Childhood adversity and metabolic outcomes

in adults with mood disorders

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Table of Contents

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2. Abstract

Background: Metabolic syndrome is a clustering of conditions that increases the risk for cardiovascular disease. These metabolic disturbances are often comorbid with mood disorders, such as depression (MDD) and bipolar disorder (BP), and are associated with poorer psychiatric prognosis and worse functional impairment. Childhood adversity has been hypothesized to be a common risk factor for both metabolic disturbances and mood disorder. However the precise association between childhood adversity, metabolic disturbances, and mood disorders is still unknown.

Objectives: (1) To examine the association between childhood adversity and metabolic outcomes. (2) To test whether specific types of childhood adversity (e.g. abuse, neglect, and family/household dysfunction) and type of mood disorder interact to worsen metabolic outcomes.

Methods: This was a cross-sectional study of 68 adult outpatients from a university-based, tertiary-care mood disorders clinic with a DSM-IV defined depression (N=28) or bipolar type I or II disorder (N=40). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III clinical criteria for defining metabolic syndrome were measured. Childhood adversity was measured using the Adverse Childhood Experience self-report questionnaire which collects categories of adversity pertaining to abuse, neglect, and family/household dysfunction. Linear and logistic regressions adjusted for age, sex, and education were conducted to examine the association between childhood adversity and metabolic outcomes. Interaction analyses were conducted to test if type of mood disorder modified the effect of childhood adversity on metabolic outcomes.

4

Results: Nearly one-third (32.3%) of the sample met the NCEP criteria for metabolic syndrome. Despite the majority of our sample being overweight (BMI = 25-29.9), all other metabolic outcomes were within a healthy range. Childhood adversity was highly prevalent in this mood sample, with 80.9% of the participants experiencing at least one category of childhood adversity. Childhood adversities included exposure to household mental illness/suicide (45.6%), emotional neglect (33.8%), alcohol/drug abuse (29.4%), emotional abuse (27.9%), physical abuse (25.0%), sexual abuse (25.0%), parental divorce/separation (23.5%), domestic violence towards mother (13.2%), physical neglect (2.9%), and imprisoned household member (1.5%). There were no statistically significant relationships between the total number of childhood adversities and the range of metabolic outcomes. Several associations between type of childhood adversity and metabolic outcomes were found. Firstly, parental divorce/separation was associated with a higher BMI (B = 3.3, p = 0.047), but after controlling for age, sex, and education, parental divorce/separation was no longer significant. Notably in interaction testing, type of mood disorder modified the effect of parental divorce/separation on BMI such that the association between parental divorce/separation and BMI was greater in the presence of BP versus MDD (B = -7.4, p = 0.016). Secondly, emotional neglect was associated with lower diastolic blood pressure (B = -7.0, p = 0.043).

Conclusion: This study provides preliminary evidence linking childhood parental divorce/separation and emotional neglect to the specific metabolic risk factors of BMI and diastolic blood pressure. Systematic assessment of childhood experiences, regular monitoring of the metabolic indices, and promotion of healthy lifestyle habits should be emphasized in routine clinical care of individuals with mood disorders.

3. Résumé

Contexte: Le syndrome métabolique augmente le risque de maladies cardiovasculaires. Ces perturbations ont souvent une morbidité associée aux troubles de l'humeur, comme la dépression (MDD) et le trouble bipolaire (BP). Elles sont associées à un moins bon pronostic psychiatrique et une dépréciation fonctionnelle plus importante. L'hypothèse a été émise que l'adversité durant l'enfance est un facteur de risque commun pour les troubles métaboliques et les troubles de l'humeur. Cependant l'association précise entre l'adversité durant l'enfance, les troubles métaboliques et les troubles de l'humeur est encore inconnue.

Objectifs: (1) Pour examiner l'association entre l'adversité durant l'enfance et les troubles métaboliques de l'hypertension artérielle, l'obésité abdominale, taux élevés de triglycérides, la glycémie à jeun élevée et peu de lipoprotéines de haute densité (HDL). (2) Pour tester si des types spécifiques d'adversité durant la petite enfance (abus, négligence, familles/ménages dysfonctionnels) et le type de trouble de l'humeur interagissent pour aggraver les résultats métaboliques.

Méthodes: Ce fut une étude transversale de 68 patients ambulatoires adultes d'une clinique universitaire de soins des troubles de l'humeur avec une dépression telle que définie selon les critères du DSM-IV (N = 28) ou de trouble bipolaire de type I ou II (N = 40). Les critères cliniques définissant le syndrome métabolique du programme national d'éducation du cholestérol (NCEP), Panel de Traitement pour Adultes III, ont été mesurés. L'adversité durant l'enfance a été mesurée à l'aide de l'auto-questionnaire sur l'expérience adverse durant l'enfance qui recueille les catégories d'adversité relatives à l'abus, la négligence et la dysfonction des familles/ménages. Les régressions linéaires et

logistiques ajustées pour l'âge, le sexe et le niveau d'éducation ont été effectuées afin d'étudier l'association entre l'adversité durant l'enfance et les résultats métaboliques. Les analyses d'interaction ont été menées afin de tester si le type de trouble de l'humeur (troubles bipolaires versus dépression) a modifié l'effet de l'adversité durant l'enfance sur les résultats métaboliques.

Résultats: Près d'un tiers (32,3%) de l'échantillon répondait aux critères pour le syndrome métabolique. En dépit de la majorité de notre échantillon étant en surpoids (IMC = 25-29,9), tous les autres résultats métaboliques étaient se situaient à un niveau normal. L'adversité durant l'enfance était très répandue dans l'échantillon des troubles de l'humeur, avec 80,9 % des participants ayant connu au moins une catégorie de l'adversité durant l'enfance. Les adversités durant l'enfance incluent l'exposition des ménages à la maladie mentale ou au suicide (45,6 %), la négligence affective (33,8 %), l'abus d'alcool et/ou de drogues (29,4 %), la violence psychologique (27,9%), la violence physique (25,0%), les abus sexuels (25,0 %), et la séparation ou le divorce des parents (23,5%). Plusieurs associations entre type d'adversité durant la petite enfance et les résultats métaboliques ont été trouvées. Tout d'abord, le divorce ou la séparation des parents a été associée à un IMC plus élevé (B = 3,3 ; p = 0,047). Cependant, après ajustement pour l'âge, le sexe et le niveau d'éducation, le divorce ou la séparation des parents, cela n'était plus significatif. Deuxièmement, la négligence émotionnelle a été associée à une baisse de la pression diastolique du sang (B = -7,0 ; p = 0,043).

Conclusion: Cette étude fournit des preuves préliminaires reliant le divorce ou la séparation des parents durant l'enfance et de la négligence émotionnelle à des facteurs de risque métaboliques tels l'IMC et la pression artérielle diastolique. L'évaluation

systématique des expériences durant l'enfance, un suivi régulier des indices métaboliques et la promotion de saines habitudes de vie doivent être soulignés dans les soins cliniques de routine des personnes souffrant de troubles de l'humeur.

4. Introduction

Mood disorders, such as major depressive disorders (MDD) and bipolar disorder (BP), are of growing concern due to its associated disability (Health Canada, 2002). In addition to mood disorders, metabolic syndrome has also become a public health concern as increasing obesity rates and sedentary lifestyles contribute to its rising global prevalence (Alberti et al., 2009). Childhood adversity has been examined in relation to these psychiatric and metabolic conditions with findings that call for further examination. Below, the definition, prevalence, and impact of mood disorders, metabolic syndrome, and childhood adversity are discussed along with the current gap in knowledge.

4.1 Mood disorders

Mental illness has been identified as the most economically burdensome diseases in Canada, with an estimated annual cost of $14.4 billion (Stephens & Joubert, 2001). Mood disorders, which affect the emotional state of a person, are among the most common and disabling mental conditions in the general population. Worldwide rates for mood disorders vary across countries, with lifetime prevalence rates ranging from 3.3% in Nigeria, 7.6% in Japan, 9.2% in Mexico, 12.6% in Lebanon, 14.1% in Belgium, 21.0% in France, to 21.4% in the United States (Kessler et al., 2007). Specifically in Canada in 2012, the lifetime prevalence of mood disorders was 12.6%, with MDD accounting for the majority of cases (Pearson, Janz , & Ali 2013). Women have a significantly higher risk than men to develop mood disorders (Kessler et al., 2005). Despite the cross-national variation in lifetime prevalence rates, a shared pattern in the age of onset is observed. The prevalence of mood disorders is low until the early teens, then linearly increases through to late-middle age, and gradually increases thereafter (Kessler et al., 2007). The National

Comorbidity Survey Replication estimated the median age of mood disorder onset to be 30 years (Kessler et al., 2005).

Mood disorders not only contribute to occupational and social impairments but also physical disease. Mood disorders were more strongly associated with earlier onset instead of later onset of medical illness. There was also a significant association between depression and onset of heart disease, with an odds ratio of 1.3 (95% C.I. 1.1 – 1.4) (Scott et al., 2013). Hospitalizations due to mood disorders are also sometimes necessary, with 25% of those who have a primary diagnosis of mood disorder requiring psychiatric hospitalization (Canadian Institute for Health Information, 2012). Suicide risk is a common reason for hospitalization in mood disorders (Lasky, Krieger, Elixhauser, & Vitiello, 2011; Patten et al., 2009). Stigma surrounding mental illness has also contributed to the burden experienced by people with mood disorders, influencing both seeking and compliance of treatment (Health Canada, 2002).

i. Depression

Definition. According to the criteria for MDD described by the Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV-TR*; 4th ed., text rev.; American Psychiatric Association, 2000), MDD is characterized by having at least one period lasting at least 2 weeks of depressed mood and/or loss of interest or pleasure in activities, most of the day, nearly every day. Additional to experiencing either depressed mood or diminished interest or pleasure, at least four more of the following symptoms have to be present during the same 2-week period, in conjunction with marked impairment to functioning: 1) weight loss or weight gain; decreased or increased appetite, 2) insomnia or hypersomnia, 3) psychomotor agitation or retardation, 4) fatigue or loss of energy, 5)

feelings of worthlessness or inappropriate guilt, 6) decreased concentration or indecisiveness, and 7) recurrent thoughts of death and/or suicidal ideation, plan, attempt.

Epidemiology. Worldwide rates for MDD vary across countries, from lifetime prevalence rates of 3.0% in Japan to 16.9% in the United States, with most countries ranging between 8.0% to 12.0% (Andrade et al., 2003). Specifically in Canada, the most recent nationally representative data from the Canadian Community Health Survey: Mental Health and Well-Being of 2012 found that the Canadian lifetime prevalence of MDD was 11.3% (Pearson et al., 2013). Comparatively, United States had a higher prevalence of lifetime MDD at 16.6% (Kessler et al., 2005). In Canada, MDD was more common in women, in younger ages, in single or previously married subjects (divorced, widowed, or separated), in those with at least one medical condition, and in those who were unemployed within the last year. The mean age of onset ranges from 24.8 to 34.8 years (Weissman et al., 1996). Level of education was not related to the prevalence of MDD (Patten et al., 2006). Due to both the aging baby boomer cohort and the increasing prevalence of chronic diseases, the number of cases of people with MDD was expected to increase in Canada (Craven & Bland, 2013).

Impact/Burden. In the first Global Burden of Disease study in 1990, MDD was identified as the most disabling disorder and fourth leading cause of disease burden that takes into account prevalence estimates, course, impairment and premature mortality (Murray & Lopez, 1994). In this same study, depression was projected to be the second leading cause of disease burden, after heart disease, by 2020 (Summary: the global burden of disease, 1996). This projection was reinforced in 2010, whereby MDD accounted for the most disability-adjusted life years and disease burden amongst all

mental and substance use disorders in the world (Whiteford et al., 2013). Depression is not only very disabling but also affects quality of life (Rapaport, Clary, Fayyad, & Endicott, 2005), reduces work productivity and performance (Gilmour & Patten, 2007; Kessler et al., 2006; Sanderson, Tilse, Nicholson, Oldenburg, & Graves, 2007), impairs social functioning (Kessler et al., 2003), is associated with less healthy lifestyle behaviours such as smoking, lack of exercise, and unhealthy eating (Lin et al., 2004), and worsens health status (Moussavi et al., 2007).

ii. Bipolar disorder

Definition. BP represents a cluster of extreme changes in mood, energy, activity levels, sleep, behaviour, and day-to-day functioning (*DSM-IV-TR, 2000*). The two main types of BP are Bipolar I Disorder (BPI) and Bipolar II Disorder (BPII). Based on the diagnostic criteria of the *DSM-IV-TR*, BPI is distinguished from MDD by at least one lifetime manic, characterized by a period lasting at least 1 week of abnormally and persistently elevated or irritable mood (or requiring hospitalization). In addition, three or more of the following symptoms are present (four if mood is only irritable) and sufficiently impaired occupational and/or social functioning: 1) inflated self-esteem or grandiosity, 2) reduced need for sleep, 3) more talkative, 4) racing thoughts, 5) distractibility, 6) increase in goal-directed activity, and 7) increase in pleasure-seeking activities which may cause harm to self and/or others (*DSM-IV-TR, 2000*). BPII is characterized by the occurrence of one or more hypomanic episodes which has the same criteria defining a manic episode, but is not severe enough to cause marked impairment and do not require hospitalization.

Epidemiology. Compared to MDD, BP is often more difficult to identify (Angst, 2006) and often misdiagnosed as MDD initially (Angst, Azorin, et al., 2011). With respect to worldwide BP rates, little differences exist across countries (Weissman et al., 1996). The Canadian lifetime prevalence of BP in 2012 was 2.6% (Pearson et al., 2013) while it was 3.9% in the United States (Kessler et al., 2005). BP is seen to affect both men and women equally (Merikangas & Low, 2004). This disorder often develops in early adulthood, with half of all cases appearing before 25 years of age (Kessler et al., 2005). The mean age of onset of BP is about 6 years earlier compared to MDD (Weissman et al., 1996). Marital status (married versus divorced, separated, or widowed) was not associated with BP (Jonas, Brody, Roper, & Narrow, 2003). Genetic and familial factors also have a role as BP was 7 times more likely among relatives of BP probands than of controls as shown in a meta-analysis (Craddock & Jones, 1999).

Impact/Burden. BP was ranked the 6th leading cause of worldwide medical disability (Murray, Lopez, & Jamison, 1994) and deemed the most costly behavioural health care diagnosis (Peele, Xu, & Kupfer, 2003). BP is associated with psychosocial, economic, and functional disability as well as reduced quality of life. Direct costs included in- and out-patient care and expenditures for the criminal justice system. Indirect costs included lost productivity for those who were employed, unemployed, institutionalized, or committed suicide (Wyatt & Henter, 1995). With suicide being a common manifestation of severe psychiatric distress, 25% to 50% of patients with BP attempt suicide at least once (Jamison, 2000). The high-risk behaviours that accompany BP compromises interpersonal relationships, financial stability, leading to shame and remorse (Fletcher, Parker, Paterson, & Synnott, 2013).

4.2 Metabolic syndrome

Definition. Metabolic syndrome is a clustering of conditions (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004). The diagnostic criteria, defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (National Institute of Health, 2001), includes high blood pressure, abdominal obesity, high levels of triglycerides, high fasting glucose, and low levels of high-density lipoprotein (HDL) cholesterol; the presence of three or more of these five indices characterizes metabolic syndrome (Alberti et al., 2009).

Epidemiology. The prevalence of metabolic syndrome was estimated at 19.1% based on the Canadian Health Measures Survey collected in 2007-2009, a cross-sectional survey representative of the Canadian population (Riediger & Clara, 2011). In the United States national survey collected in 1988-1994, metabolic syndrome was present in almost one-quarter (23.7%) of their population. Little differences could be found between the prevalence in men and women, but bigger differences were accounted for by age; the presence of metabolic syndrome increased with age from 6.7% among those aged 20 to 29 years to 43.5% among those aged 60 to 69 years (Ford, Giles, & Dietz, 2002). The Canadian Health Measures Survey also found higher rates of metabolic syndrome and increased number of its components among people in households with lower education and income (Riediger & Clara, 2011). Smokers are also found to have higher rates of metabolic syndrome than non-smokers (Wang et al., 2013).

Impact/Burden. Metabolic disturbances such as abdominal obesity, low HDL, and hypertriglyceridemia are precursors to cardiovascular disease (CVD) (Grundy et al., 2005; Lakka et al., 2002; Riediger & Clara, 2011). Patients with metabolic syndrome

14

have a two-fold risk to develop CVD and five-fold risk to develop type 2 diabetes

mellitus (Alberti et al., 2009). In addition to CVD, metabolic syndrome was found to

increase not only the risk for myocardial infarction, cardiovascular mortality, and stroke

two-fold but also all-cause mortality 1.5-fold in a recent meta-analysis (Mottillo et al.,

2010). Women were found to have greater cardiovascular risk compared to men in

relation to metabolic syndrome (Gami et al., 2007). Abdominal obesity defined by greater

waist circumference was associated with increased total health care costs (Cornier, Tate,

Grunwald, & Bessesen, 2002). Personal and socioeconomic burden of metabolic

syndrome also exists (Schwarz et al., 2007), including poorer perceptions of overall

health, physical health, and mental health compared to those without metabolic syndrome

(Okosun, Annor, Esuneh, & Okoegwale, 2013).

4.3 Childhood adversity

Definition. The attention on childhood abuse has significantly expanded since the

initially reported findings on childhood physical abuse (Kempe, Silverman, Steele,

Droegemueller, & Silver, 1962). Childhood maltreatment is commonly designated in four

categories: physical abuse, sexual abuse, emotional abuse, and neglect. Physical abuse

may involve excessive force that can result in bodily injuries or forcing a child to engage

in physically harmful activities. Emotional abuse involves coercive, demeaning, or overly

distant parenting/care-giving. Sexual abuse involves the exposure of a child to sexual acts

or materials, the passive use of a child as sexual stimuli for adults, and actual sexual

contact between children and older people. Finally, neglect is recognized to be the most

common form of childhood maltreatment (Wissow, 1995). Neglect is defined by the

Centers for Disease Control and Prevention as a failure to provide basic physical,

emotional, or educational needs for the child or to protect a child from harm or potential

harm (Leeb et al., 2008). Physical neglect is defined as a failure to provide basic physical

safety and security (Bernstein et al., 2003; English, Thompson, Graham, & Briggs, 2005).

Emotional neglect is defined as emotional unresponsiveness and unavailability of a

caregiver to a child's needs and desires, characterized by lack of interaction between

parent and child (Glaser, 2002). Childhood adversity also encompasses exposure to

domestic violence, household substance abuse, parental separation or divorce, criminal

household member, and household mental illness (Chapman et al., 2004). Within the

domain of childhood adversity research, there are a range of definitions for childhood

adversity and its types. Due to the lack of a standardized and reliable measure of

childhood adversity, there is heterogeneity within the definitions of childhood adversity,

and therefore comparison across studies is limited. In addition, variation in the study

samples (e.g. community, hospital, school, protective services, shelters, and legal/police

records) (Afifi, 2011) further contributes to difficulty in comparison.

     Epidemiology. The true prevalence of childhood maltreatment is difficult to

obtain as many cases are unreported or underreported (Rosenberg & Krugman, 1991).

Nationally representative Canadian prevalence estimates of child maltreatment do not

exist (Afifi, 2011). The most recent Canadian child maltreatment data comes from the

Canadian Incidence Study of Reported Child Abuse and Neglect (CIS), a national

representation of cases of child maltreatment reported to child welfare agencies. When

112 child welfare services across Canada were surveyed regarding child maltreatment

investigations, an estimated 85 440 investigations were conducted, a rate of 14.2

investigations per 1000 children. Of the cases for maltreatment, 34% involved neglect,

34% involved intimate partner violence, 20% involved physical abuse, 9% involved emotional maltreatment, and 3% involved sexual abuse. Rates of investigations decreased with age, with children under the age of one year being the most likely to be investigated. Multiple categories of maltreatment were identified in 18% of cases, with the most frequent combinations being neglect and exposure to intimate partner violence (Public Health Agency of Canada, 2010). Canada had lower rates of maltreatment compared to the United States, but had higher rates than Australia (Trocmé, Tourigny, MacLaurin, & Fallon, 2003). Risk factors for recurrent child maltreatment include alcohol and drug abuse in caregivers as well as socioeconomic disadvantage (Laslett, Room, Dietze, & Ferris, 2012).

Impact/Burden. Although occurring during childhood, a range of immediate and long-term impacts may follow early adversity. Childhood adversities are associated with poor child health (Flaherty et al., 2006) and childhood risk factors for adult cardiovascular disease by increasing body mass index (BMI), waist circumference, and heart rate (Pretty, O'Leary, Cairney, & Wade, 2013). Early adversity affects adolescent personality such that adolescents who have undergone trauma have higher scores on neuroticism and psychoticism (Li et al., 2013) and is associated with adolescent onset of psychiatric disorders (McLaughlin et al., 2012) and suicidal behaviour (Miller, Esposito-Smythers, Weismoore, & Renshaw, 2013). In an adolescent psychiatric clinical sample, those who experienced high levels of childhood abuse compared to those without childhood abuse had significantly higher levels of dependency, suicidality, violence, impulsivity, substance abuse, and borderline personality traits (Grilo, Sanislow, Fehon, Martino, & McGlashan, 1999). A graded effect of childhood adversities was also seen in

young adults whereby the increasing frequency of adverse childhood events was significantly associated with increasing impact on depressive symptoms, drug use, and antisocial behaviour (Schilling, Aseltine, & Gore, 2007).

The impacts of childhood adversity extend into adulthood in both clinical (G. R. Brown & Anderson, 1991; McCauley et al., 1997; Windle, Windle, Scheidt, & Miller, 1995) and general populations (Afifi et al., 2007; Clark, Caldwell, Power, & Stansfeld, 2010; MacMillan et al., 2001; Molnar, Buka, & Kessler, 2001; Mullen, Martin, Anderson, Romans, & Herbison, 1996; Mullen, Romans-Clarkson, Walton, & Herbison, 1988; Springer, Sheridan, Kuo, & Carnes, 2007). In a recent literature review of childhood maltreatment and Axis I mental disorders, childhood maltreatment was associated with increased risk for mental disorders, whereby an earlier age of onset of childhood maltreatment was linked with poorer mental disorders (Afifi, 2012). The onset of disorders differed between sexes following childhood maltreatment, with more anti-social behaviours found in men while more depression, post-traumatic stress disorder, and substance use disorders found in women. Parental divorce during childhood was associated with increased the odds by 1.4-fold of having any lifetime mood disorder (Afifi, Boman, Fleisher, & Sareen, 2009).

In the Adverse Childhood Experiences (ACE) Study (1998), seven categories of childhood adversities were examined: psychological, physical, or sexual abuse; violence against mother; living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned. In the sample of 9508, people who had experienced four or more categories of childhood adversities compared to those who had experienced none had greater adult health risks for alcoholism, drug abuse, depression, suicide attempt,

18

smoking, having ≥50 sexual intercourse partners, sexually transmitted disease, physical inactivity, and severe obesity (Felitti et al., 1998). In the only known birth cohort study examining a prospective measure of childhood adversity and mortality, early adversity was associated with premature mortality (Kelly-Irving et al., 2013). A history of childhood abuse also contributes to a difficulty in establishing and maintaining intimate adult relationships (Colman & Widom, 2004; Davis & Petretic-Jackson, 2000) and poorer self-esteem (Mullen et al., 1996).

The impacts of early adversity last into older age; 7080 older adults aged 65 years and older of a population-based study with childhood adversity were found to have higher rates of mood, anxiety, and personality disorders (Raposo, Mackenzie, Henriksen, & Afifi, 2013).

A relationship between the frequency of childhood adversities and deleterious outcomes has also been documented. The greater number of adversities was associated with ischemic heart disease, cancer, chronic lung disease, skeletal fracture, and liver disease in adulthood (Felitti et al., 1998). In a retrospective cohort study examining 10 categories of childhood adversity, the total number of childhood adversities was associated with greater risk of drug use from early adolescence into adulthood (Dube et al., 2003). A strong graded relationship between the total number of early adversities and the onset of suicidal ideation and attempts was found in a longitudinal population-based study of 7076 people (Enns et al., 2006). Finally, the more types of abuse experienced as a child was related to more hospitalizations for illnesses, greater perceptions of physical and psychological problems, and lower ratings of overall health in adulthood (Bell & Belicki, 1998; Moeller, Bachmann, & Moeller, 1993).

4.4 Rationale

Metabolic disturbances are often comorbid with mood disorders (Casey, 2005; Kilbourne et al., 2004; Kupfer, 2005; McIntyre, Konarski, & Yatham, 2004). In two meta-analysis studies, the prevalence of metabolic syndrome was about 37.3% in clinical samples of BP and about 30.5% in clinical samples of MDD. Higher rates of metabolic syndrome was found in these clinical samples of mood disorders compared to the general population, with odds ratio of 1.98 (95% CI=1.74-2.25) in patients with BP and odds ratio of 1.55 (95% CI=1.21-1.97) in patients with MDD (Vancampfort, Correll, et al., 2013; Vancampfort, Vansteelandt, et al., 2013). Metabolic risk factors are observed more frequently in those who are depressed (Bai, Su, Chen, Chen, & Chang, 2013; Carnethon, Kinder, Fair, Stafford, & Fortmann, 2003). Obesity, as defined by body mass index (BMI) of 30 kg/m^2 or greater, was related to lifetime mood disorders in both Canadian and American populations, with obesity increasing the odds of mood disorders by nearly 1.25-fold (Mather, Cox, Enns, & Sareen, 2009; Simon et al., 2006). Weight gain, increased appetite, and reduced physical activity are common symptoms of depression and may contribute to the increase in weight and BMI (Simon et al., 2006).

Metabolic syndrome and its components are of concern as they increase the risk for cardiovascular disease (CVD) (Guize et al., 2008; Rao, Donahue, Pi-Sunyer, & Fuster, 2001; Roeters van Lennep, Westerveld, Erkelens, & van der Wall, 2002; Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005). MDD has been associated with CVD (Lett et al., 2004; Rowan, Haas, Campbell, Maclean, & Davidson, 2005) and has been shown to predict heart disease in a review and meta-analysis of cohort studies (Rugulies, 2002). Cardiovascular risk was found to increase with BMI and the presence of metabolic

syndrome in patients with BP (Garcia-Portilla et al., 2009). It has been documented that people with mood disorders are 1.5 to 2.0 times more likely than the general population to have risk factors for CVD (Casey, 2005; Lett et al., 2004). Epidemiological studies have shown a bidirectional relationship between coronary heart disease and mood disorders whereby depression is a risk factor for coronary heart disease and 30% of patients with coronary heart disease also have mood disorders (Chauvet-Gélinier, Trojak, Vergès-Patois, Cottin, & Bonin, 2013; Goldston & Baillie, 2008).

The co-occurrence of mood disorders and clustering of metabolic disturbances have been associated with worsened prognosis, with illness chronicity (Calkin et al., 2009), more psychiatric hospitalizations (McIntyre et al., 2010), suicidality (Fagiolini, Frank, Scott, Turkin, & Kupfer, 2005; Fagiolini et al., 2008), disease risk for diabetes and vascular disease, and functional impairment (Taylor & MacQueen, 2006). The greatest decrements in health occurred when MDD was comorbid with diabetes compared to the independent effects of MDD or diabetes (Moussavi et al., 2007). In patients with BP, more depressive and manic episodes and shorter time to develop an affective recurrence was found in those who were obese compared to those who were non-obese (Fagiolini, Kupfer, Houck, Novick, & Frank, 2003). The risk of mortality in patients with CVD is 2.0 times greater in those with MDD compared to those without MDD (Barth, Schumacher, & Herrmann-Lingen, 2004). Greater health care costs have also been associated with having a metabolic and psychiatric comorbidity (Centorrino, Mark, Talamo, Oh, & Chang, 2009).

Some evidence supports that the common comorbidity of mood disorders and metabolic disturbances may be due to a shared risk factor. It has been hypothesized that

childhood adversity may mediate the association between mood disorders and metabolic disturbances (McIntyre et al., 2012).

Childhood adversity has been associated with metabolic syndrome and its components, in both community (Danese et al., 2009; Lee, Tsenkova, & Carr, 2014; Riley, Wright, Jun, Hibert, & Rich-Edwards, 2010) and clinical populations (Post et al., 2013). In the 2005 CCHS, childhood physical abuse was associated with obesity in the Canadian population (Fuller-Thomson, Sinclair, & Brennenstuhl, 2013). In the US National Longitudinal Study of Adolescent Health, the co-occurrence of childhood sexual and physical abuse was associated with increased risk of severe obesity in adulthood compared with individuals without any history of childhood abuse (Richardson, Dietz, & Gordon-Larsen, 2013). A study of a community sample of 342 women found that childhood physical abuse was associated with the presence of metabolic syndrome (Midei, Matthews, Chang, & Bromberger, 2013). In another community sample of 1234 people, emotional and physical abuse was found to increase the risk of developing metabolic syndrome for both sexes whereas sexual abuse was a risk factor for metabolic syndrome in only women (Lee et al., 2014). Specifically in a mood disorders population, the childhood adversity score was associated with 11 medical conditions, including hypertension (Post et al., 2013).

Childhood adversity is an established risk factor for mood disorders in both cross-sectional (Gonzalez et al., 2012; Raposo et al., 2013) and prospective studies (Weich, Patterson, Shaw, & Stewart-Brown, 2009; Widom, DuMont, & Czaja, 2007). Evidence for associations of childhood adversities with adult mood disorders is extensive, including loss of parent through divorce (Afifi et al., 2009) or death (Agid et al., 1999),

sexual abuse (Molnar et al., 2001), physical abuse (MacMillan et al., 2001; Springer et al., 2007; Widom et al., 2007), emotional abuse (Ritchie et al., 2009), lack of parental care (Harris, Brown, & Bifulco, 1986; Widom et al., 2007) or neglect (Widom et al., 2007), domestic violence (Johnson et al., 2002; Russell, Springer, & Greenfield, 2010), and parental mental illness (Kessler, Davis, & Kendler, 1997; Pilowsky, Wickramaratne, Nomura, & Weissman, 2006).

The impacts of early adversity on psychiatric outcomes in mood disorders have been documented. Childhood adversities predict severity of depression and greater disorder-related impairment in mood disorders (Klein, Shankman, & Rose, 2008; McLaughlin et al., 2010b), elevate the risk for chronicity in mood disorders (Angst, Gamma, Rossler, Ajdacic, & Klein, 2011; McLaughlin et al., 2010a), associated with a lack of response or remission during treatment for depression (Nanni, Uher, & Danese, 2012). A history of childhood adversity predisposed individuals to an earlier age of onset of symptoms by about 2 years (Young, Abelson, Curtis, & Nesse, 1997). More exposure to early adversities was related to worsened clinical correlates, including substance use disorders, younger age of hospitalization, and suicide attempts (Lu, Mueser, Rosenberg, & Jankowski, 2008).

Significant gaps still remain in this domain of research as only one study has examined the influence of childhood adversity on indices of metabolic syndrome in mood disorders. This study found that in a clinical population of mood disorders, individuals who experienced any form of childhood adversity had higher blood pressure and individuals who experienced childhood sexual abuse had higher rates of obesity (McIntyre et al., 2012). Despite these findings, several limitations do exist. First, the

differential effects of childhood adversity on metabolic syndrome between the two types of mood disorders, MDD versus BP, have not been examined. Second, although physical and sexual abuse and neglect have been examined in relation to metabolic syndrome, other forms of childhood adversity (e.g. parental divorce/separation, alcoholism or mental illness in family, and emotional abuse) have not been evaluated in relation to increased risk for metabolic syndrome and metabolic disturbances. Third, no study has assessed the cumulative effect of multiple childhood adversities on metabolic outcomes in a mood disorders sample. Lastly, the potential interaction between mood disorder and childhood adversity on metabolic outcomes have not been examined. Identifying the pathways linking childhood adversity to metabolic syndrome and potential mood disorder differences is important as it may help inform adversity- or mood-specific interventions aimed to modify behaviours associated with metabolic syndrome and improve overall mental and physical health outcomes.

4.5 Objectives

This research project examines novel questions in addition to expanding previous research by using a mood disorders population:

(1) To examine the association between childhood adversity (number and specific types) and metabolic outcomes of blood pressure, waist circumference, triglycerides, fasting glucose, HDL, and BMI.

(2) To test whether specific types of childhood adversity (e.g. abuse, neglect, household dysfunction) and type of mood disorder interact to worsen metabolic outcomes.

5. Methods

5.1 Sample

Data were gathered from the Mood Disorders Program (MDP), a tertiary-care, outpatient psychiatric clinic at the McGill University Health Centre (MUHC) in Montreal, Quebec. Eligible subjects had a current or lifetime DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) diagnosis of MDD or BP (type I or type II) and were at least 18 years of age. Exclusion criteria were inability to understand and communicate in English or French. 68 subjects met inclusion criteria and were willing to participate in this study, of which 28 (41%) had a diagnosis of MDD and 40 (59%) had a diagnosis of BP. Subjects (who had attained legal age) provided written informed consent before participating in the study. The study was approved by the McGill University Health Centre Research Ethics Board.

5.2 Procedures

Recruitment. Subjects were introduced to the research study at their outpatient appointment with their psychiatrist or nurse. A trained research student explained the purpose and procedure of the study to each subject and asked for signed consent if the subject was willing to participate. Subjects were given a phone-call reminder one day prior to the scheduled appointment for the fasting blood test and interview.

Fasting blood test and metabolic indices. Each subject was asked to fast after midnight the night immediately before the blood test. The blood test was done at the blood clinic of the Allan Memorial Institute upon the arrival of the subject. The waist circumference was measured at the level of the subject's umbilicus. A blood pressure monitor measured seated blood pressure twice.

Interview. The research version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID) (First, Spitzer, Gibbon, and Williams, 2010), designed for subjects identified as psychiatric patients, was conducted to diagnose the current and past psychiatric disorders and to collect diagnostically useful information including disorder subtypes and severity. The SCID also included an overview collecting information on the subject's demographics, education, work, and social functioning. This structured interview was administered by four trained masters-level graduate students who underwent a four-month SCID-training conducted by a SCID-certified trainer. The structured interviews varied in duration between 45 minutes and two hours.

Self-report questionnaire. This questionnaire regarding sociodemographic information and childhood adversity was given to subjects to complete on the day they came to participate in the study.

5.3 Measures

Sociodemographic characteristics. Seven items were collected to describe the sample, including (1) age, (2) gender, (3) racial background, (4) education, (5) marital status, (6) living situation, and (7) employment. All items were obtained from the SCID and self-report questionnaire.

Current and lifetime psychiatric conditions. The following modules of the SCID were used to assess both current and lifetime (A) mood episodes, (B) psychotic and associated symptoms, (C) psychotic disorders, (D) mood disorders, (E) substance use disorders, (F) anxiety disorders, (G) somatoform disorders, and (H) eating disorders. The age of onset and if applicable, the number of depressive, manic/hypomanic episodes and

duration of substance use disorders were also captured by the SCID (First, Spitzer, Gibbon, and Williams, 2010).

Metabolic indices. Metabolic indices were measured according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III clinical criteria for defining metabolic syndrome (National Institute of Health, 2001) that include high blood pressure ($\geq$ 130 mm Hg systolic blood pressure or $\geq$ 85 mm Hg diastolic blood pressure, or on an antihypertensive drug treatment), central obesity ($\geq$ 102 cm in men or $\geq$ 88 cm in women), high levels of triglycerides ($\geq$ 150 mg/dL or $\geq$ 1.7 mmol/L, or on a drug treatment for elevated triglycerides), high fasting glucose ($\geq$ 100 mg/dL or on a drug treatment for elevated glucose), and low levels of high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men or <50 mg/dL in women, or on a drug treatment for reduced HDL). The fasting blood test measured levels of fasting glucose, cholesterol, HDL, and triglycerides. A trained research student on site measured blood pressure and waist circumference on the day of the study. Two variables of metabolic outcomes were created: 1) a dichotomous measure indicating whether the participant meets the NCEP definition of metabolic syndrome (three or more symptoms) and 2) continuous measures of each NCEP defined index and BMI.

Childhood adversity. Childhood adversity up until age 18 years were measured using a modified 10-item childhood adversity questionnaire used in the Adverse Childhood Experiences (ACE) Study (Felitti et al., 1998). Three categories of childhood abuse were used: emotional abuse (2 questions), physical abuse (2 questions), and sexual abuse (2 questions). Neglect was measured with two categories: emotional neglect (2 questions) and physical neglect (2 questions). Five categories of household dysfunction

were measured: parental divorce/separation (1 question), exposure to substance abuse (2 questions), exposure to mental illness (2 questions), exposure to domestic violence towards mother or stepmother (3 questions), and exposure to criminal behaviour (1 question). Subjects were defined as exposed to a category if they responded "yes" to 1 or more of the questions in each category. A total of ten categories of childhood abuse, neglect, and household dysfunction were measured and summed, whereby exposures ranged from 0 representing no childhood adversity to 10, representing exposure to all categories. The questionnaire used in the ACE Study was constructed using questions from four different scales: the Conflicts Tactics Scale assessing emotional and physical abuse and domestic violence (Straus & Gelles, 1990), Childhood Trauma Questionnaire assessing emotional and physical neglect (Bernstein et al., 1994), questions assessing sexual abuse were adapted from Wyatt (1985), and questions adapted from the National Health Interview Survey (1988) assessing exposure to alcohol and drug abuse (National Center for Health Statistics, 1991). Based on the previous research that showed associated adverse health or social implications, these 10 categories were chosen to be included in the survey. Test-retest reliability analyses of the components of the ACE questionnaire showed moderate to substantial agreement, with kappa coefficients ranging from 0.46 – 0.86 (Dube, Williamson, Thompson, Felitti, & Anda, 2004).

5.4 Statistical analysis

Data analyses were performed using IBM SPSS statistics, version 20.0 (IBM Corp., Armonk, NY). Linear regression analyses were conducted when examining the relationship between types of childhood adversity and metabolic indices. The relationship between types of childhood adversity and metabolic syndrome was examined using a

logistic regression model. To test the dose-response relationship to metabolic outcomes, the total number of categories of childhood adversities (as an ordinal variable ranging from 0 through 10) was entered into separate linear regressions. Sex, age, and education were adjusted for in all analyses. A significance threshold of p-values < 0.05 was used.

6. Results

6.1 Sociodemographic characteristics

The sociodemographic characteristics of the participants are presented in Table 1 and represent comparisons between 28 subjects with MDD and 40 subjects with BP. The participants ($N = 68$; 57.4% female) had ages ranging from 20 to 72 years (mean = 48.0 years, SD = 13.3 years). Participants with MDD were significantly older than those who had BP. The sample was predominantly (78.0%) Caucasian. Nearly half (47.1%) of the sample had completed university. About one-third (36.8%) of the sample were married or common-law, about one-third (35.3%) was single, and about one-third (27.9%) were divorced or separated. Nearly half (44.1%) of the sample lived alone while one-third (33.8%) lived with their spouse and/or children. Close to one-third (30.9%) of the sample was employed in part-time or full-time while a quarter (26.5%) was unemployed, one-fifth (19.1%) on sick leave, nearly one-fifth retired (16.2%), and one-tenth (7.4%) were students. There were no significant differences between MDD and BP for level of education, marital status, nor employment status.

6.2 Metabolic indices

The summary of metabolic indices is presented in Table 2. The average blood pressure was within a healthy range of about 120.6 (22.7)/76.2 (13.0) mmHg. Average

levels of serum triglycerides, HDL, and glucose were also within a healthy range of 1.4

(0.9) mmol/L, 1.4 (0.4) mmol/L, and 4.8 (1.2) mmol/L, respectively. However, the mean

BMI of the sample was overweight (27.4). The weight status of the sample ranges from

1.5% underweight, 32.8% normal weight, 37.3% overweight, and 28.4% obese. One-third

(32.3%) of the sample met criteria for NCEP defined metabolic syndrome. To note, a

greater proportion of participants with MDD met the criteria of higher blood pressure

than compared to participants with BP. There were no significant differences in

metabolic indices or the presence of metabolic syndrome between participants with MDD

and with BP.

6.3 Childhood adversity

Table 3 presents the prevalence of childhood adversity up until age 18 years.

Participants reported a range of 0 to 9 types of childhood adversity (e.g. physical abuse,

emotional neglect, household domestic violence), with a median of 2.0 types (IQR = 2.0).

Four out of five (80.9%) participants experienced at least one type of childhood

adversity. Nearly half of the sample experienced household mental illness, one-third

experienced emotional neglect, close to one-third experienced household substance

abuse, close to one-third experienced emotional abuse, one-quarter experienced sexual

abuse, one-quarter experienced physical abuse, nearly one-quarter experienced parental

divorce/separation, and over one-tenth experienced domestic violence towards mother or

stepmother. There was more than a five-fold difference in the proportion of participants

with BP compared to MDD who experienced sexual abuse (37.5% versus 7.1%, p =

0.005). In contrast, participants with MDD had a five-fold proportion of experiencing

domestic violence towards the mother or stepmother than participants with BP (25.0% versus 5.0%, $p = 0.027$).

6.4 Association between childhood adversity and metabolic outcomes

Table 4 and Table 5 presents the results of the multiple regression analyses, including interaction testing for type of childhood adversity by mood disorder. In order to control for confounders, 4 multivariate models were conducted with each metabolic outcome as the dependent variables. The rate of metabolic syndrome was not significantly different among subjects with or without childhood adversity, or any category of childhood adversity. However, associations between two categories of childhood adversity and metabolic outcomes were found.

First, we found that parental divorce/separation was associated with a higher BMI ($B = 3.3$, $p = 0.047$). However, after controlling for age, sex, and education, parental divorce/separation was no longer a significant predictor of BMI. An older age was consistently associated with a higher BMI ($B = 0.139$, $p = 0.008$). Notably, interaction analysis found that in the presence of BP versus MDD, the association between parental divorce/separation and BMI was greater. Figure 1 depicts the interaction between parental divorce/separation and type of mood disorder on BMI.

Second, we found that emotional neglect was associated with lower diastolic blood pressure ($B = -7.019$, $p = 0.028$), after controlling for covariates. Specifically, participants who experienced emotional neglect had an average diastolic blood pressure of 71.7 (12.7) mmHg compared with 78.7 (12.6) mmHg in those who did not experience emotional neglect. After controlling for covariates, emotional neglect remained a

significant predictor of lower diastolic blood pressure. There was no interaction between

emotional neglect and type of mood disorder on diastolic blood pressure.

7. Tables and figures

Table 1
Sociodemographic Characteristics of Subjects Diagnosed with Major Depressive or Bipolar Disorder

Sociodemographic characteristics	Total (N = 68) %	MDD (N = 28) %	BP (N = 40) %	p-value
Age in years				
Mean (SD)	48.0 (13.3)	52.0 (12.1)	45.2 (13.5)	0.036*
Gender				0.219
Female	57.4	50.0	62.5	
Male	42.6	50.5	37.5	
Racial background				0.287
White	77.9	78.6	77.5	
Chinese	2.9	3.6	2.5	
South Asian	7.4	3.6	10.0	
Black	2.9	7.1	0.0	
Latin American	1.5	3.6	0.0	
Other	7.4	3.6	10.0	
Completed education				0.393
Elementary school	5.9	10.7	2.5	
High school	47.1	39.3	52.5	
Bachelors	26.5	25.0	27.5	
Masters	20.6	25.0	17.5	
Marital status				0.894
Single	35.3	32.1	37.5	
Married/common-law	36.8	39.3	35.0	
Divorced/separated	27.9	42.1	27.5	
Lives				0.197
Alone	44.1	53.6	37.5	

With spouse (+/- children)	33.8	37.5	32.5	
Children	1.5	3.6	0.0	
Parents	4.4	3.6	5.0	
With friends/room-mates	11.8	3.6	17.5	
With group/foster home	4.4	0.0	7.5	
Employment status				0.398
Student	7.4	3.6	10.0	
Employed	30.9	21.4	37.5	
Unemployed	26.5	28.6	25.0	
Sick leave	19.1	25.0	15.0	
Retired	16.2	21.4	12.5	

Note. MDD = Major Depressive Disorder. BP = Bipolar Disorder. SD = Standard Deviation.
*$p < 0.05$

Table 2

Metabolic Syndrome and its Components in Mood Disorders

	Total (N = 68)	MDD (N = 28)	BP (N = 40)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Metabolic indices				
Waist circumference (cm)	96.7 (15.4)	96.2 (13.2)	97.1 (17.0)	0.817
Systolic blood pressure (mmHg)	120.6 (22.7)	121.9 (24.7)	119.7 (21.4)	0.706
Diastolic blood pressure (mmHg)	76.2 (13.0)	77.8 (14.2)	75.2 (12.1)	0.422
Triglycerides (mmol/L)	1.4 (0.9)	1.4 (0.8)	1.4 (1.0)	0.935
HDL (mmol/L)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.436
Glucose (mmol/L)	4.8 (1.2)	5.1 (1.3)	4.6 (1.1)	0.094
BMI (kg/m^2)	27.4 (5.8)	27.0 (4.0)	27.7 (6.8)	0.612
Proportion meeting criteria for metabolic index	%	%	%	
Waist circumference	54.5	50.0	57.5	0.624
Blood pressure	44.1	60.7	32.5	0.027*
Systolic blood pressure	33.3	44.4	25.6	0.122
Diastolic blood pressure	22.7	33.3	15.4	0.135
Triglycerides	25.0	25.0	25.0	1.000
HDL	36.8	35.7	37.5	1.000
Metabolic syndrome	32.3	37.0	28.6	0.586

Note. MDD = Major Depressive Disorder. BP = Bipolar Disorder. SD = Standard Deviation. HDL = High Density Lipoprotein. BMI = Body Mass Index.

*p < 0.05

Table 3
Prevalence of Childhood Adversity

Category of childhood adversity	Total (N = 68) %	MDD (N = 28) %	BP (N = 40) %	*p*-value
Abuse, by category				
Physical	25.0	17.9	30.0	0.394
Parent or other adult in the household often or very often push, grab, slap, or throw something at you	19.1	10.7	25.0	0.212
Parent or other adult in the household ever hit you so hard that you had marks or were injured	14.7	14.3	15.0	1.000
Emotional	27.9	32.1	25.0	0.588
Parent or other adult in the household often or very often swear at you, insult you, put you down, or humiliate you	23.5	25.0	22.5	1.000
Parent or other adult in the household often or very often act in a way that made you afraid that you might be physically hurt	25.0	32.1	20.0	0.272
Sexual	25.0	7.1	37.5	0.005**
Adult or person at least 5 years older than you ever touch or fondle you or have you touch their body in a sexual way	23.5	7.1	35.0	0.009**
Adult or person at least 5 years older than you ever attempt or actually have oral, anal, or vaginal intercourse with you	10.3	0.0	17.5	0.036*
Neglect, by category				
Physical	2.9	7.1	0.0	0.166
You often or very often feel that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you	1.5	3.6	0.0	0.412
You often or very often feel that your parents were too drunk or high to take care of you or take you to the doctor if you needed it	1.5	3.6	0.0	0.412

Emotional	33.8	28.6	37.5	0.603
You often or very often feel that no one in your family loved you or thought you were important or special	26.5	21.4	30.0	0.578
You often or very often feel that your family didn't look out for each other, feel close to each other, or support each other	20.6	17.9	22.5	0.765
Family/Household dysfunction, by category				
Parental divorce/separation	23.5	28.6	20.0	0.562
Substance abuse	29.4	32.1	27.5	0.789
Lived with anyone who was a problem drinker or alcoholic	25.0	32.1	20.0	0.272
Lived with anyone who used street drugs	10.3	3.6	15.0	0.226
Mental illness	45.6	39.3	50.0	0.462
Had a household member depressed or mentally ill	41.2	35.7	45.0	0.466
Had a household member attempt suicide	8.8	7.1	10.0	1.000
Domestic violence	13.2	25.0	5.0	0.027*
Your mother or stepmother was often or very often pushed, grabbed, slapped, or had something thrown at her	7.4	14.3	2.5	0.151
Your mother or stepmother was sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard	7.4	14.3	2.5	0.151
Your mother or stepmother was ever repeatedly hit at least a few minutes or threatened with a gun or knife	2.9	7.1	0.0	0.166
Imprisoned household member	1.5	0.0	2.5	1.000
Summary ACE score				
Any category reported	80.9	78.6	82.5	0.759
Presence of 4 or more ACE	22.1	21.4	22.5	1.000
ACE score, median (IQR), 0-10	2.0 (2.0)	1.0 (2.0)	2.0 (2.0)	0.685

Note. MDD = Major Depressive Disorder. BP = Bipolar Disorder. ACE = Adverse Childhood Experience.

*p < 0.05, **p < 0.01

Table 4

The Interaction between Parental Divorce/Separation and Type of Mood Disorder on BMI

	Model 1			Model 2			Model 3			Model 4		
	Unst. B	β	*p*-value	Unst. B	β	*p*-value	Unst. B	β	*p*-value	Unst. B	β	*p*-value
Main effect												
Parental divorce/separation	3.269	0.243	0.047*	2.340	0.174	0.162	2.528	0.188	0.129	2.954	0.220	0.067
Covariates												
Age				0.120	0.277	0.022*	0.142	0.327	0.009*	0.139	0.320	0.008*
Sex				-2.148	-0.186	0.115	-2.425	-0.210	0.075	-2.438	-0.211	0.063
Education				-0.751	-0.113	0.359				-0.776	-0.117	0.319
Modifier												
Mood disorder							-2.192	-0.189	0.122	-2.072	-0.178	0.129
Interaction: Parental divorce/separation x mood disorder										-7.393	-0.276	0.016*

*$p < 0.05$.

Table 5

The Interaction between Emotional Neglect and Type of Mood Disorder on Diastolic Blood Pressure

	Model 1			Model 2			Model 3			Model 4		
	Unst. B	β	*p*-value	Unst. B	β	*p*-value	Unst. B	β	p-value	Unst. B	β	*p*-value
Main effect												
Emotional neglect	-6.945	-0.257	0.037*	-6.872	-0.255	0.045*	-6.859	-0.254	0.048*	-7.019	-0.260	0.028*
Covariates												
Age				0.204	0.212	0.084	0.202	0.210	0.103	0.186	0.194	0.113
Sex				-2.495	-0.096	0.442	-2.474	-0.096	0.453	-2.438	-0.211	0.423
Education				1.004	0.068	0.575	1.003	0.068	0.579	0.917	0.008	0.610
Modifier												
Mood disorder							0.160	0.006	0.962	0.199	0.008	0.952
Interaction:												
Emotional neglect x mood disorder										-8.464	-0.152	0.216

*$p < 0.05$.

Figure 1.

The Interaction between Parental Divorce/Separation and Type of Mood Disorder on BMI
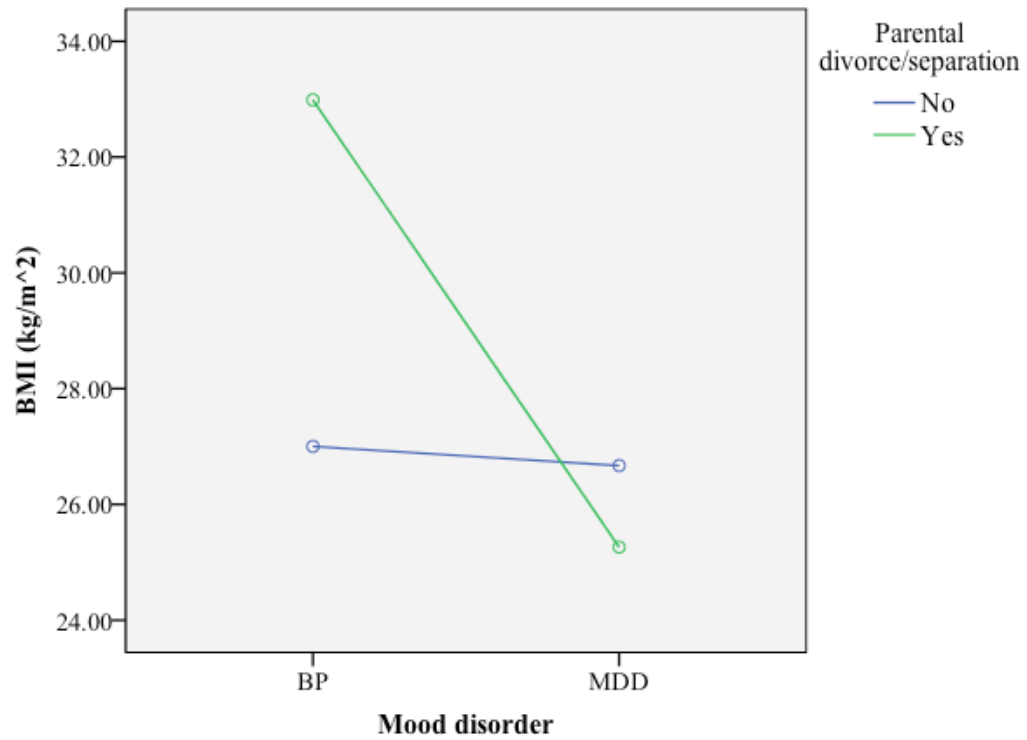
8. Discussion

8.1 Main findings

This paper examines the associations between childhood adversity, mood disorders, and metabolic indices of metabolic syndrome. Despite the majority of the sample being overweight, all other metabolic outcomes assessed were within a healthy range. Childhood adversity was highly prevalent, with 4 out of 5 participants experiencing at least one category of childhood adversity. Childhood sexual abuse was reported more frequently in people with BP compared to MDD. In contrast, childhood exposure to domestic violence was reported more in people with MDD compared to BP. We did not detect a dose-response relationship between the number of childhood adversity categories and metabolic disturbances. Finally, two associations between childhood adversity and metabolic outcomes were found. First, after controlling for confounders, an interaction was found between childhood parental divorce/separation and mood disorder on BMI, such that in the presence of BP versus MDD, the association between parental divorce/separation and BMI was greater. Second, emotional neglect was associated with lower diastolic blood pressure.

8.2 Strengths

This study extends the only other previous findings (McIntyre et al., 2012) both methodologically and analytically in this field of research of childhood adversity, metabolic disturbance, and mood disorder. First, we used the SCID, a gold standard instrument that incorporates clinical judgment for diagnosing psychiatric disorders. Second, a broader range of childhood adversities was measured, allowing us to examine more types of childhood adversity in relation to metabolic disturbances. With respect to

analyses, the examination of two types of mood disorders allowed us to compare differences in metabolic indices by mood disorder type. This is also the first study in a clinical mood disorders sample to examine whether a dose-response relationship exists between cumulative childhood adversities and metabolic outcomes. Finally, no previous study has tested for interactions between types of childhood adversity and type of mood disorder on metabolic indices.

8.3 Previous literature

With respect to the prevalence of metabolic outcomes in our study, it was consistent with the literature where nearly one-third of the participants with mood disorders met criteria for metabolic syndrome. In a sample of adults with mood disorders, 27% of the sample met the definition of metabolic syndrome (McIntyre et al., 2012). In a clinical sample of bipolar disorder, 30% of the sample with bipolar disorder met NCEP-ATP III criterion for metabolic syndrome (Fagiolini et al., 2005). This is a higher prevalence rate of metabolic syndrome compared to the general population of 20% (Riediger & Clara, 2011) that is consistent with the literature (Vancampfort, Correll, et al., 2013; Vancampfort, Vansteelandt, et al., 2013). Also, it was found that a greater proportion of participants with MDD had generally higher blood pressures to meet the diagnostic threshold for metabolic syndrome compared to participants with BP. This is not consistent with previous findings whereby the prevalence of hypertension was statistically greater in BPI than in MDD (Goldstein, Fagiolini, Houck, & Kupfer, 2009).

Regarding childhood adversity in adult mood disorder populations, any childhood adversity was present in 46.7% of the clinical sample (McIntyre et al., 2012). In comparison, childhood adversity was highly prevalent in our sample, with 80.9%

experiencing at least one category. However, similar to our study were the rates of physical (22%) and sexual abuse (25%) reported. Another study also reported rates of specific types of childhood adversity in a clinical sample of 103 adults with MDD that were in agreement with our clinical sample; it was found that 34% experienced emotional abuse, 20% experienced physical abuse, 12% experienced sexual abuse, 43% experienced marital conflict/divorce, 59% experienced psychopathology in parent, and 39% experienced substance abuse in parent (Young et al., 1997). In a review of childhood maltreatment in BP, the prevalence rates ranged from 14-24% reporting physical abuse, 12-21% reporting sexual abuse, 37% for emotional abuse, 24% for emotional neglect, 12% for physical neglect (Fisher & Hosang, 2010).

With respect to the association between the number of childhood adversities and metabolic outcomes, there was surprisingly no dose-response relationship between the total number of childhood adversities and metabolic syndrome and its indices, despite the presence of fairly prevalent adversities in this sample. This differs from what is anticipated as the sum of exposures to childhood abuse increased health risk factors, including physical inactivity and severe obesity, and heart disease, in adulthood (Felitti et al., 1998), which would be expected to influence metabolic indices. However, this study was examining the relationship of childhood adversity in an adult population sample instead of a mood disorders sample. In another population sample study, it was also found that individuals who experienced more cumulative abuse were at greater risk for developing metabolic syndrome (Lee et al., 2014). This difference in findings may be explained in the limitation of our small sample size that may lead to lower power to detect findings. As well, the relatively high levels of education of the participants may

contribute to healthier metabolic outcomes due to greater awareness of healthy lifestyle practices and dietary habits and therefore reduce the impact of childhood adversity on later physical health.

With respect to the association between type of childhood adversity and metabolic outcomes, two types of childhood adversity (parental divorce/separation and emotional neglect) were associated with two metabolic outcomes (BMI and diastolic blood pressure). However, after adjusting for age, sex, and education, only childhood emotional neglect remained significantly associated with reduced diastolic blood pressure. Previous studies have found that diastolic blood pressure is not significantly affected by the quality of parental emotional care (Almeida et al., 2010). In a 35-year follow-up study, midlife hypertension was present in those who rated their parents significantly lower on perceived parental care while in college (Russek & Schwartz, 1997). Our finding that emotional neglect was associated with reduced blood pressure was unexpected. However, because medications were not controlled for in our analyses, the use of anti-hypertensives may have played a role in lowering blood pressure for participants. Thus, this finding should be interpreted with caution and requires replication in future studies.

With respect to interactions, we found one interaction between parental divorce/separation and mood disorder on BMI. This is notable given that no other study has examined interaction between childhood adversity and mood disorder on metabolic outcomes. The effect of family divorce was identified as a significant predictor of higher BMI in a population-based cross-sectional study of school-aged children (Yannakoulia et al., 2008). In this same study, children of divorced parents had 6% higher BMI values compared with those from non-divorced parents, independent of socioeconomic factors.

44

A possible explanation for the interaction that occurred in our study may be attributed to the greater effects of duration of illness characterized in BP compared to MDD; the total disability score was found to increase with the duration of illness and was significant in patients with BP instead of MDD (Chacko, Narayan, & Prabhavathy, 2011). This may be associated to life impairments and unhealthier lifestyle practices leading to a higher BMI in participants with BP compared to participants with MDD. Medications use for BP, such as mood stabilizers and antipsychotics, may also lead to greater weight gain compared to antidepressant medications in MDD.

8.4 Mechanism of associations

The mechanisms of the associations found in this study are complex and challenging to interpret as various biologic, psychological, and social factors throughout life may act independently, cumulatively, and interactively on adult health (Gans, 2006). However, it has been postulated that a potential mechanism by which early adversity influences later metabolic outcomes is mediated by allostatic load (McIntyre et al., 2012). Stress in early childhood can contribute to the disruption of the neurodevelopment of the hypothalamic-pituitary-adrenal axis (HPA axis), leading to metabolic dysregulation (McEwen, 2004). The enduring changes of the HPA axis, which initiates and regulates the stress response, has been documented in both animal and human models (Gorman, Mathew, & Coplan, 2002; Heim et al., 2000; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Teicher et al., 2003) and results in lasting impacts of an increased stress response to stressors (Heim & Nemeroff, 2001). These long-term changes in brain structure and function extends into adulthood, including social, emotional, and cognitive impairment can accumulate to health-risk behaviours, major chronic diseases, and even premature

mortality (Repetti, Taylor, & Seeman, 2002). In addition, the effect of family disruption may decrease family attachment, reduce self-regulation, and lead to risky health behaviours (Low et al., 2012). The adoption of these unhealthy behaviours associated with childhood adversity, including alcoholism, drug abuse, smoking, and physical inactivity (Felitti et al., 1998), can increase risks for metabolic disturbances and becoming overweight.

8.5 Limitations

This study has several limitations pertaining to its design and measures. Firstly, due to the small sample size, the study may underpowered to examine the differences of childhood adversity by specific type of mood disorder. This may lead to under-detection of childhood adversity effects on metabolic indices by mood disorder. Secondly, information on childhood adversity was collected using retrospective reports which may be subject to recall bias and substantial underreporting (Hardt & Rutter, 2004). Underestimates of childhood adversities may affect the estimates of the relationships between childhood adversity and adult metabolic outcomes. However, most studies (Chapman et al., 2004; Felitti et al., 1998) rely on retrospective reports of childhood adversity and is used commonly in mood disorder populations (Fisher & Hosang, 2010; McIntyre et al., 2012; Nanni et al., 2012). In addition, recall of childhood adversity of people with depression has been documented to be stable, irrespective of their mood state over periods of up to 20 years (Lizardi & Klein, 2005; Wilhelm, Niven, Parker, & Hadzi-Pavlovic, 2005).

Regarding measures, several potentially confounding variables were not taken into account. First, the potential confounder of economic and social status during

childhood was not included in the association models. Abuse and neglect are more often found in disrupted and disturbed families (Mullen et al., 1996) and those of lower socioeconomic status (J. Brown, Cohen, Johnson, & Salzinger, 1998; Chaffin, Kelleher, & Hollenberg, 1996; Jones & McCurdy, 1992). Second, the potentially confounding role of medications for both medical and psychiatric disorders should also be taken into account. The use of psychotropic medications may lead to weight gain and changes in metabolism (De Hert et al., 2012; Lieberman et al., 2005). Specifically, medications that treat BP, including lithium, valproic acid, and other antipsychotic agents are associated with weight gain (Toalson, Ahmed, Hardy, & Kabinoff, 2004). Thus, both childhood socioeconomic status and current medications should be included in the association models to help determine the strength of an association between childhood adversity and adult metabolic outcomes. In addition to potential confounders, the scope of childhood adversity measured was limited to exposures captured in the ACE questionnaire and did not include other aspects of each of the childhood adversities such as frequency, duration, or perpetrator of maltreatment. Because our sample was highly educated, the relationship between childhood adversity and metabolic outcomes may have been reduced, as higher education is associated with healthier lifestyle and lower risk of metabolic indices. Lastly, inferences about the role of childhood adversity directly on metabolic disturbances and BMI cannot be made due to the cross-sectional nature of this study.

8.6 Future directions

The present study shows that the impacts of childhood maltreatment and neglect are likely to be complex. Both the design and measures could be improved for a more comprehensive understanding of childhood adversity impacts on metabolic indices in

adulthood. First, due to the small-scale nature of this study, using a larger sample would improve the power of the analyses and strengthen the robustness of the findings. Second, the age at which adversities occurred as well as the sequencing and duration of childhood adversities were also not taken into account in our analysis (Schilling et al., 2007). This is an interesting avenue for future studies to examine as the age of the adversity may be associated differently with metabolic indices in adulthood. Third, research could also investigate how childhood adversity influences or mediates the course of metabolic indices over time. Fourth, data on specific medications, physical activity, and dietary habits would help examine whether childhood adversity may be differentially associated with metabolic disturbances (Goldstein et al., 2009). Lastly, more cross-sectional studies and prospective study designs would assist in validating our results.

8.7 Clinical implications

This study is relevant for practitioners as it provides a rationale for the systematic assessment of childhood experiences, regular monitoring of the metabolic indices, and promotion of healthy lifestyle habits in clinical care of individuals with mood disorders. First, as specific forms of childhood adversity may require early preventative attention and tailored therapeutic interventions (Glaser, 2002), routine assessments of childhood experiences can provide valuable information for treatment options and prognosis of mood disorders. Second, specifically in those who have childhood adversity, medications that are less prone to causing weight gain and metabolic disturbances should be avoided or reduced. In addition, a thorough medical history is encouraged in order to assure there are no medical disorders that could worsen the effect of childhood adversity. As patients with mood disorders have a heightened risk for a range of medical disorders, which are

often unrecognized and untreated, opportunistic screening should be integrated into routine care as preventative and early detection strategies (McIntyre et al., 2006). If medical disorders are detected, they should be treated with the awareness that they may be more refractory to treatment. Lastly, each component of metabolic syndrome can be moderated by lifestyle changes (Riediger & Clara, 2011). As weight loss is a challenge, especially for patients with mental illness, preventative and intervention efforts to improve dietary and physical activity habits can help prevent obesity in this population. Early intervention, through diet and exercise counseling, should be provided to all patients for weight management (Fagiolini et al., 2003). It is also important to assess the degree to which patients exhibit unhealthy behaviours that can be addressed and managed clinically (e.g. talk therapy, occupational therapy, or cognitive-behavioural therapy) (Lu et al., 2008).

8.8 Conclusion

This study provides preliminary evidence linking childhood parental divorce/separation and emotional neglect to specific metabolic outcomes in adulthood. Although all cases of childhood adversity may be difficult to prevent and are common in mood disorder populations, its negative impact on overall health can be mediated. Through early detection and prevention of unhealthy lifestyle behaviours associated with childhood adversity in adults with mood disorders, both mental and physical health can be improved. This study was designed as an extension of the existing knowledge and to provide an impetus for further research to explore the complex relationships between childhood adversity and metabolic outcomes in adults with mood disorders.

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