is an important risk factor to address. It has also been associated with many adverse psychological and physiological consequences. With the burden of CVD becoming greater among women, investigating the impact of childhood trauma on CVD among women when compared to men may provide information that will help to reduce the burden of CVD among women through the development of policy and intervention strategies.

These findings have important public health implications because (1) childhood trauma can be reduced through behavioural changes of parents and coping mechanisms of those dealing with childhood trauma and (2) many of the risk factors for CVD are modifiable. Also, women delay in seeking help,

and are less likely to see a physician or detect signs of CVD than men (Worrall-Carter, Ski et al. 2011). This may be because the symptoms of heart disease in women are less obvious than it is for men (Pilote, Dasgupta et al. 2007). For example, chest pain is an expected symptom of CVD that does not frequently occur as an early symptom among women (Worrall-Carter, Ski et al. 2011).

In addition, trends in the United States show that no symptoms are displayed in 64% of women who suddenly die from CVD (Rosamond, Flegal et al. 2007). In the Framingham Study it has been found that of acute myocardial infarction (AMI) experienced by women 50% is unrecognized whereas 33% of AMI experienced by men is unrecognized (Kannel and Abbott 1984). The more subtle signs of CVD for women might thus contribute to the greater risk of mortality from CVD observed among women.

Raising awareness concerning the burden of CVD among women and risk factors that pertain to the development of CVD among women specifically, may promote more health seeking behavior among women who may have signs of CVD. Women who know that they have an increased risk for CVD due to a history of childhood trauma may be more attentive to subtle signs of CVD. Also, since many CVD risk factors are modifiable, findings that many health risk behaviours further heighten the risk for CVD among those who have experienced childhood traumatic events may help to reduce engagement in health risk behaviors among this high-risk population.

Further awareness of the adverse effect of childhood trauma on psychological and physical health may lead parents to be more cautious of the influence of their actions on their children. In situations where the trauma is difficult to prevent such as hospitalizations, divorce, or a very traumatic event that is thought about for years after its occurrence, one possible treatment is to give the parents a consultation to be able to treat the child at home (Coates and Gaensbauer 2009). Another option would be a psychotherapeutic intervention with the length depending on the extent to which the child is traumatized by the situation (Coates and Gaensbauer 2009).

Psychosocial interventions are suggested for children with PTSD rather than the use of medications except in very extreme cases due to uncertainty concerning the effect they may have on the developing brain (Coates and Gaensbauer 2009). Also, it is suggested that caregivers work closely with therapists to prevent retraumatization that young children may experience when meeting a new person (Coates and Gaensbauer 2009). The treatment of PTSD in young children includes desensitization to the effect of traumatic triggers and helping the child to psychologically process the trauma through the use of storytelling, drawing and language play (Coates and Gaensbauer 2009).

In terms of the impact of recent stressful life events on heightening the influence of childhood trauma on CVD in adulthood, cognitive behavioural therapy (CBT) such as cognitive restructuring and breathing retraining has been shown to be effective for reducing anxiety (Mueser, Rosenberg et al.

2008). Interventions may also be aimed at the secondary outcomes addressed in this study. For example, CBT has also been shown to be effective for reducing depression (Mueser, Rosenberg et al. 2008).

Also, for those suffering with depression the increased risk for CVD may be reduced by the use of antidepressants. Antidepressant use has been found to lead to a lower likelihood for depression eight years later in a sample representative of the Canadian population (Colman, Zeng et al. 2011). Research also shows that antidepressants can lead to hippocampal neurogenesis (Warner-Schmidt and Duman 2006). This may reverse atrophy of the hippocampus, which can occur as a result of depression and anxiety (Warner-Schmidt and Duman 2006) and impairs negative feedback of the HPA axis (Jacobson and Sapolsky 1991; Herman and Cullinan 1997).

In addition, smoking cessation and healthy eating programs could be implemented and specifically targeted at high-risk youth with a history of trauma. Community-based interventions in environments where there are more high-risk youth may be one way to achieve this. Community based interventions have been found to be effective in reducing obesity. For example, an intervention conducted in a school setting called the Annapolis Valley Health Promoting Schools Project (AVHPSP) instituted nutrition programs and found lower rates of obesity and better nutrition habits among students when compared to schools which did not implement this program (Veugelers and Fitzgerald 2005).

Also, traumatic events of patients should be taken into account given its adverse effect on several mental and physical health factors. Specifically when dealing with reducing depression and anxiety, active screening of childhood trauma and focusing on traumatic childhood events when conducting CBT has been shown to be more effective than when the trauma is not taken into account (Vitriol, Ballesteros et al. 2009). Since those who have experienced childhood trauma tend to experience retraumatization in their adult interpersonal experiences, these coping mechanisms developed from CBT that is focused on traumatic childhood events may help to either prevent revictimization or attenuate the influence of such experiences on depression or anxiety (Gladstone, Parker et al. 2004).

4.5. Strengths & Limitations

This study has potential limitations in that those who develop CVD may have been more likely to drop out than those that do not, which may lead to survivor bias and thus potentially lead to an underestimate of the results. The cumulative attrition rate for the NPHS by cycle 8 (2008/09) was 42% (Statistics Canada 2010a).

There is also the possibility of non-sampling related biases due to the use of survey data such as the interviewer misreading the question, a misunderstanding of the question by the respondent (due to language barriers for example), the respondent may answer the question incorrectly either intentionally or by accident, and the data may have been improperly imputed.

This potential bias cannot be accounted for since the true population responses to the survey questions are unknown.

Another limitation is the possibility of residual confounding. Since SES was controlled for and was a dichotomous variable, it is possible that residual confounding may have occurred within strata. However a sensitivity analysis was conducted using income adequacy with four categories as the measure for SES rather than the dichotomous variable. There were no differences when using the SES measure with four categories, suggesting that residual confounding may not be a problem for the dichotomous SES measure.

Also, we could not control for neighborhood SES or the age at which childhood trauma occurred which are both possible confounders in the association between childhood trauma and CVD. There is no information in the NPHS on the age at which the childhood trauma occurred, which should be controlled for since those who experience trauma at younger ages are less likely to remember childhood trauma (Harvey and Herman 1994; Fergusson, Horwood et al. 2000) and thus may be less likely to be affected by it.

Also, the NPHS does not assess childhood SES, which is related to both childhood trauma (Trickett, Carlson et al. 1991) and cardiovascular disease (Galobardes, Smith et al. 2006) but is not on the causal pathway between them, and is thus a possible confounding factor which cannot be controlled for in this study. However, there is also evidence which shows that the association between childhood SES and health in adulthood disappears

once adult SES is taken into account (Marmot, Shipley et al. 2001). It is suggested that this is because SES in adulthood is influenced by childhood SES.

Neighborhood factors such as neighborhood level of impoverishment, social cohesion and perceived neighborhood safety were not assessed by the NPHS. Such neighborhood factors however have been associated with both CVD (Sundquist, Theobald et al. 2006) and childhood trauma (Coulton, Korbin et al. 1999). Thus, neighborhood factors may have been a confounding variable that could not be controlled for. However, neighborhoods are strongly linked with SES, which was accounted for.

Another possible limitation is non-differential misclassification for childhood traumatic events, which may have underestimated the impact of the childhood trauma on CVD. Previous evidence shows that child abuse is generally underreported (Dellafemina, Yeager et al. 1990). Also, depression has been associated with negative memory bias, especially for information that is emotionally toned (Dalgleish and Watts 1990). However, those who were inconsistent in their reports of childhood traumatic events were excluded in an attempt to minimize possible mood-congruent memory bias.

A limitation concerning the use of data from the NPHS is that we did not have control over the measures that were used in the study to assess the variables of interest. Many of the factors we assessed were examined by the NPHS using self-reports rather than more objective measures. However, the

NPHS used a measure for depression that corresponded to DSM-IV criteria for a major depressive episode and has an accuracy of 93% for classifying major depressive disorder (Kessler RC 1998).

Also, the NPHS excluded residents of some remote areas in Ontario and Quebec, health institutions, Native reserves and Crown lands, and Canadian Forces bases (those who were full-time Canadian Forces members), which may be high-risk populations for both childhood trauma and CVD. For example, death rates due to CVD are higher among Aboriginal women than women in the general Canadian population(Heart and Stroke Foundation of Canada 1995). This limits the external validity of our findings and also might have led to an underestimate of the results.

This study has strengths in that the data was collected prospectively. Prospective cohorts are less prone to bias than other forms of observational study designs. In relation to this, retrospective reporting of early childhood trauma was assessed at multiple cycles in the NPHS, which allows for the exclusion of inconsistent reporters. This makes recall bias for the reporting of childhood trauma less likely than if it were to be reported at only one point in time in adulthood and thus increases validity.

This cohort is also nationally representative of Canadians and thus provides further protection from bias, and increases external validity. In addition, since the data were assessed in a retrospective cohort design,

concerns about cost and time, which are disadvantages of prospective cohort studies, were averted.

4.6. Future directions

This study looked at the relationship between childhood trauma and CVD, possible mediators and moderators for this association, and sex differences. Future studies may benefit from using more objective measures of the variables addressed for the purposes of this study, rather than self-reports. Future studies may also benefit from using survival analysis to assess the effect of sex in modifying the association between childhood trauma and CVD.

Survival analyses were not conducted for this study because the induction period between when the childhood traumatic event occurred and when the CVD event occurred were unknown since the age at which the childhood traumatic event occurred was not recorded, and participants were asked “do you have heart disease” without specifying the time at which heart disease occurred. However, for studies that have information concerning when childhood traumatic events occur and more objective measures for CVD, the use of survival analysis is suggested.

Also, the effect of other mental health factors on the relationship between childhood trauma and CVD should be investigated, since an increased risk of mortality from heart disease and stroke among those with schizophrenia, schizoaffective disorder, bipolar disorder and delusional

disorder has been found (Osborn, Levy et al. 2007). Another suggestion is the assessment of childhood trauma with information concerning age at which the trauma occurred.

The effect of childhood trauma may not lead to hyperactivity to stress for all individuals. For example, the stress inoculation hypothesis suggests that adversity in childhood may act as a buffer against stressful life events in adulthood and may thus be less likely to develop depression (Rudolph and Flynn 2007). Future research could thus investigate potential resilience factors and whether those who have experienced childhood trauma but are more resilient, are less likely to develop CVD.

The impact of childhood trauma on adverse physical and psychological consequences in adulthood has generally been found to be higher among women than among men. For example, women with psychosis have been found to be three times more likely than women without psychosis to report childhood physical abuse while this association was not found to be significant among men (Fisher, Morgan et al. 2008). Future studies should thus also investigate sex differences in the relationship between childhood trauma and other psychological and physical health factors. Lastly, the stress amplification hypothesis for physical health factors should be investigated.

4.7. Conclusions

In conclusion, the results of this study suggest that the impact of childhood trauma on CVD is heightened among women when compared to men. The results also suggest that depression, smoking, and diet partially mediate the relationship between childhood trauma and CVD. Also, we found that the effect of childhood trauma on smoking and poor diet is heightened among women when compared to men.

This suggests that sex differences in the relationship between childhood trauma and CVD risk may be influenced by adverse behavioral responses to stress, particularly among women. Stressful life events were also found to heighten the impact of childhood trauma on CVD, overweight/obesity and smoking among women but not men. These findings indicate the need for early interventions as well as health promotion and awareness efforts directed towards those who have experienced childhood traumatic events, particularly women.

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