The Effects of Childhood Adversity on Anxiety in People with Mood Disorders

by

Ruth Shelton

Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
August 2023

Table of Contents

LIST OF TABLES **……..…… iii**

LIST OF FIGURES **…….…….....iv**

ABSTRACT **……...…… v**

LIST OF ABBREVIATIONS USED **……..…… vi**

ACKNOWLEDGEMENTS **…….…… vii**

CHAPTER 1 INTRODUCTION **…….…….1**

1.1 Mood Disorders and Their Outcomes ……1

1.2 Anxiety and Related Disorders and Their Outcomes ……. 5

1.3 The Comorbidity of Mood & Anxiety Disorders ……..8

1.4 Childhood Adversity and Its Outcomes ……10

1.5 The Mechanisms of the Relationship Between Childhood Adversity and Mood and Anxiety Disorders……11

1.6 Summary and Hypotheses ……13

CHAPTER 2 **METHODS…….…..…….……15**

2.1 Inclusion and Exclusion Criteria.……15

2.2 Participant Recruitment……15

2.3 Measures ……15

2.4 Procedure ……19

2.5 Research Visits ……19

2.6 Data Entry ……19

2.7 Analysis Plan……20

2.8 Research Ethics Board Approval……21

CHAPTER 3 RESULTS….……..……23

3.1 Sample Characteristics ……23

3.2 Effect of Childhood Adversity on Average Anxiety ……26

3.3 Effect of Childhood Adversity on Number of Anxiety Disorders per Participant……33

3.4 Multi Level Modelling ……36

3.5 SCAARED Anxiety Score over Time……40

CHAPTER 4 DISCUSSION **……..……...44**

Appendix 1……..……...53

REFERENCES **……..……...55**

List of Tables

Table 3.1 Sample Characteristics by Mood Disorder Diagnosis……..……24

Table 3.2 Mood and Anxiety Disorder Comorbidity……...…….25

Table 3.3 Regression Statistics for Regression of the Effect of Childhood Adversity Score on Average Anxiety Score……..……28

Table 3.4 Regression Statistics for Multiple Regression of the Effect of Average Mood Score, Sex, and Childhood Adversity Score on Average Anxiety Score ……...…….……34

Table 3.5 Regression Statistics for Regression of the Effect of Childhood Adversity on Number of Anxiety Disorders……...……...37

Table 3.6 Comparison of Multilevel Models…….……...42

Table 3.7 Results of Multilevel Modelling of Effect of Childhood Adversity Score and Time on SCAARED Anxiety Score ……..……..……43

List of Figures

Figure 3.1 Relationship between Average Anxiety Score and Average Mood Score…...……...26

Figure 3.2 Model Diagnostics for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score……..29

Figure 3.3 Influential Observations by Cooks Distance for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score…….…...30

Figure 3.4 Distribution of the Average Mood Scores for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score……32

Figure 3.5 Model Diagnostics for the Multiple Regression of the Effect of Average Mood Score, Sex, and Childhood Adversity Score on Average Anxiety Score……..35

Figure 3.6 Model Diagnostics for the Linear Regression Effect of Childhood Adversity on Number of Anxiety Disorders Per Participant……...38

Figure 3.7 Influential Observations by Cooks Distance for the Linear Regression Effect of Childhood Adversity on Number of Anxiety Disorders Per Participant……...……39

Figure 3.8 Distribution of the Residuals from Multilevel Modelling of the Effect of Childhood Adversity Score and Time on SCAARED Anxiety Score ……41

ABSTRACT

Mood and anxiety disorders are among the leading causes of disability worldwide. Both childhood adversity and the presence of an anxiety disorder contribute to unfavorable outcomes for those who have mood disorders. The chronicity of anxiety is higher in general population with experiences of childhood adversity; however, it is unclear whether the severity and persistence of anxiety in people with mood disorders increase with higher levels of adversity. In addition, prospective assessment of anxiety at multiple time points is not common in the literature. (1) Our primary hypothesis was that people with mood disorders who experienced greater levels of childhood adversity will have a higher average anxiety score over the six months preceding their first assessment. (2) We also hypothesized that people with mood disorders who experienced greater levels of childhood adversity will have a higher number of lifetime anxiety and related disorders and (3) will prospectively report more anxiety symptoms. We included participants with major depressive disorder, bipolar I disorder, or bipolar II disorder, confirmed by the Structured Clinical Interview for DSM-5 (SCID-5). During the initial assessment, we determined the participant's mood and anxiety disorders. We also administered The Longitudinal Interval Follow-Up Evaluation (LIFE), The Childhood Experience of Care and Abuse (CECA), and The Screen for Adult Anxiety Related Disorders (SCAARED). The LIFE interview was used to derive both the average mood disorder severity score and average anxiety score over the preceding six months. The CECA was used to create the childhood adversity score. We used the SCAARED monthly following the initial assessment to measure participants' anxiety prospectively. Childhood adversity was found to have no effect on the participants' average anxiety measured retrospectively over the previous six months or the severity of participants' anxiety measured prospectively. Nor was it found to have an effect on the number of anxiety disorders per participant. It is possible that we did not find an effect of childhood adversity on anxiety severity among people with mood disorders for several reasons. Firstly, participants in our sample experienced very little childhood adversity. Secondly, most participant scored low on the anxiety measures. This study is unique in that it captured a detailed view of six months of participants' experiences with mood and anxiety disorders and because anxiety was also assessed prospectively. The main limitation of our study was a small sample size. Future studies on childhood adversity and anxiety in people with mood disorders should focus on collecting larger samples.

LIST OF ABBREVIATIONS USED

MDD	Major Depressive Disorder
BD	Bipolar Disorder
BDI	Bipolar I Disorder
BDII	Bipolar II Disorder
NICE	The National Institute for Health and Care Excellence
CANMAT	The Canadian Network for Mood and Anxiety Treatment
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders Version 5
OCD	Obsessive Compulsive Disorder
PTSD	Post Traumatic Stress Disorder
CBT	Cognitive Behavioral Therapy
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SCID-5	Structured Clinical Interview for DSM-5
LIFE	The Longitudinal Interval Follow-Up Evaluation
CECA	The Childhood Experience of Care and Abuse
MADRS	Montgomery and Åsberg Depression Rating Scale
CTQ	Childhood Trauma Questionnaire
SCAARED	The Screen for Adult Anxiety Related Disorders
NSH	Nova Scotia Health

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Dr. Barbara Pavlova who has supported me and helped me with all of my research work throughout my Master's. I would also like to thank my committee members Dr. Rudolf Uher and Dr. Martin Alda for their guidance.

I would also like to thank my mom Dr. Joanne Morgan for her help and support, as well as Dr. Dorletta Garcia senior researcher, AZTI, Spain for her statistical advice. I would also like to thank Steven Jackson, Katerina Dikaios, and Dr. Raegan Mazurka for their contributions to this project.

Finally, I would like to thank the participants of the study for making this work possible.

CHAPTER 1 INTRODUCTION

1.1 Mood Disorders and their Outcomes

Mood disorders are among the most common and disabling mental illnesses worldwide (Costello et al., 2002, Haroz et al., 2017). Major depressive disorder (MDD) and bipolar disorder (BD) affect approximately 16.2% and 2.4% of the world's population respectively (Martin-Key et al., 2021). People with mood disorders often experience functional impairment in social and occupational domains (Simon, 2003). The social and economic burden of mood disorders is vast and extends far beyond the person with a mood disorder and their immediate family to friends, employers, taxpayers, and strain on the health care system (Simon, 2003; Martin-Key et al., 2021).

MDD is diagnosed when an individual experiences one or more major depressive episodes (American Psychiatric Association, 2013). The essential feature of a major depressive episode is a period of at least two weeks during which people experience depressed mood and/or a loss of interest or pleasure in nearly all activities (American Psychiatric Association, 2013). Additional symptoms include significant changes in appetite and/or weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, or loss of energy, feeling of worthlessness or inappropriate guilt, diminished ability to concentrate, and recurrent thoughts of death (American Psychiatric Association, 2013). At least five symptoms of MDD must be present most of the day, nearly every day for at least two weeks to meet the diagnostic threshold (American Psychiatric Association, 2013). Impairment among those with MDD may range from mild to complete incapacity to care for themselves, mutism, or catatonia (American Psychiatric Association, 2013, Judd et al., 1998).

When treating people with depression, it is vital to follow the evidence-based recommendations summarized by, for example, The National Institute for Health and Care Excellence (NICE) (NICE, 2021) and The Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines (Kennedy et al., 2009; Patten, 2016; Parikh et al., 2016). These include completing an assessment of need, developing a treatment plan, consideration of physical health problems, consideration of any coexisting mental health problems, and regular liaison between healthcare professionals (NICE, 2021). A comprehensive assessment and management plan, including attention to safety, is the foundation of care for people with mood disorders (Patten, 2016). A thorough psychiatric assessment of depression should incorporate a comprehensive symptom investigation, including an evaluation of co-occurring disorders such as anxiety disorders and substance use disorders, as these are frequently comorbid with depression (Patten, 2016). Depression can be categorized as mild, moderate, or severe based on the symptoms, duration, and impact (NICE, 2021). Treatment for mild depression includes group cognitive behavioral therapy, group behavioral activation, individual cognitive behavioral therapy, individual behavioral intervention, self-help with support, group exercise, group mindfulness or meditation, interpersonal psychotherapy, selective serotonin reuptake inhibitors, counselling, and short-term psychodynamic psychotherapy (NICE, 2021). The first-line treatment recommendation for moderate to severe major depressive episodes is a combination of individual cognitive behavioral therapy and an antidepressant, followed by individual cognitive behavioral therapy, individual behavioral activation, antidepressants, individual problem solving, counselling, short-term psychodynamic psychotherapy, interpersonal psychotherapy, self-help with support, and group exercise (NICE, 2021). The first-line psychological treatment for MDD according to the CANMAT guidelines are cognitive behavioural therapy, behavioural activation

and interpersonal therapy. For maintenance treatment, the CANMAT guidelines recommend cognitive behavioural therapy and mindfulness based cognitive therapy as the first-line psychological treatments (Parikh et al., 2016). The CANAMT guidelines also list fifteen different drugs as the first-line treatment for people with MDD (Kennedy et al., 2016). If the person with severe depression does not respond to the first-line treatments, there are other options available, including the combination of an antidepressant and an antipsychotic, an antidepressant and psychotherapy, or electroconvulsive therapy (Davidson, 2010).

Bipolar Disorder (BD) and related illnesses usually onset during late adolescence or early adulthood (Shao et al., 2019). In addition to depression, individuals with bipolar disorder also experience episodes of mania or hypomania (American Psychiatric Association, 2013). The core diagnostic criterion for both mania and hypomania is elevated/expansive/irritable mood and goal-directed activity or energy (American Psychiatric Association, 2013). In addition to the core criterion, three (or four if the mood is only irritable) of the following criteria need to be met: inflated self-esteem or grandiosity, decreased need for sleep, being more talkative than usual, flight of ideas, distractibility, increase in goal-directed activity, and excessive involvement in activities that have a high potential for painful consequences (American Psychiatric Association, 2013). For mania, the symptoms must be present for at least one week or require hospitalization (American Psychiatric Association, 2013). The disturbance caused by mania must also be sufficiently severe to cause marked impairment in social or occupational function (American Psychiatric Association, 2013). If there are any psychotic symptoms present in the elevated mood episode, it is classified as mania regardless of the impairment (American Psychiatric Association, 2013). For hypomania, the symptoms are only required to be present for four days. The episode must not be severe enough to cause significant impairment socially or

occupationally, must not require hospitalization, and there must be no psychotic features present regardless of duration (American Psychiatric Association, 2013). Individuals who have met diagnostic criteria for at least one manic episode in their lifetime are diagnosed with bipolar I disorder. Bipolar II disorder is defined by at least one lifetime hypomanic episode and at least one lifetime major depressive episode (American Psychiatric Association, 2013; McIntyre et al., 2020). Bipolar disorder is a severe mental illness that often has a chronic course (McIntyre et al., 2020). While some people with bipolar disorder may experience a return to their normal mood state between mood episodes, many are still affected by symptoms even outside of full mood episodes (Jaworska-Andryszewska & Rybakowski, 2018; Judd, 1995). Bipolar disorder significantly reduces psychological and social functioning and is associated with the loss of ten to twenty potential years of life (McIntyre et al., 2020). Bipolar disorder is one of the leading causes of disability among working-age people and young adults (Cardoso et al., 2017).

In terms of treatment, therapeutic objectives for BD include the prevention and treatment of hypomania, and mania, the improvement of quality of life, abatement of inter-episodic depressive symptoms and major depressive episodes, and the reduction of suicidality (McIntyre et al., 2020). First-line long-term treatment options for bipolar disorder include quetiapine, lithium, valproate, lamotrigine, and lurasidone (Yatham et al., 2012). Lithium, introduced by John Cade in 1949, remains the most established long-term treatment for bipolar disorder (Miklowitz & Johnson, 2006). At maintenance, the goals of treatment are relapse prevention, reduction of subthreshold symptoms, and enhanced social and occupational functioning (Geddes & Miklowitz, 2013). Treatment of both phases of the illness is complex because some of the treatments that alleviate depression can cause mania, hypomania, or rapid cycling, and the treatments that reduce mania might cause depressive episodes (Geddes & Miklowitz, 2013).

Psychotherapy, such as cognitive behavioral therapy (CBT) and psychoeducation, are essential adjunct treatment methods (Miklowitz & Johnson, 2006) and are often needed for long-term treatment (Geddes & Miklowitz, 2013). The current treatments for BD are suboptimal, which is demonstrated by evidence that shows that the relapse rate for individuals who have recovered from first-episode mania is approximately 40-60% within 1-2 years (McIntyre et al., 2020).

In summary, effective treatments for people with mood disorders exist, but outcomes vary. While some people may experience only one lifetime episode and return to full functioning, other people with mood disorders have a chronic or recurrent illness that significantly impacts their functioning.

1.2 Anxiety and Related Disorders and their Outcomes

Anxiety and related disorders are characterized by excessive fear, worry, and avoidance that are disproportionate to the real or imagined threat as well as physical symptoms such as sweating and shortness of breath (American Psychiatric Association, 2013). They include agoraphobia, social anxiety disorder, panic disorder, generalized anxiety disorder, and specific phobia (Yonkers et al., 2003). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Diagnostic and Statistical Manual Version Five (DSM-5) classifies obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) as separate categories. However, for the purpose of this study, we classified them together with anxiety disorders as "anxiety and related disorders". This decision was made because of the overlap in the core criteria (anxiety, fear, and avoidance).

Everyone may feel anxious at times. Experiencing anxiety is a normal part of life, with external pressures and significant events in life causing worry or even fear. However, it is

essential to note the differences between feeling anxious and having an anxiety disorder. In anxiety disorders, the feelings of anxiety, worry, and panic interfere with daily activities, are difficult to control, and lead to distress. The symptoms must be present more time than not for at least six months for generalized anxiety disorder, specific phobia, social anxiety disorder (SAD), and agoraphobia (American Psychiatric Association, 2013). To meet the diagnostic criteria for panic disorder, an individual must experience repeated unexpected panic attacks followed by at least one month of persistent concern or worry about additional panic attacks and/or a significant maladaptive change in behavior (American Psychiatric Association, 2013). Symptoms of PTSD, such as nightmares, flashbacks, and hypervigilance, develop in response to a traumatic event and must be present for at least one month for an individual to receive a diagnosis of PTSD (American Psychiatric Association, 2013). For OCD, either obsessions or compulsions (or both) must be present; however, there is no specified duration in the DSM-5 (American Psychiatric Association, 2013).

Anxiety is the sixth-leading cause of disease-related disability worldwide (Anxiety and Depression Association of America, 2021). Even with significant under-recognition and under-reporting of anxiety disorders, population-based surveys indicate that up to one third of the population will be affected by an anxiety disorder in their lifetime (Bandelow & Michaelis, 2015). Persistent anxiety disorders have a large negative influence on social relationships, school, and work performance across the lifespan (Hovenkamp-Hermelink, 2020).

Treatment options for anxiety and related disorders include both psychological and pharmacological treatments (Katzman et al., 2014). Among psychological treatments, CBT is generally considered the gold standard treatment for anxiety disorders (Carpenter at al., 2018). Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-

norepinephrine reuptake inhibitors (SNRIs), have demonstrated efficacy in the treatment of anxiety and related disorders (Katzman et al., 2014). SSRIs and SNRIs are usually initial pharmacological treatments since they are generally safer than benzodiazepines and well tolerated (Katzman et al., 2014). Relapse of anxiety symptoms is frequent after SSRIs are withdrawn, even after the period of withdrawal symptoms from the drug have passed (Tyrer & Baldwin, 2006). Benzodiazepines are also commonly used to treat anxiety disorders; however, there is concern about benzodiazepines causing dependence which has led to recommendations that these drugs should be avoided in long-term treatment (Tyrer & Baldwin, 2006).

While anxiety and related disorders are treatable, in around half of the sufferers they take a chronic course. The predictors of chronicity include higher levels of avoidance, more behavioural inhibition, more panic attacks, and a history of childhood trauma. There has been significant interest in the role of anxiety sensitivity in the anxiety disorders (Olatunji & Wolitzky-Taylor, 2009). According to research a high level of anxiety sensitivity or fear of anxiety increases the risk for anxiety disorders (Taylor et al., 1992). It has also been shown to play a particularly important role in panic disorder (Taylor et al., 1992). Greater anxiety sensitivity has been found among those with anxiety disorders when compared to controls, and among the anxiety disorders, panic disorder and post traumatic stress disorder are associated with the greatest anxiety sensitivity (Olatunji & Wolitzky-Taylor, 2009). Aside from those two disorders the other anxiety disorders have generally not been shown to differ from each other in anxiety sensitivity (Olatunji & Wolitzky-Taylor, 2009).

1.3 The Comorbidity of Mood & Anxiety Disorders

Comorbidity is the presence of two or more medical or psychiatric conditions in the same individual (Kaufman & Charney, 2000). Mood and anxiety disorders are highly prevalent and frequently comorbid diagnoses (Kaufman & Charney, 2000). Although mood and anxiety disorders frequently co-occur, the reasons for their comorbidity remain poorly understood (DeRubeis & Strunk, 2017). The rate of comorbidity between anxiety and mood disorders is significantly greater than one would expect by chance (Kaufman & Charney, 2000). Epidemiological data suggest that the presence of either a depressive or anxiety disorder significantly increases the likelihood that the other disorder may also be present (Belzer & Schneier, 2004). Regardless of which of the two disorders arises first, a mood disorder or an anxiety disorder, there is an increased risk of subsequently developing the other disorder (Saha et al., 2020). Fava et al. (2000) found that comorbid anxiety disorders were present in 50.6% of people with MDD. The lifetime prevalence of anxiety disorders in people with bipolar disorder is 45%, with no difference between bipolar I and bipolar II disorder (Pavlova et al., 2015). Based on studies that compared people with and without bipolar disorder, those with bipolar disorder are three times more likely to have an anxiety disorder (Pavlova et al., 2015). The presence of depressive and anxiety disorder comorbidity substantially increases medical utilization and is associated with greater chronicity, slower recovery, increased rates of recurrence, and greater psychosocial disability among sufferers (Hirschfeld, 2001). People with depression who also have comorbid anxiety disorders are more likely to have unfavorable outcomes, including more mood episodes, substance use problems, as well as higher rates of premature treatment termination, and worse response to antidepressants compared to those with mood disorders who

do not have a cooccurring anxiety disorder (Kaiser et al., 2021). Anxiety disorders are also a strong predictor of poor outcomes among those with bipolar disorder (Pavlova et al., 2018).

Two factors widely acknowledged to be involved in the pathogenesis of mood and anxiety disorders are genetics and stressful life events (Mandelli et al., 2006; Meier & Deckert, 2019). Genetic vulnerability may also moderate individuals' responsiveness to stressful life events, which could explain the similarity in the etiology between mood and anxiety disorders (Meier & Deckert, 2019). A recent meta-analysis conducted by Cerdá et al. in 2010 found that genetic factors play a particularly strong role in comorbidity between major depression and generalized anxiety disorder or posttraumatic stress disorder. They also found that non-shared environments make an important contribution to comorbidity in affective disorders (Cerdá et al., 2010). While GAD and MDD share the same genetic factors, their environmental determinants are mostly distinct (Kendler, 1996; Roy et al., 1995). The role of genetic factors decreases with age, while environmental factors have an increasing impact (Kendler et al., 2011).

The presence of a depressive disorder may mask the presence of an anxiety disorder and vice versa; this is partly due to the overlap of symptoms in these disorders (Belzer & Schneier, 2004). Comorbid anxiety disorders among people with mood disorders complicate diagnosis and can cause treatment to be more challenging; it is essential when treating comorbid mood and anxiety disorders to complete a careful and comprehensive diagnostic assessment (Coplan, 2015).

In summary, people with mood disorders are at a greater risk for anxiety disorders than people without mood disorders. Current literature suggests that comorbid anxiety disorders in people with mood disorders worsen prognosis. Understanding the factors involved in this

relationship can help us develop better treatments for this group at an increased risk of negative outcomes.

1.4 Childhood Adversity and its Outcomes

Childhood adversity is a broad term that includes all forms of childhood maltreatment (physical abuse, sexual abuse, emotional abuse, neglect, and exploitation) and experiences of parental conflict, parental loss, or separation from parents (Trotta et al., 2015). Childhood adversity is known to have an enduring effect on the health outcomes of survivors (Kuuire, 2019), and decrements in mental health occur in a dose-response manner when childhood adversity is examined (Edwards et al., 2003). While not all studies define childhood adversity in the same way the majority of them do include all forms of maltreatment, neglect, and experiences of parental loss in their definitions.

In recent years, there has been an increase in publications relating adverse childhood events to a range of health risk behaviors and ill health, including psychiatric disorders (LaNoue et al., 2010). Childhood adversity is more prevalent in people with psychiatric disorders, including bipolar disorder, anxiety disorders, and depression (Jaworska-Andryszewska & Rybakowski, 2018; Li et al., 2023 Marangoni et al., 2016; Mckay et al., 2021; Palmier-Claus et al., 2016; Yap et al., 2014). There is increasing evidence that childhood adversity also impacts the course of unipolar depression and bipolar disorder; it has been shown to be associated with an earlier onset and with higher recurrence rates of mood episodes in BD and MDD (Angst et al., 2010). Individuals with depression who have experienced childhood adversity are also 1.5 times more likely to be non-responders to treatment than individuals with depression who have not experienced childhood adversity, regardless of whether the treatment is psychotherapy, pharmacotherapy, or combined therapy (Nelson et al., 2017). Childhood maltreatment also

predicts unfavorable outcomes for those with BD (Agnew-Blais & Danese, 2016). People with BD who have a history of childhood maltreatment are more likely to experience more severe symptoms of manic episodes and a poorer course of illness than those who have not experienced childhood maltreatment (Agnew-Blais & Danese, 2016). Studies have also found that childhood trauma is among the strongest predictors of chronic and challenging depression in adulthood (Angst et al., 2010; LaNoue et al., 2010; Nanni et al., 2012). There is also evidence that indicates that childhood adversity is associated with increased chronicity of anxiety disorders in the general population (De Venter et al., 2017). Among people with BD, those with a co-occurring anxiety disorder were found to have experienced more childhood adversity than those without a comorbid anxiety disorder (Pavlova et al., 2016). People with depression who recall a history of childhood trauma experience a significantly greater number of comorbid mental disorders, including anxiety disorders (Bernet & Stein, 1999).

In summary, childhood adversity increases the likelihood of a person having a mood or an anxiety disorder. People with mood disorders who experienced childhood maltreatment are more likely to have an anxiety disorder. The literature that this finding is based on almost exclusively focused on dichotomously defined anxiety disorders (lifetime anxiety disorder present or absent). Given that the level of burden of anxiety disorders affects outcome, this definition seems to be lacking in precision. What is not known is whether childhood adversity is associated with multiple anxiety disorders and greater persistence of anxiety disorders.

1.5 Possible Reasons for the Association between Childhood Adversity and Mood and Anxiety Disorders

Emotional regulation is a process by which individuals monitor, evaluate, and modify, their emotional states to achieve a desired goal or outcome (Gross, 2015). Affect dysregulation,

refers to an impaired ability to regulate and/or tolerate negative emotional states. It has been shown that traumatic events, including childhood maltreatment, negatively influence people's ability to regulate their emotions and use effective regulatory strategies (Byrne & Kangas, 2022; Dvir et al., 2014). Trauma exposure in childhood is associated with reduced ability to understand and regulate emotions and with increased levels of internalizing and externalizing psychopathology (Dvir et al., 2014). Affect dysregulation also plays a role in many psychiatric conditions, including anxiety and mood disorders (Dvir et al., 2014).

Adverse childhood events are risk factors for the development of both anxiety and mood disorders in adulthood (Young et al., 1997). Research has shown that childhood adversity increases symptom severity and contributes to an earlier age of onset of mood and anxiety disorders (Young et al., 1997). However, there is a strong association between childhood maltreatment and parental mental illness (Ben David, 2021) which suggests that genetic and environmental factors are difficult to separate as etiological factors in vulnerability.

Childhood adversity exerts a substantial influence on the central nervous system (Jaworska-Andryszewska & Rybakowski, 2018). This results in both functional and structural changes in the hippocampus and the amygdala which are associated with the development of mood disorders (Jaworska-Andryszewska & Rybakowski, 2018).

The serotonin transporter gene and the FKBP5 gene play an important role in the pathogenesis of mood disorders (Jaworska-Andryszewska & Rybakowski, 2018). It has been demonstrated that the interaction of these genes with childhood adversity produce pathological clinical phenomena in adulthood (Jaworska-Andryszewska & Rybakowski, 2018). Childhood adversity has also been found to effect epigenetic mechanisms such as DNA methylation, which

can alter brain function over long periods (Jaworska-Andryszewska & Rybakowski, 2018). Childhood maltreatment is also associated with disturbances of stress axis, immune-inflammatory mechanisms, and metabolic dysregulation (Jaworska-Andryszewska & Rybakowski, 2018). Although significant associations of childhood adversities with adult mental disorders have been consistently documented studies generally have examined only one type of childhood adversity per study (Green, McLaughlin, & Berglund, 2010). Childhood adversities are often clustered (Green, McLaughlin, & Berglund, 2010), our research examined multiple forms of childhood adversities for each participant allowing a clear picture of how childhood adversity affected their mood and anxiety disorders.

1.6 Summary and Hypotheses

In summary, the relationship between childhood adversity and mood disorders and between childhood maltreatment and anxiety disorders is well established. People who experienced childhood adversity are more likely to have a mood or an anxiety disorder and their mood episodes are more likely to be chronic and severe. Those with mood disorders and a history of childhood adversity are also more likely to have a comorbid anxiety disorder. While the chronicity of anxiety is higher among those who have experienced childhood adversity, it is not clear whether the severity and persistence of anxiety disorders in people with mood disorders increases with higher levels of adversity. Most previous research was hampered by retrospective reporting, often focussing only on one time point and a dichotomic approach to anxiety disorders (yes or no). This method of reporting is particularly susceptible to memory bias and mood dependent memory, and it may miss some anxiety disorders that present less severely. The current thesis will attempt to cover the gaps in literature by 1) assessing the severity of anxiety

retrospectively for each week over the previous six months, 2) focussing on the number of anxiety disorders, and 3) assessing participants' anxiety prospectively.

We hypothesise that more childhood adversity is associated with more severe and persistent anxiety in people with mood disorders.

Specifically, our first hypothesis is that people with mood disorders who experienced higher levels of childhood adversity will report a higher average anxiety retrospectively over the six months preceding their first assessment.

Our second hypothesis is that people with mood disorders who experienced greater levels of childhood adversity will have a higher number of lifetime anxiety and related disorders.

Our third hypothesis is that among people with mood disorders, those who experienced greater levels of childhood adversity will prospectively report more anxiety.

CHAPTER 2 METHODS

2.1 Inclusion and Exclusion Criteria

We included participants with major depressive disorder, bipolar I disorder, or bipolar II disorder confirmed by the research version of the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015). Participants were 18 years of age or older in order to assess the impact of childhood adversity on adults. Participants had to have a sufficient command of the English language to participate in an interview.

Participants who were at a high risk of suicide as assessed by SCID-5 were unable to participate as this would necessitate immediate intervention. Any participants with current hypomania or mania as assessed by SCID-5 were ineligible as mania may interfere with the accurate recall of symptoms and potentially interfere with the capacity to consent

2.2 Participant Recruitment

Participants were recruited through the Nova Scotia Health Mood Disorders Program, and through Community Mental Health Teams in Nova Scotia, Canada. We also advertised the study in community locations such as Dalhousie University, Saint Mary's University, and at a private practice psychology clinic, as well as on social media.

2.3 Measures

Demographic and treatment information

Demographic and treatment information included the participant's sex, gender, age, ethnicity, a history of medical disease and treatment, and history of treatment for psychiatric diseases.

The Structured Clinical Interview for DSM-5 Research Version

We confirmed the mood disorder diagnosis (bipolar I disorder, bipolar II disorder, or major depressive disorder) and established lifetime diagnoses of comorbid anxiety and related disorders using the SCID-5 research version (First, 2015). We computed the number of anxiety and related disorders experienced by each participant. The SCID-5 is the most widely used structured diagnostic instrument for assessing *DSM*-5 mental illnesses (First, 2015). It has demonstrated excellent reliability and high specificity, and the clinical validity of the instrument has also been confirmed (Lima Osório et al., 2019).

The SCID interviews were conducted by trained research team members. We assessed mood disorders, anxiety disorders, obsessive compulsive disorder, and post-traumatic stress disorder. The research team members were trained by a clinical psychologist through role playing, explanations of the diagnostic criteria, and observation of SCID interviews. Narratives were written for each participant's initial assessment, and diagnoses were confirmed in consensus meetings between research team members and the project's principal investigator, who is a licensed clinical psychologist.

The Longitudinal Interval Follow-Up Evaluation

We recorded the longitudinal course of the mood and anxiety disorders using the Longitudinal Interval Follow-Up Evaluation (LIFE) interview (Keller et al., 1987). LIFE records symptomatic status separately for mood and for anxiety retrospectively for each week of the 6-month period (i.e., 26 weeks) preceding the assessment. The LIFE interview has been shown to be a reliable and valid instrument for retrospectively characterizing the weekly course of anxiety and mood disorders (Bryant et al., 2022; Warshaw et al., 1994; Warshaw et al., 2001). The LIFE interview was used to create an average LIFE anxiety score and an average depression score for participants based on their symptoms during each week over the six months preceding the

baseline assessment. The score was created by summing the weekly anxiety scores from the preceding six months and dividing the sum by the number of weeks. The same procedure was used for the depression scores.

The Childhood Experience of Care and Abuse

Using the Childhood Experience of Care and Abuse (CECA; Bifulco, Brown, & Harris, 1994), we determined whether participants experienced childhood adversity, at what age they experienced the adversity, and what type of adversity they experienced. The adversity could have occurred anytime up until the age of 18. The CECA assesses physical abuse, sexual abuse, emotional abuse, and parental discord. The component ratings of the CECA interview have been shown to have satisfactory inter-rater reliability and validity (Bifulco et al., 1994; Brown et al., 2007). The CECA was used to create an adversity total score for participants. As is standard when scoring the CECA, vignettes (detailed narratives) were written for each participant using standardized language, to allow for scores be created using the standard CECA scoring benchmarks. Please find a copy of the vignette template in the supplemental items section. The vignettes were created by listening to the recordings of the CECA interviews as well as rereading the CECA interview notes that had been taken. Vignettes were written first describing the background of participants. They continued to detail experiences of parental discord, psychological abuse, physical abuse, and sexual abuse. Scoring of the CECA vignettes was done by a trained CECA scorer after their scoring was calibrated during a consensus meeting with other trained CECA scorers. During the consensus meeting, scoring of the vignettes was reviewed and ratings were calibrated between scorers by assessing the vignettes and comparing them to the vignettes in the CECA training manual. We scored the four categories of adversity: Parental discord, psychological abuse, physical abuse, and sexual abuse. As per the standard

CECA rating, each category could receive a score between 0 and 3 (0=none, 1=some, 2= moderate, 3= marked) besides parental discord which could receive a score between 0 and 4 (4 = violence). Bifulco et al. (1994) developed the CECA and tested multiple scoring methods. They concluded that the dichotomous scoring is the most appropriate (Bifulco et al., 1994). We dichotomized the scores for each section (parental discord, psychological abuse, physical abuse, and sexual abuse) into 0 = absent and 1 =present, scores of 2 or above for any given section were coded as a 1, and scores below 2 were coded as 0. This method of dichotomizing the scores is also in line with other research in the field (Chakrabarty et al., 2020; Carbone et al., 2019; Çevik et al., 2019) The combined categories of moderate and severe abuse have been previously shown to be associated with chronic depression in adulthood (Brown et al., 2007). The overall adversity score was created by summing the dichotomized scores for each participant. A childhood maltreatment variable was created from the CECA measures of abuse, excluding parental discord.

The Screen for Adult Anxiety Related Disorders

The Screen for Adult Anxiety Related Disorders (SCAARED) is a questionnaire that consists of 44 items that are rated on a 3-point scale ranging from 0 (not true) to 2 (very true or often) (Angulo et al, 2017). The SCAARED assesses symptoms of SAD, GAD, panic, agoraphobia, and somatic anxiety (Angulo et al., 2017). The SCAARED total score was used for the prospective analyses in our study. The SCAARED has been shown to have high internal consistency between items in the same factor and strong discriminant validity (Angulo et al., 2017).

2.4 Procedure

Potential participants were approached by their clinician and asked whether they would be interested in receiving additional information about the study. They were also asked if it would be acceptable for a member of the research team to contact them. If the person agreed to be contacted by the research team, one of the members approached them either by phone or by email (depending on the participant's preference). The research team member gave the potential participant information about the study and provided opportunities for them to ask questions. For the self-referrals from the community, participants contacted the research team via phone or email. If the potential participant agreed to participate, the research team member booked the initial appointment for the full consent discussion. The initial appointment could occur via videoconferencing or in person, depending on the participant's preference.

2.5 Research visits

Recruitment was ongoing for the duration of the study. Assessments were conducted between October 2021 and June 2022. Participants were invited to attend an initial assessment upon enrollment. At baseline, the participants completed the informed consent. If they provided the informed consent, they participated in the research assessment, including the demographic and treatment information, the SCID-5, the SCAARED, the LIFE, and the CECA. Thereafter, participants were contacted monthly to complete the SCAARED. All assessments could be conducted in person or via teleconferencing, depending on the participant's preference.

2.6 Data Entry

The data were recorded using the existing Canadian Depression Research & Intervention Network (CDRIN) registry platform available through the Nova Scotia Health (NSH) intranet. The CDRIN registry has secure data storage in a relational database on an NSH server. The

CDRIN registry allowed participants to complete the questionnaires either in person or online.

2.7 Analysis Plan

Demographic information such as the average age, the age range, and the number of females and males, as well as the diagnoses, will be reported.

We hypothesized that in our sample of people with mood disorders, people who experienced more childhood adversity would have a higher average anxiety over the six months preceding the assessment (i.e., a higher average LIFE anxiety score). To test our primary hypothesis, we conducted a linear regression with childhood adversity CECA score as the independent variable and average LIFE anxiety score as the dependent variable. A linear regression enabled us to assess the relationship between childhood adversity and average anxiety score as well as to control for variables, including sex and mood measured by LIFE. Model assumptions were checked with diagnostic plots of the residuals as well as testing the residuals for normality using the Shapiro-Wilk normality test and calculating Cook's distance to examine the data for influential outliers.

Varying levels of depression may affect mood-dependent memory influencing participants' ability to accurately recount their childhood adversity (Lewis & Critchley, 2003). Anxiety disorders have also been found to be more prevalent among women than among men (Bekker & van Mens-Verhulst, 2007). As we expected the average mood score and sex to impact the average anxiety score, we controlled for these variables in the analysis. We, therefore, used multiple regression to examine the impact of childhood adversity score on average anxiety score while controlling for average mood score and sex. We used Mahalanobis Distance to test for the presence of multivariate outliers. Normality of the residuals was tested using the Shapiro-Wilk

normality test and diagnostic plots of the residuals were examined to assess other model assumptions.

Our second hypothesis was that people with mood disorders with more severe childhood adversity would have more lifetime anxiety and related disorders. To test this hypothesis, linear regression was conducted with the number of anxiety disorders as determined by the SCID-5 as the dependent variable and childhood adversity score as the independent variable. Model assumptions were checked as detailed for the regressions of the effect of childhood adversity score on average anxiety score. We also controlled for sex in this analysis.

Our third hypothesis was that people with mood disorders who experienced greater levels of childhood adversity would report more anxiety prospectively. To test this hypothesis, we used data from the monthly follow-up interviews using the SCAARED. Each participant's data consisted of the childhood adversity score and the SCAARED anxiety score from their initial assessment and for each month for which a follow-up interview was completed. We used multilevel modelling to allow us to account for the repeated measures design through the use of a random intercept. SCAARED anxiety scores were the dependent variable, with the independent variables being the childhood adversity score, sex, and time in monthly intervals starting with their initial assessment. Residuals were screened for normality.

The final sample size for the study was small (please see the Results section for details). To help interpret results considering the limited sample size, we performed post-hoc power analyses according to Faul et al. (2009). The power analyses were done using the effect size estimated from the regression of the effect of childhood adversity score on average anxiety score, as this was the primary hypothesis. In order to further aid in the interpretation of results and

inform future research, we also calculated how many participants would be required to achieve a power of 0.80.

All analyses were conducted using R version 4.1.0 (R Core Team, 2021). The p-value indicating the level of significance was adjusted using the Bonferroni correction. However, none of the negative results were close to significance even without the adjustment. Diagnostics testing model assumptions are reported with the results of each model.

2.8 Research Ethics Board Approval

Research Ethics Board (REB) approval was granted by the Nova Scotia Health (NSH) Research Ethics Board (REB File #: 1026971).

CHAPTER 3 RESULTS

3.1 Sample Characteristics

Our sample consisted of 33 participants. Twenty of our participants were referred from the NSH Mood Disorders Clinic, 3 from community mental health teams, 3 were self-referrals from community advertisements, and 7 were self-referrals from Facebook. Table 3.1 provides the sample characteristics by mood disorder diagnosis. Table 3.2 denotes the comorbidity between mood and anxiety disorders in our sample. The average age was 42.2 (*SD* =15.20) and the age range was 20 to 74. Ninety-one percent of the participants were Caucasian. Twenty were female (60.6%). Sixteen (48.5%) participants had generalized anxiety disorder, 4 (12.1%) had post-traumatic stress disorder, 4 (12.1%) had obsessive compulsive disorder, 11 (33.3%) had social anxiety disorder, 5 (15.2%) had panic disorder, 3 (9.1%) had specific phobia, and 1 (3.0%) had agoraphobia. Nine (27.3%) of participants had BDI, 10 (30.3%) had BDII, and 14 (42.4%) had MDD. Nine (27.3%) participants had no anxiety disorders, 12 (36.4%) had 1 anxiety disorder, 6 (18.2%) had 2 anxiety disorders, 5 (15.2%) had 3 anxiety disorders and 1 (3.0%) person had 5 anxiety disorders. Twenty (60.6%) participants experienced parental discord, 9 (27.3%) experienced psychological abuse, 6 (18.2%) experienced physical abuse, and 3 (9%) experienced sexual abuse. These were not mutually exclusive categories.

Table 3.1 Sample Characteristics by Mood Disorder Diagnosis

Diagnosis	**Age (Years) (*SD*)**	**Number of Female Participants (*%*)**
Bipolar I Disorder	51.9 *(16.4)*	6 (*66.7*)
Bipolar II Disorder	34.6 *(11.3)*	5 (*50*)
Major Depressive Disorder	40.4 *(11.3)*	9 (*64.3*)

Notes. This table shows the age of participants by mood disorder diagnosis and the number and percent of female participants by mood disorder diagnosis.

Table 3.2 Mood and Anxiety Disorder Comorbidity

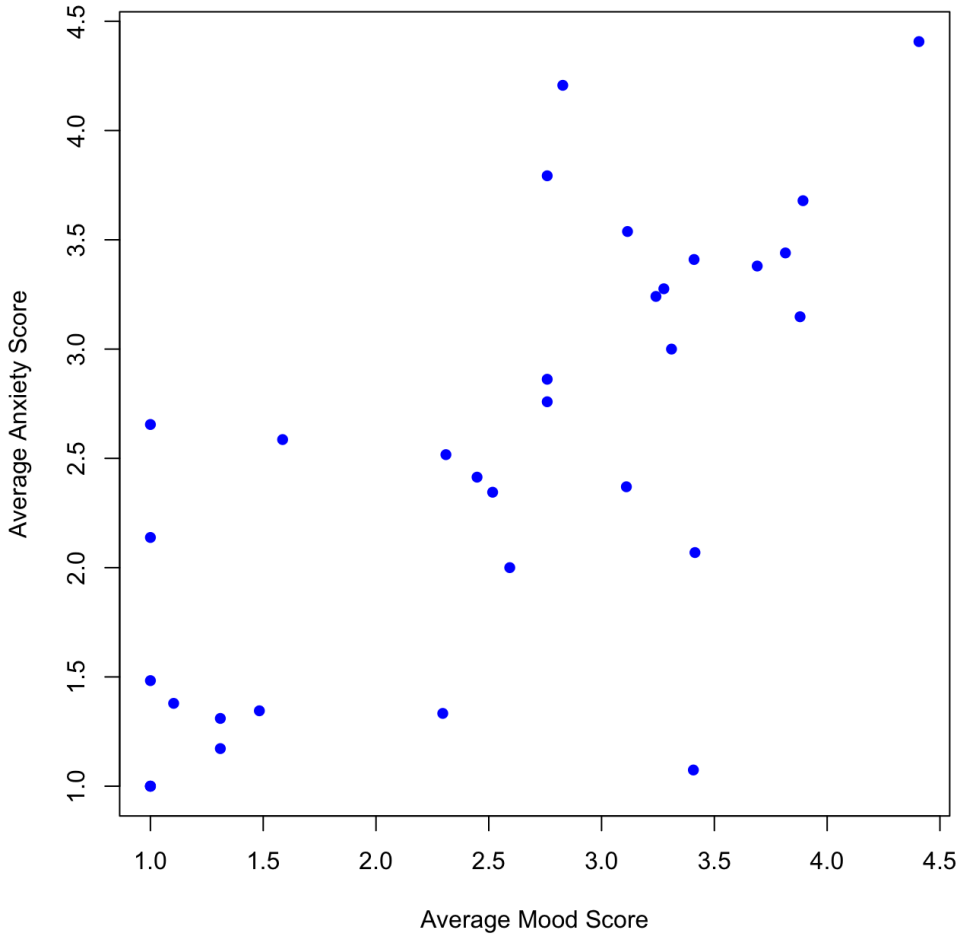
Mood Disorder	Anxiety Disorder n (*%*)						
	Generalized Anxiety Disorder	**Post Traumatic Stress Disorder**	**Social Anxiety Disorder**	**Obsessive Compulsive Disorder**	**Agoraphobia**	**Panic Disorder**	**Specific Phobia**
Bipolar I Disorder	3 (*33*)	0 (*0*)	1 (*12.5*)	1 (*12.5*)	0 (*0*)	0 (*0*)	0 (*0*)
Bipolar II Disorder	7 (*70*)	2 (*20*)	5 (*50*)	1 (*10*)	0 (*0*)	3 (*30*)	1 (*10*)
Major Depressive Disorder	6 (*42.9*)	3 (*21.4*)	5 (*35.7*)	2 (*14.3*)	1 (*7.1*)	2 (*14.3*)	2 (*14*)
Total	16 (*49.5*)	5 (*15.2*)	11 (*33.3*)	4 (*12.1*)	1 (*3*)	5 (*15.2*)	3 (*9.1*)

Notes. This table shows the comorbidities between mood and anxiety disorders in our sample. n is the number of participants. Some participants had more than 1 anxiety disorder.

3.2 Relationship between Average Anxiety Score and Average Mood Score

A Pearson correlation coefficient was computed to assess the linear relationship between average anxiety score and average mood score. There was a positive correlation between the two variables, $r(33) = 0.73$, $p<0.001$ (Figure 3.1).

Figure 3.1 Relationship between Average Anxiety Score and Average Mood Score



As several statistical tests were conducted to evaluate our hypotheses (10), we adjusted the level of p indicating significance to account for the number of tests so that tests with a p value of less than 0.005 were considered significant**.**

We conducted a linear regression to determine the effect of childhood adversity on the average anxiety score. Increased levels of childhood adversity were not found to be associated with higher levels of anxiety (average anxiety score from the LIFE interview). The effect of childhood adversity on the average anxiety score was not significant (unstandardized slope = -0.08, ß = -0.06, adjusted $r^2 = 0$, $p = 0.74$, Table 3.3). Diagnostics showed some deviation of the residuals from normality and some indication of outliers (Figure 3.2). We conducted the Shapiro-Wilk normality test to test the normality of the residuals; they were found to be normally distributed with a p-value of 0.09. Cooks test identified one influential outlier (Figure 3.3). This outlier was removed and the regression re-run. The regression without the outlier identified by Cooks test, also showed no significant effect of childhood adversity score on average anxiety score (unstandardized slope = 0.01, ß = 0.01, adjusted $r^2 = 0$, $p = 0.95$).

Post-hoc power analyses were conducted using the results and sample size (33) of the linear regression with childhood adversity score as the independent variable and average anxiety score as the dependent variable, and assuming a significance level of 0.05. The power of this regression was very low at 0.10, which means there was a high probability of not detecting an effect when it was present. There would need to be 1700 participants to increase the power to 0.80.

Table 3.3 Regression of the Effect of Childhood Adversity Score on Average Anxiety Score

Multiple R Square	0.004
Adjusted R Square	0
Residual Standard Error	1.03
Observations	33

ANOVA

	Df	**SS**	**MS**	**F**	**Significance of F**
Childhood Adversity Score	1	0.12	0.12	0.11	0.74
Residual	31	32.63	1.05		
Total	32				

Notes. Df is degrees of freedom, SS is sum of squares, MS is mean square, F is F statistic.

	Coefficients	**Standard Error**	**Standardized coefficients**	**t Stat**	**P-value**
	B		**ß**		
Intercept	2.53	0.27		9.34	<0.0001
Childhood Adversity Score	-0.08	0.25	-0.06	-0.33	0.74

Figure 3.2 Model Diagnostics for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score

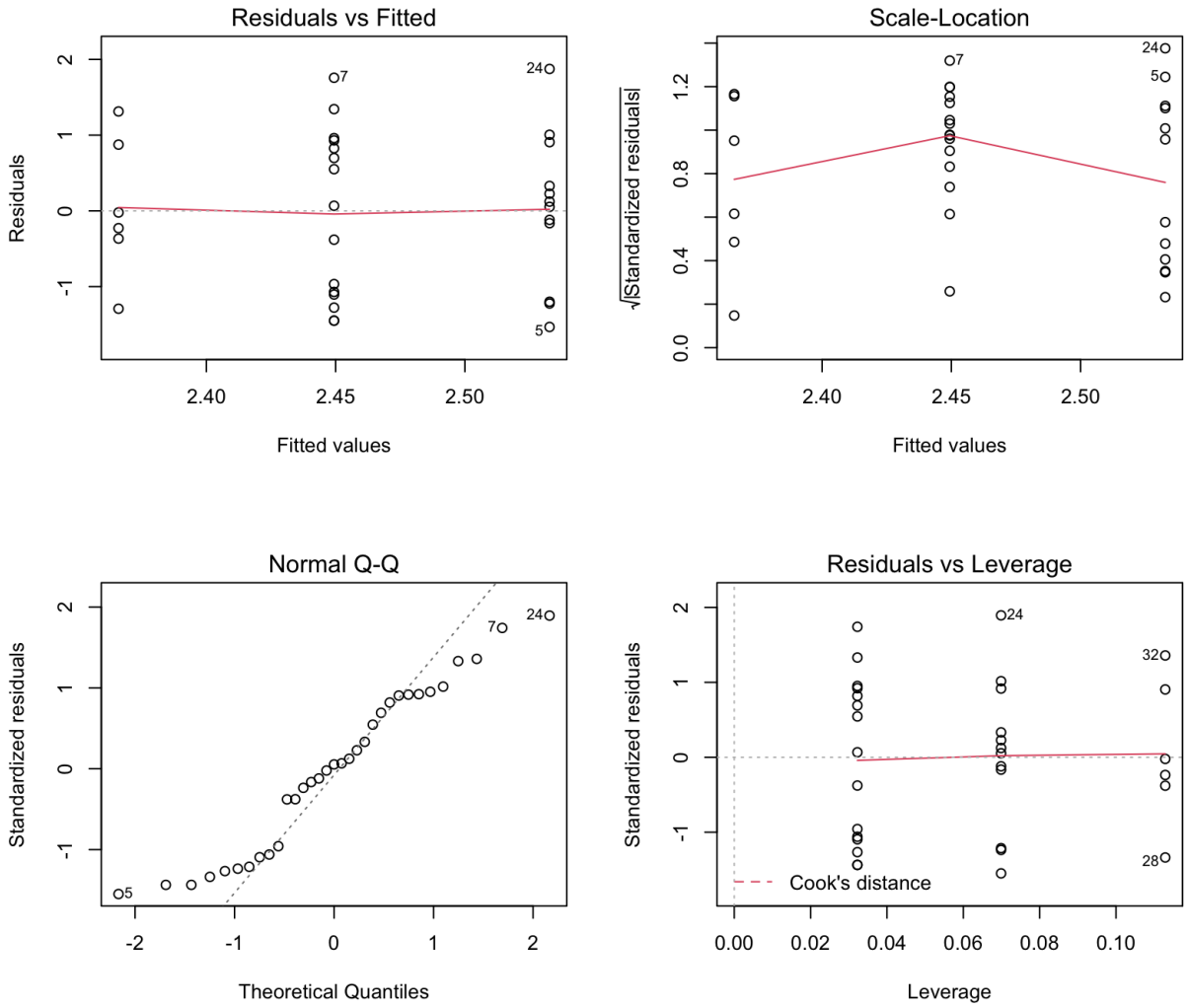
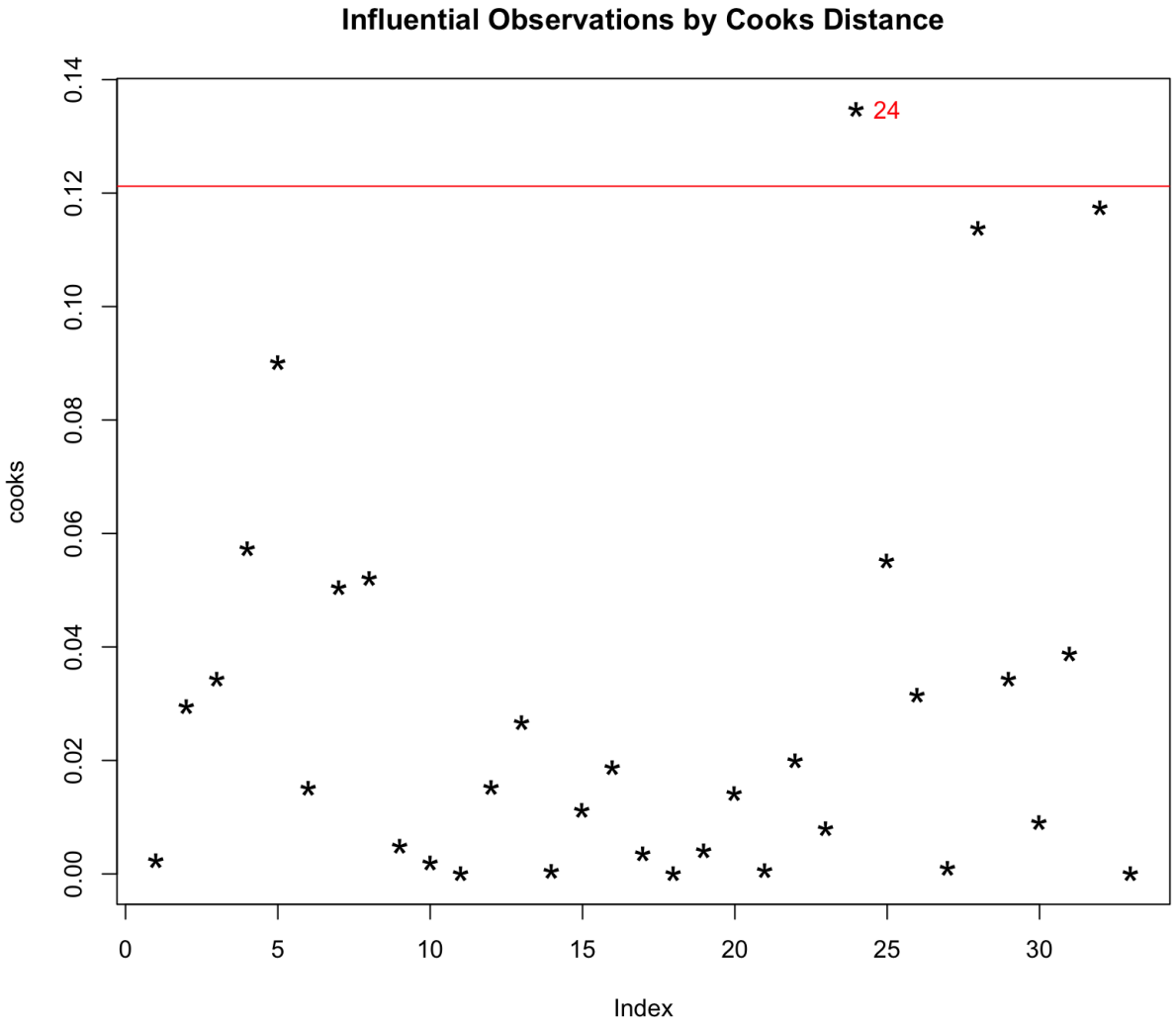
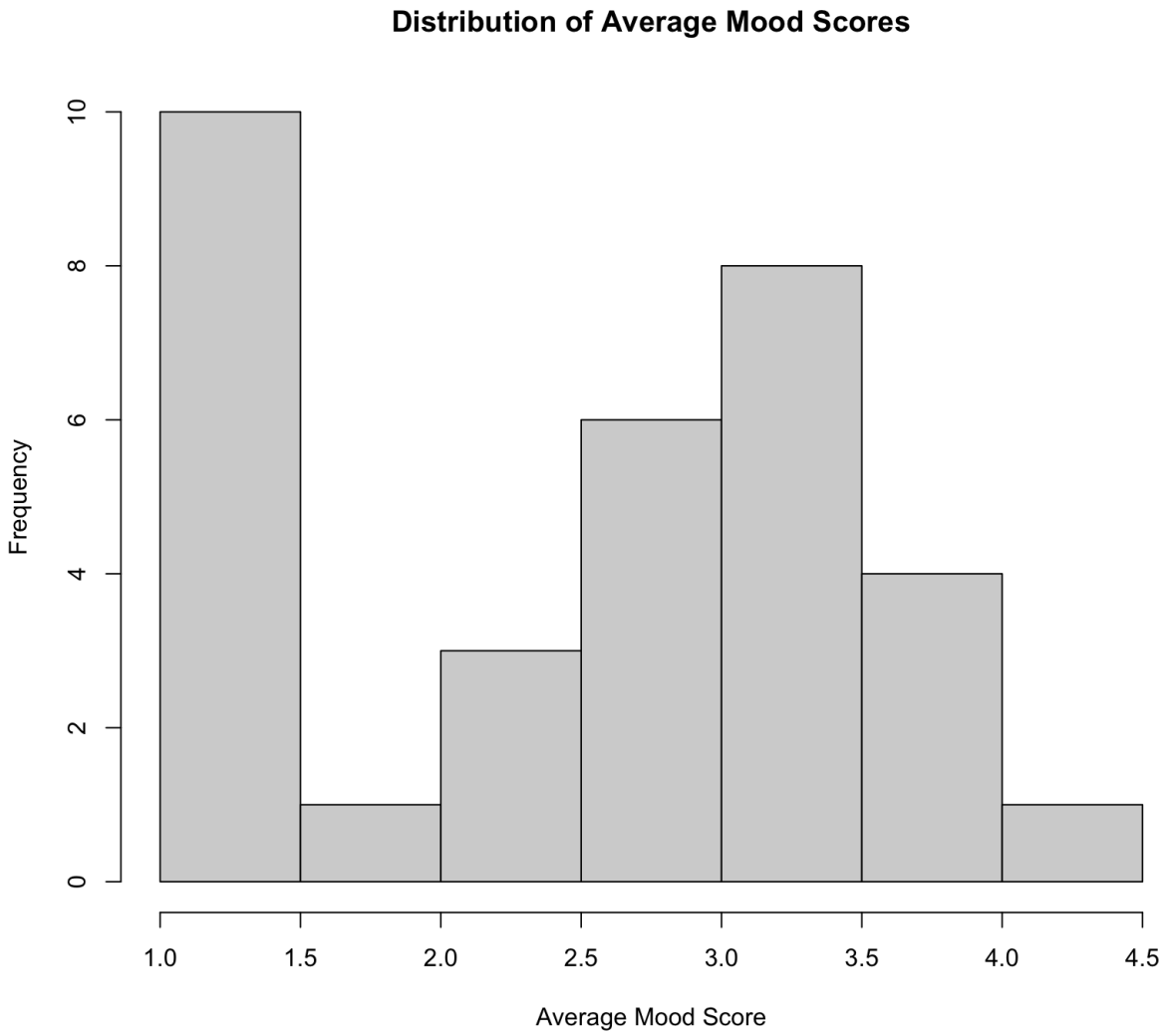


Figure 3.3 Influential Observations by Cooks Distance for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score



As shown in Figure 3.4, a large proportion (10 out of 33) of participants had an average mood score (measured by LIFE) of less than 1.5, indicating that the levels of depression over the 6 months prior to their interview were low. We decided to conduct this regression using participants with an average mood score above 1.5 to determine if there would be an effect of childhood adversity on the average anxiety score among participants with more severe mood problems. We conducted a linear regression with childhood adversity score as the independent variable and average anxiety score as the dependent variable using only participants with an average mood score above 1.5 but we found no significant effect of childhood adversity score on the level of average anxiety score (unstandardized slope = 0.13, ß = -0.12, adjusted $r^2 = 0$, $p = 0.49$).

Figure 3.4 Distribution of the Average Mood Scores for the Regression of the Effect of Childhood Adversity Score on Average Anxiety Score



Notes. A large proportion of participants have an average mood score (measured by LIFE) of less than 1.5

The childhood adversity score used in the analyses includes a score for parental discord. We created a childhood maltreatment variable from the CECA measures of abuse, excluding parental discord. This was the only analysis in which we used the childhood maltreatment variable. We conducted a linear regression with childhood maltreatment as the independent variable and average anxiety score as the dependent variable. This regression detected no significant effect of childhood maltreatment on average anxiety score (unstandardized slope = 0.08, ß = 0.03, adjusted $r^2 = 0$, $p = 0.86$).

3.3 Multiple Regression Effect of Average Mood Score (LIFE), Sex, and Childhood Adversity Score (CECA) on Average Anxiety Score (LIFE).

This regression showed a significant effect of average mood score on average anxiety (unstandardized coefficient = 0.7, ß = 0.73, $p<0.0001$) but no significant effect of sex (unstandardized coefficient = 0.10, ß = 0.05, $p = 0.71$) or of childhood adversity (unstandardized coefficient = -0.15, ß = -0.11, $p = 0.41$) (Table 3.4) on average anxiety score, in each case holding all other variables constant. The Mahalanobis distance test did not reveal any multivariate outliers. Diagnostics did not reveal any other concerning deviations from assumptions (Figure 3.5) and the Shapiro-Wilk test did not indicated deviations of the residuals from normality ($p = 0.79$).

Table 3.4 Multiple Regression of the Effect of Average Mood Score, Sex, and Childhood Adversity Score on Average Anxiety Score,

Multiple R Square	0.55
Adjusted R Square	0.50
Residual Standard Error	0.71
Observations	33

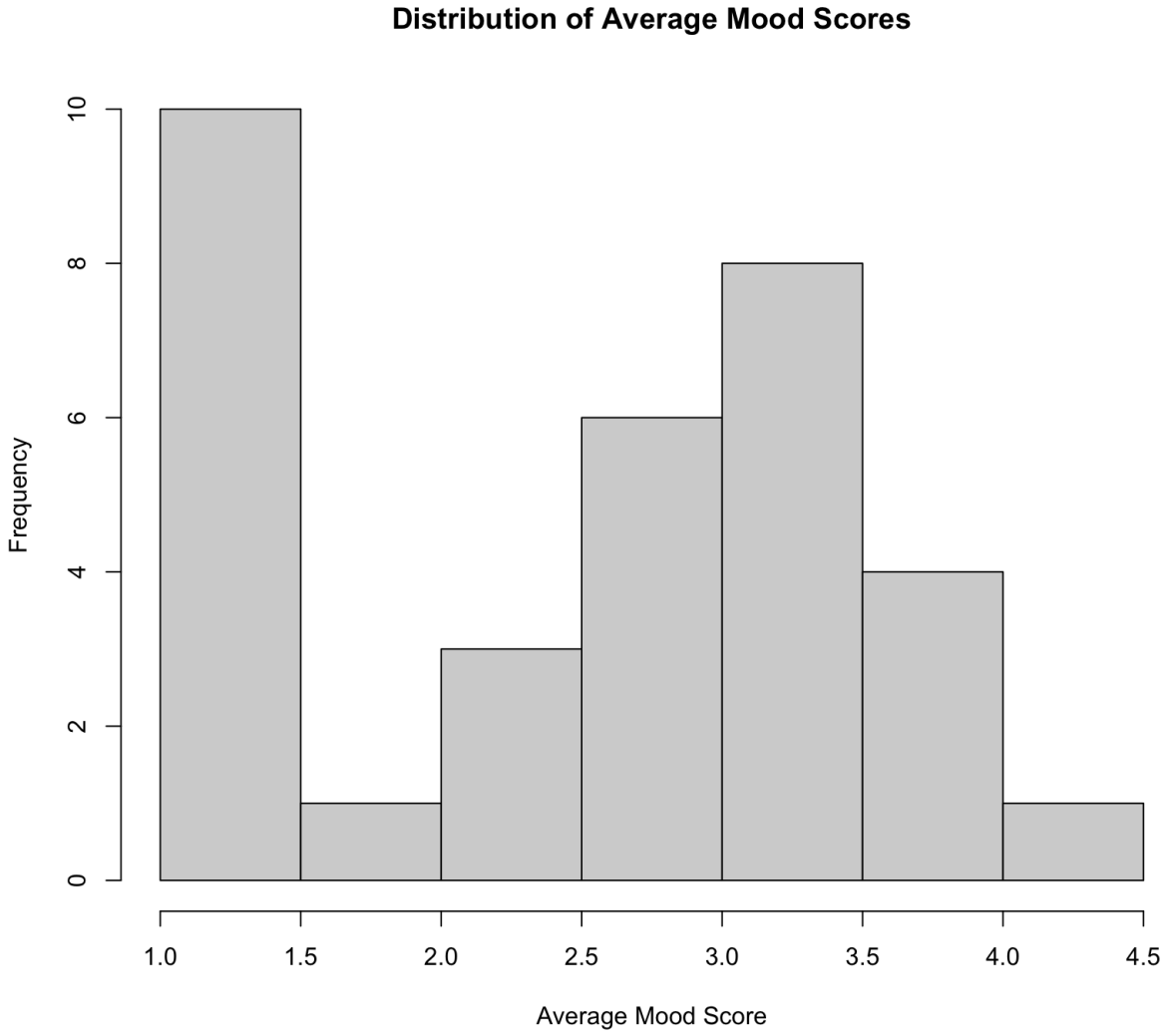
ANOVA

	df	**SS**	**MS**	**F**	**Significance of F**
Average Mood Score	1	17.52	17.52	34.55	<0.0001
Sex	1	0.18	0.18	0.35	0.56
Childhood Adversity Score	1	0.35	0.35	0.69	0.41
Residual	29	14.7	0.51		
Total	32				

Notes. Df is degrees of freedom, SS is sum of squares, MS is mean square, F is F statistic.

	Coefficients	**Standard Error**	**Standardized Coefficients**	**t Stat**	**P-value**
	B		**ß**		
Intercept	0.81	0.35		2.29	0.03
Average Mood Score	0.70	0.12	0.73	5.83	<0.0001
Sex	0.10	0.26	0.05	0.38	0.71
Childhood Aversity Score	-0.15	0.18	-0.11	-0.83	0.41

Figure 3.5 Model Diagnostics for the Multiple Regression of the Effect of Average Mood Score, Sex, and Childhood Adversity Score on Average Anxiety Score



Notes. Diagnostics did not reveal any concerning deviations from assumptions.

3.4 Linear Regression Effect of Childhood Adversity (CECA score) on Number of Anxiety Disorders per Participant

Childhood adversity had no significant effect on the number of anxiety disorders per participant (unstandardized slope = 0.24, ß = 0.14, adjusted $r^2 = 0$, $p = 0.43$) (Table 3.5). Model diagnostics (Figure 3.6) indicated that there could be some deviation of the residuals from normality and the possibility of influential outliers. Shapiro-Wilk normality test indicated that the residuals were not normally distributed ($p = 0.02$). Cooks Distance detected the presence of two influential outliers (Figure 3.7). These outliers were removed, and the analysis rerun. The removal of the two outliers resulted in residuals that did not deviate significantly from normality (Shapiro-Wilk $p = 0.05$) but did not change the significance of childhood adversity (unstandardized slope = 0.31, ß = 0.22, adjusted $r^2 = 0.01$, $p = 0.24$).

Table 3.5 Regression of the Effect of Childhood Adversity on Number of Anxiety Disorders

Multiple R Square	0.02
Adjusted R Square	0
Residual Standard Error	1.22
Observations	33

ANOVA

	Df	**SS**	**MS**	**F**	**Significance of F**
Childhood Adversity Score	1	0.95	0.95	0.63	0.43
Residual	31	46.39	1.50		
Total	32				

Notes. Df is degrees of freedom, SS is sum of squares, MS is mean square, F is F statistic.

	Coefficients	**Standard Error**	**Standardized coefficients**	**t Stat**	**P-value**
	B		**ß**		
Intercept	1.14	0.33		3.52	0.001
Childhood Adversity Score	0.24	0.30	0.14	0.80	0.243

Figure 3.6 Model Diagnostics for the Linear Regression Analysis Effect of Childhood Adversity on Number of Anxiety Disorders Per Participant

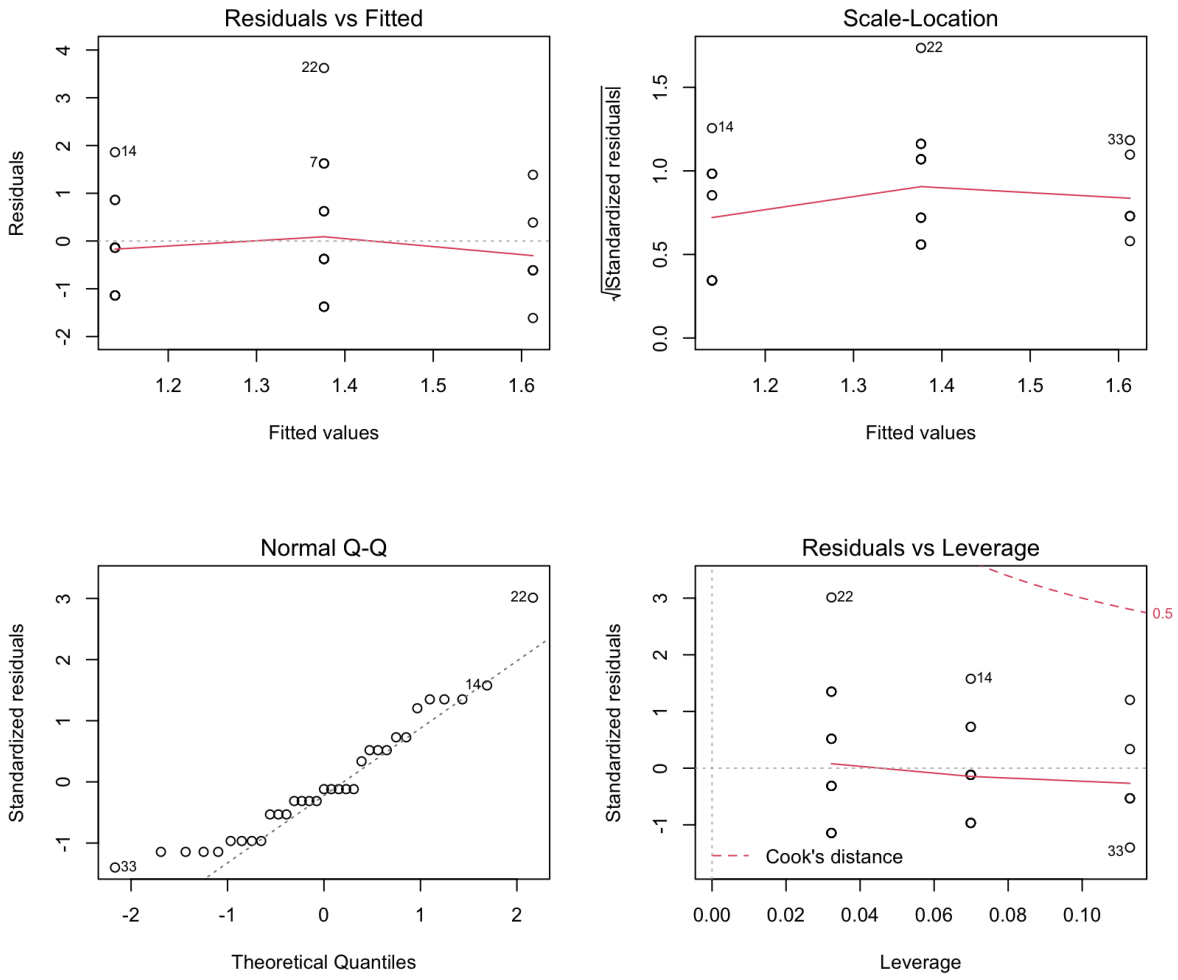
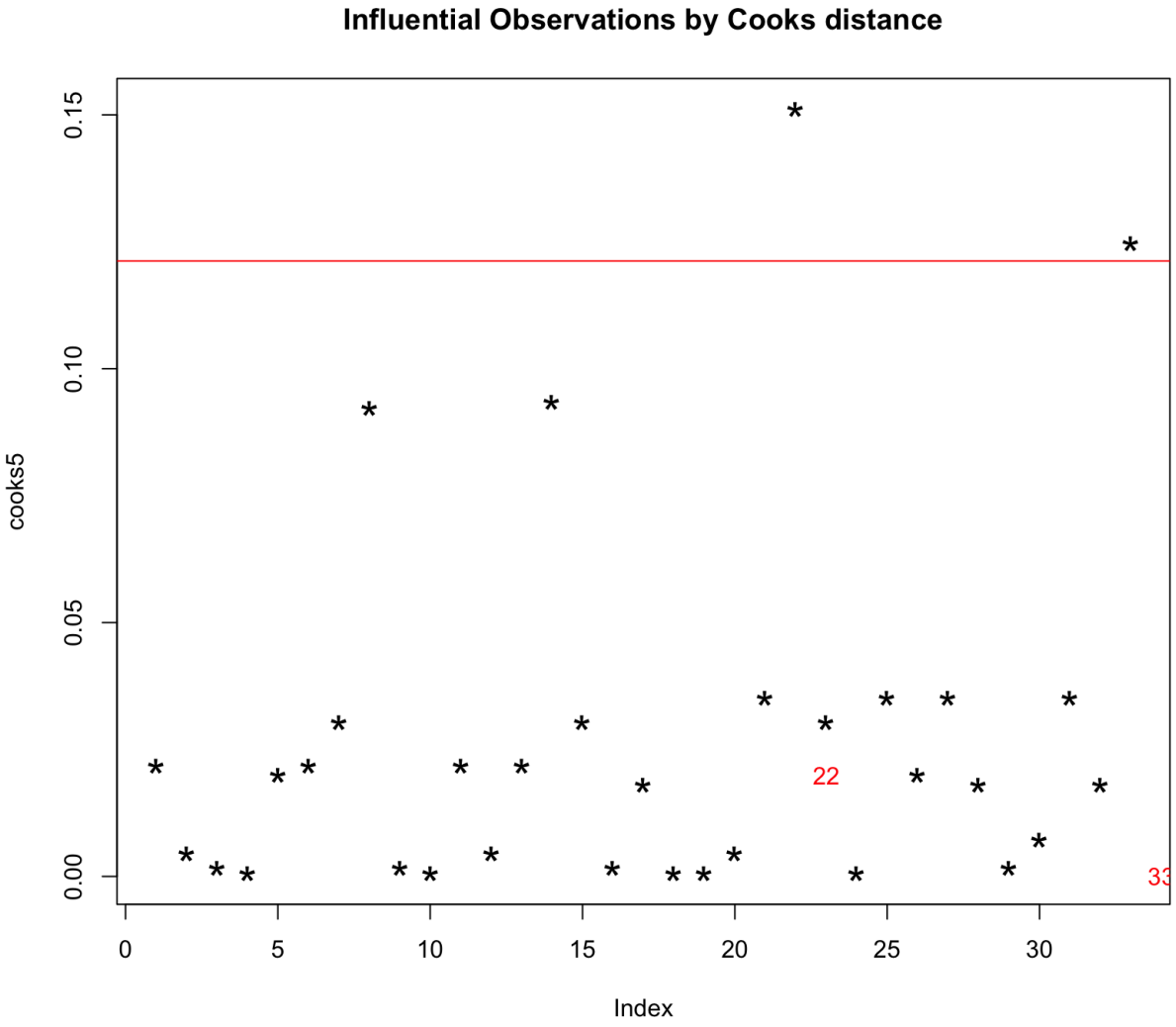


Figure 3.7 Influential Observations by Cooks Distance for the Linear Regression Effect of Childhood Adversity on Number of Anxiety Disorders Per Participant



3.5 SCAARED Anxiety Score over Time

There were 167 observations across the 33 participants. The largest number of observations for a participant was 10 (initial evaluation plus 9 monthly follow-ups), and the smallest 1 (3 participants had only the initial evaluation). There were 16 participants that were followed for at least 6 months (initial evaluation plus 5 follow-ups). The variation in the number of monthly evaluations was mainly the result of the continual recruitment of participants over the course of the data collection period. Some participants were not available for one or more of their follow-ups, but only one participant withdrew from the study.

A baseline model was included, which only had a random intercept (participant) as an explanatory variable. The model (model 2), which included childhood adversity score and time as fixed effects, was significantly different from this baseline (Table 3.6). The comparison of the model with childhood adversity and time as fixed effects and participant as a random intercept to that which included time also as a random slope (model 3) showed no significant difference in model fit (Table 3.6). In the comparison of the model with childhood adversity and time, as fixed effects, and participants as random intercepts to that which included sex as a fixed effect, as well as fixed effects of time, and childhood adversity (model 4), showed no significant difference in model fit. Since there are fewer parameters in the model with random intercept and fixed slope and not including sex as an independent variable, this model was considered the best. The fixed intercept model showed that there was a significant effect of time with the average SCAARED score decreasing over time (unstandardized coefficient = -0.76, ß = -0.15, t = -3.73, p = 0.0003), but no significant effect of childhood adversity score (unstandardized coefficient = -0.56, ß = -0.02, t = -0.16, p = 0.87, Table 3.7). Examination of the residuals shows no obvious deviations from normality (Figure 3.8)

Figure 3.8 Distribution of the Residuals from Multilevel Modelling of the Effect of Childhood Adversity Score and Time on SCAARED Anxiety Score

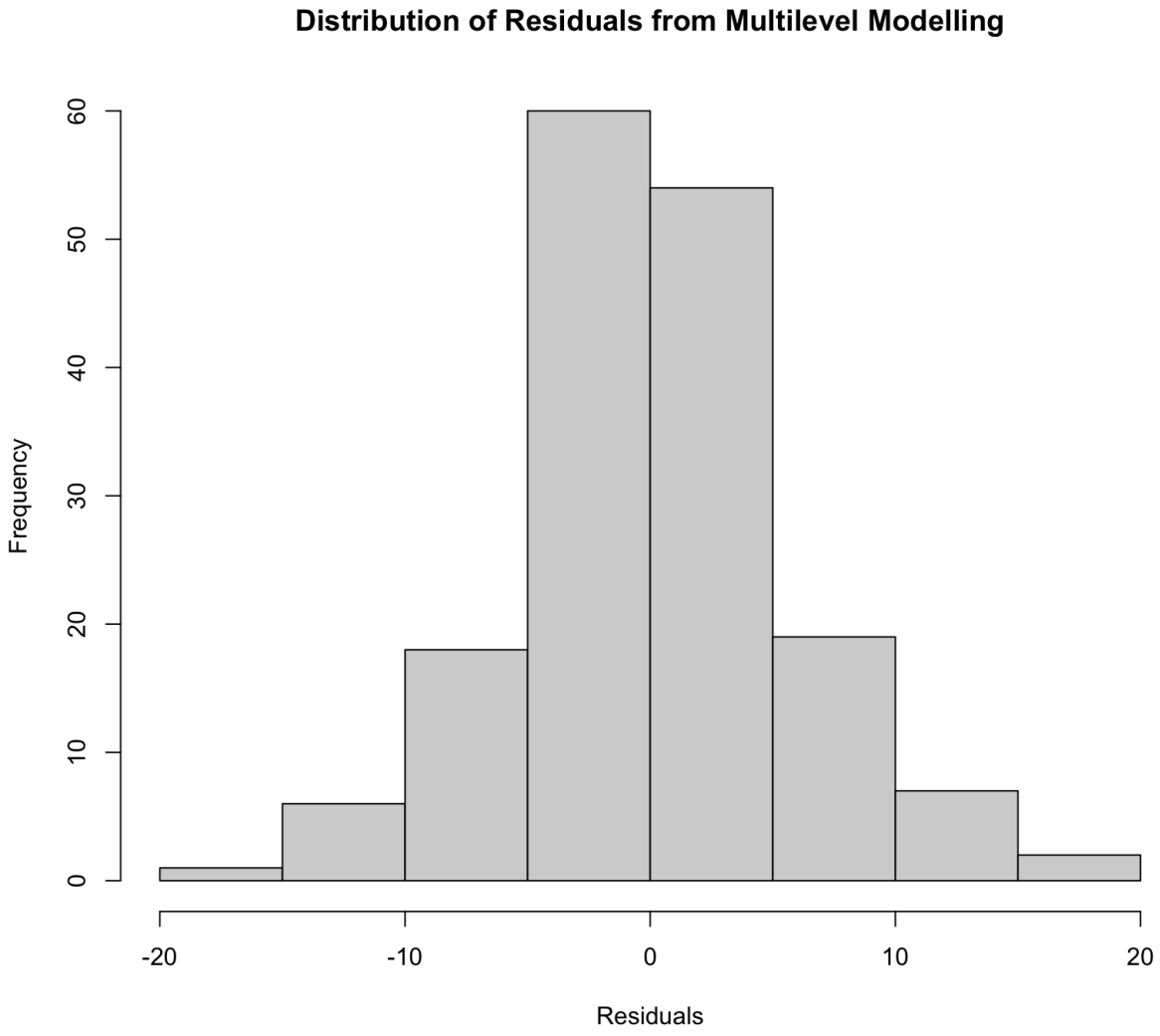


Table 3.6 Comparison of Multilevel Models

Model 1 SCAARED anxiety = Random intercept (baseline)
Model 2 SCAARED anxiety = Childhood adversity + time Random intercept
Model 3 SCAARED anxiety = Childhood adversity + time Random intercept Random slope
Model 4 SCAARED anxiety = Childhood adversity + time +sex Random intercept

Model	Parameters	AIC	BIC	Log likelihood	Deviance	Chisq	df	P
1	3	1212.5	1221.9	-603.3	1206.5			
2	5	1203.3	1218.9	-596.6	1193.3	13.24	2	0.001
3	7	1204.7	1226.5	-595.3	1190.7	2.60	2	0.272
4	6	1205.1	1223.9	-596.6	1193.1	0.14	1	0.71

Notes. Parameters = number of parameters in model, AIC = Akaike information criterion, BIC=Bayesian information criterion, df = degrees of freedom, P = p value. Results are for Model 2 compared to Model 1, Model 3 compared to Model 2 and Model 3 compared to Model 2. Chisq is the test statistic for these model comparison on which the p value is based and is the change in deviance between the models being compared.

Table 3.7 Results of Multilevel Modelling of Effect of Childhood Adversity Score and Time on SCAARED Anxiety Score

Random component	Variance	Std. Deviation
Intercept	196.46	14.12
Residual	40.43	6.36

Fixed components	Estimate	Std Deviation	Std. Error	df	t-value	p-value
Intercept	39.12		3.81	35.59	10.26	<0.0001
Childhood adversity	-0.56	-0.02	3.52	34.15	-0.16	0.87
Time	-0.76	-0.15	0.20	139.6	-3.74	0.0003

Notes. Std. Deviation = standard deviation, df=degrees of freedom

CHAPTER 4 DISCUSSION

Comorbidity is not the exception but the rule with anxiety and mood disorders (Kaufman & Charney, 2000). The comorbidity of major depressive and anxiety disorders, as well as bipolar and anxiety disorders, is associated with worse psychiatric outcomes, including treatment resistance, premature termination of treatment, increased risk of suicide, and a greater chance for recurrence of symptoms (Kaiser et al., 2021; Ott, 2018). In our study, the severity of depression over the past six months was found to have a highly significant relationship with the severity of anxiety in the same time period. This was found both through a simple correlation of the effect of average mood score and average anxiety score and in a multiple regression with childhood adversity score and sex as covariates. This finding is in line with literature that shows a strong concurrent and longitudinal correlation between the course of depression and anxiety among those with mood disorders (Mantere et al., 2010).

Experiencing adversity in childhood has been found to be associated with an increased risk of psychopathology, including depressive and anxiety disorders (Hayward et al., 2020). Although childhood adversity has been found to be strongly associated with the comorbidity between mood and anxiety disorders in adulthood (Hovens et al., 2012), we did not find this relationship in our sample of participants with mood disorders. Our finding is not in line with the current literature that shows an increase in anxiety for those with mood disorders who have also experienced childhood adversity (Agnew-Blais & Danese, 2016; Bernet & Stein, 1999).
We also expected to find a relationship between childhood adversity and the number of anxiety disorders of each participant, with those who experienced more childhood adversity having more anxiety disorders; however, no such relationship was found.

As a final analysis, we examined the SCAARED anxiety data collected from the initial assessment as well as the monthly follow-ups and their relationship with childhood adversity. We expected that participants with higher childhood adversity scores would have on average higher SCAARED anxiety scores than those with lower childhood adversity scores, because childhood adversity has been found to be associated with an increase in adult anxiety, particularly among those with mood disorders, and this impact would persist over time (Bernet & Stein, 1999; Hayward et al., 2020: Kuuire, 2019). We found that there was no significant effect of childhood adversity on the SCAARED scores of participants when measured over time.

There are three possible reasons why in our sample of participants with mood disorders, childhood adversity was not found to be associated with anxiety disorders. The first is that among our small sample, childhood adversity scores (CECA scores) were quite low, indicating that many of our participants reported that they experienced little to no childhood adversity. This may be because people with childhood adversity are less likely to trust others (Gobin & Freyd, 2014), possibly including health care professionals and researchers and hence may be less likely to volunteer for research. It is also possible that our participants were less willing to disclose information during an interview and that they may have been more comfortable revealing childhood adversity or maltreatment through a questionnaire. The second reason that we may not have found a strong association between childhood adversity and average LIFE anxiety score and number of anxiety disorders might be that most of our participants reported very few major mood episodes during the study, and most participants scored low on the anxiety measures. Our participants were likely not experiencing major mood episodes or major anxiety symptoms based on their average anxiety and average depression scores since all participants were receiving treatment for their mental illnesses. The third possibility as to why we did not find an effect of

childhood adversity on anxiety severity among people with mood disorders is because we examined average anxiety severity. Average anxiety severity was defined as the severity of the participant's anxiety symptoms instead of an anxiety disorder. It is possible that average anxiety severity is different from anxiety disorders and that childhood adversity is not as predictive of average anxiety severity among people with mood disorders. To our knowledge, no research has examined how childhood adversity affects average anxiety severity among people with mood disorders, so it is possible that there is, in fact, no relationship and that this is a novel finding. Finally, it is possible that our results are impacted by the method we used to measure childhood adversity. It has been demonstrated before that subjective evaluation of adversity is more closely associated with psychopathology than the actual objectively established adversity (Danese & Widom, 2020). Most of previous research on the relationship between childhood adversity and anxiety was conducted using questionnaires, which assess one's understanding of the experiences more than the interview measures do.

Our participants' scores on the SCAARED decreased throughout the duration of the study, indicating that anxiety decreased over time. CBT has been found to be effective in the treatment of anxiety disorders (Otte, 2011). Many of our participants were Mood Disorder Clinic patients and were receiving CBT treatment, and this may be why their anxiety on the SCAARED measure decreased over time. All our participants were also taking medication for their mental illnesses, which would also have an impact on their SCAARED anxiety score decreasing over time. Despite the effectiveness of treatments for anxiety disorders, this is still an interesting finding since childhood adversity has been shown to lead to more unfavorable treatment outcomes among those with mood and anxiety disorders (Nelson et al., 2017). It is also possible that those who experienced childhood adversity may be less likely to access mental health

services, but when they do, they may potentially respond to treatment as well as those who have not experienced childhood adversity, especially when treated in a specialist setting.

We found mood and anxiety disorders to be highly related in this sample, with symptom severity often fluctuating together. This finding is in line with current literature, which shows that high levels of depression are associated with high levels of concurrent anxiety, both persisting over time (Mantere et al., 2010). Another possible reason why we found such a strong relationship between mood and anxiety is because both our measures of average mood score as well as average anxiety score came from the LIFE interview, and both were reported retrospectively and at the same time, possibly leading to general reporting of distress rather than mood or anxiety specifically.

Clinical Implications

Despite the fact that we found no relationship between childhood adversity and anxiety in people with mood disorders, a history of childhood adversity should still be assessed. A possible reason why we found no effect of childhood adversity on anxiety disorders among our sample of individuals with mood disorders is that people may be reluctant to disclose this information until they know their clinician well. Clinicians should be prepared to reassess for childhood adversity. It is important that we continue to assess anxiety due to its impact on the outcomes of mood disorders. Comorbid anxiety disorders among people with mood disorders complicate the diagnosis and can cause treatment to be more challenging thus impacting clinical outcomes (Coplan, 2015).

Small Sample Size and Low Power

Sample size is an important determinant of statistical power (the probability of detecting a true effect). Increasing sample size generally increases statistical power, as larger sample size

provides more information and reduces the likelihood of sampling error. Another important factor determining the power of a test is the effect size of the factor being examined, with large effects being easier to detect (Sokal and Rohlf, 2012 The statistical power of our analyses was low as a result of the small sample size and the small estimated effect size of childhood adversity on the average anxiety score. A sample of 1700 participants would be needed to have a statistical power of 0.80 at this effect size. With a sample size of 33 the effect would need to be 50 times greater to achieve a statistical power of 0.8. If the effect of childhood adversity on average anxiety score is as small as measured here, it is difficult to know how much real-world significance this would have. Some possible reasons for an apparently low effect of childhood adversity on the average anxiety score among our participants are discussed below.

Prospective versus Retrospective Measures of Childhood Maltreatment

A systematic review conducted by Baldwin et al. in 2019 found there to be a poor agreement between prospective and retrospective measures of childhood maltreatment. They found that 52% of individuals with prospective observations of childhood maltreatment did not retrospectively report it (Baldwin et al., 2019). Fifty-six percent of individuals retrospectively reporting childhood maltreatment did not have concordant prospective observations (Baldwin et al., 2019). Findings from various studies indicate that prospective and retrospective reports of childhood maltreatment capture largely non-overlapping groups of individuals (Baldwin et al., 2019; Newbury et al., 2018). However, despite this, it would still have been expected that this study would have found a relationship between childhood maltreatment and anxiety among those with mood disorders. Those who retrospectively self report childhood maltreatment are at an elevated risk for psychopathology (Baldwin et al., 2019).

Dichotomization of the CECA Scores

It is possible that through the dichotomization of the CECA score we may have lost some of the sensitivity of the measure. While deciding to code scores of one as zero is in line with other research in the field (Bifulco et al., 1994; Brown et al., 2007), creating a category of little to no abuse does mean that scores of one indicating that a participant experienced little abuse were grouped with those who had experienced no abuse. Perhaps, if we had chosen not to dichotomize the scores we may have found more of an effect as many of our participants fell into the category of one (little abuse). However, in a study conducted by Brown et al. in 2007, the authors dichotomized CECA scores in the same way as in this study and found the CECA scores to be predictive of chronic depression. It is possible that CECA scores do not predict anxiety. It is also possible that our measure of anxiety was perhaps not measuring a long enough period of time or not sensitive enough.

Strengths

The LIFE interview provides a detailed look at a relatively long period of time (every week of a six-month period), which allowed us to collect rich data on our participants' mood and anxiety over the preceding six months. We also collected prospective data on anxiety severity using the SCAARED. We had an entirely clinical population which allowed us to examine the effects of childhood adversity on a population with mood disorders severe enough to warrant treatment in an under-resourced health system.

Prospective longitudinal studies complement retrospective surveys by providing unique information about lifetime prevalence (Moffitt et al., 2009). Retrospective studies have found that early adversity is associated with a greater prevalence of anxiety disorders and mood disorders in adulthood (Green et al., 2010; Lähdepuro et al., 2019). Using both prospective and retrospective reports allowed us to account for cumulative comorbidity. Cumulative comorbidity

refers to disorders occurring during a lifetime but not necessarily simultaneously (Moffitt et al., 2007); this can lead to an underestimate of the extent to which individuals experience the disorders (Moffitt et al., 2007). Using both prospective and retrospective measures of anxiety is a strength of this study.

Limitations

Our research was limited by our relatively small sample size of 33 participants partially due to the study being conducted during the Covid-19 pandemic, which made recruitment more difficult.

Our small sample size meant we were unable to evaluate the impact of childhood adversity on individual anxiety disorders. We were also unable to tease apart the impact of various forms of childhood maltreatment on comorbid anxiety disorders to determine whether different forms of childhood maltreatment differ in their effects on comorbid anxiety disorders in people with mood disorders.

Due to adversity being assessed retrospectively, it is possible that our accounts of childhood adversity were influenced by mood-dependent memory (Lewis & Critchley, 2003). It is also possible that people's memories may have been altered by the passing of time as they were trying to recall experiences from their childhood (Öztaş Ayhan & Işiksal, 2005). Recalling mood and anxiety symptoms over the past six months as is done in the LIFE interview could also be a limitation as people often make recall errors (Öztaş Ayhan & Işiksal, 2005), and their recall could also be heavily influenced by their mood-dependent memory (Lewis & Critchley, 2003). Another limitation of our study was the lack of diversity in our sample; our sample was 91% Caucasian.

The majority of the participants (20) were recruited from a specialized clinic setting which likely affects the generalizability of the results (Layde et al., 1996).

We also did not control for some factors that could have influenced our results, such as the socio-economic status of our participants, which has been shown to contribute to poorer mental health (Shao et al., 2019), which we did not account for in our study. We also did not control for the type of mood disorder that participants experienced; it is possible that the relationship between childhood adversity and anxiety disorders may differ in people with major depressive disorder and people with bipolar disorder.

Future Research

Future research should focus on collecting data from a larger and more diverse sample of participants, including people with untreated mood disorders. This would enable us to look separately at the impact of various types of childhood adversity on different anxiety disorders, taking into account the type of mood disorder as well. Ideally, this sample should be followed for several years to capture the relationship between mood and anxiety in the long run. Additionally, administering a questionnaire as well as an interview assessment of childhood adversity may help us disentangle the impact of the method on the findings. It would be beneficial to use the Childhood Trauma Questionnaire (CTQ) in the future in order to determine whether our low rates of reported childhood trauma were due to our assessment method. The CTQ provides a reliable, brief, and valid assessment of traumatic experiences in childhood (Bernstein et al., 1994).

Summary

In this study, we found a strong relationship between the average mood score and the average anxiety score over the six months preceding our initial interview with participants. This

is in line with current literature that supports levels of depression being associated with levels of anxiety and them changing together over time (Mantere et al., 2010). We did not find an effect of childhood adversity on average mood score, average anxiety score, the number of anxiety disorders, or the prospectively collected SCAARED anxiety score. This may be due to the methodological limitations of our study, as well as due to the low amounts of childhood adversity in our sample. A larger sample of people is needed before making firm conclusions about the relationship between childhood adversity in anxiety in people with mood disorders.

CHILDHOOD EXPERIENCE OF CARE AND ABUSE (CECA)
MINI CECA VIGNETTE FORM

Date of visit: / / **Subject ID:**
Day Month Year

1. Background

2. Parental Discord

3. Psychological Abuse

4. Physical Abuse

5. Sexual Abuse

References

Agnew-Blais, J., & Danese, A. (2016). Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry*, *3*(4), 342–349. https://doi.org/10.1016/s2215-0366(15)00544-1

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental disorders* (5th ed.). American Psychiatric Association.

Angst, J., Gamma, A., Rössler, W., Ajdacic, V., & Klein, D. N. (2010). Childhood adversity and chronicity of mood disorders. *European Archives of Psychiatry and Clinical Neuroscience*, *261*(1), 21–27. https://doi.org/10.1007/s00406-010-0120-3

Angulo, M., Rooks, B. T., Gill, M., Goldstein, T., Sakolsky, D., Goldstein, B., Monk, K., Hickey, M. B., Diler, R. S., Hafeman, D., Merranko, J., Axelson, D., & Birmaher, B. (2017). Psychometrics of the screen for adult anxiety related disorders (SCAARED)- A new scale for the assessment of DSM-5 anxiety disorders. *Psychiatry Research*, *253*, 84–90. https://doi.org/10.1016/j.psychres.2017.02.034

Anxiety and Depression Association of America. (2021). *Facts & Statistics | Anxiety and Depression Association of America, ADAA*. Adaa.org. https://adaa.org/understanding-anxiety/facts-statistics

Baldwin, J. R., Reuben, A., Newbury, J. B., & Danese, A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment. *JAMA Psychiatry*, *76*(6), 584. https://doi.org/10.1001/jamapsychiatry.2019.0097

Bandelow, B., & Michaelis, S. (2015). Epidemiology of anxiety disorders in the 21st century. *Anxiety*, *17*(3), 327–335. https://doi.org/10.31887/dcns.2015.17.3/bbandelow

Bekker, M. H. J., & van Mens-Verhulst, J. (2007). Anxiety disorders: sex differences in prevalence, degree, and background, but gender-neutral treatment. *Gender Medicine*, *4*, S178–S193. https://doi.org/10.1016/s1550-8579(07)80057-x

Belzer, K., & Schneier, F. R. (2004). Comorbidity of Anxiety and Depressive Disorders: Issues in Conceptualization, Assessment, and Treatment. *Journal of Psychiatric Practice*, *10*(5), 296–306. https://doi.org/10.1097/00131746-200409000-00003

Ben David, V. (2021). Associations between parental mental health and child maltreatment: the importance of family characteristics. *Social Sciences*, *10*(6), 190. https://doi.org/10.3390/socsci10060190

Bernet, C. Z., & Stein, M. B. (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depression and Anxiety*, *9*(4), 169–174. https://doi.org/10.1002/(sici)1520-6394(1999)9:4%3C169::aid-da4%3E3.0.co;2-2

Bernstein, D. P., Handelsman, L., & Foote, J. (1994). *Childhood Trauma Questionnaire*. Psycnet.apa.org. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft02080-000

Bifulco, A., Brown, G. W., & Harris, T. O. (1994). Childhood experience of care and abuse (CECA): A Retrospective Interview Measure. *Journal of Child Psychology and Psychiatry*, *35*(8), 1419–1435. https://doi.org/10.1111/j.1469-7610.1994.tb01284.x

Brown, G. W., Craig, T. K. J., Harris, T. O., Handley, R. V., & Harvey, A. L. (2007). Development of a retrospective interview measure of parental maltreatment using the childhood experience of care and abuse (CECA) instrument — A life-course study of adult chronic depression — 1. *Journal of Affective Disorders*, *103*(1-3), 205–215. https://doi.org/10.1016/j.jad.2007.05.022

Bryant, R. A., Moot, W., Maree Inder, Crowe, M., Douglas, K. M., Carter, J. D., & Frampton, C. (2022). Validation of the longitudinal interval follow-up evaluation for the long-term measurement of mood symptoms in bipolar disorder. *Brain Sciences*, *12*(12), 1717–1717. https://doi.org/10.3390/brainsci12121717

Byrne, A., & Kangas, M. (2022). Emotion regulation and memory in response to a trauma analogue: An online experimental comparison of humor and acceptance. *Journal of Contextual Behavioral Science*, *24*(1), 23–30. https://doi.org/10.1016/j.jcbs.2022.03.002

Carbone, E. A., Pugliese, V., Bruni, A., Aloi, M., Calabrò, G., Jaén-Moreno, M. J., Segura-Garcia, C., & De Fazio, P. (2019). Adverse childhood experiences and clinical severity in bipolar disorder and schizophrenia: A transdiagnostic two-step cluster analysis. *Journal of Affective Disorders*, *259*, 104–111. https://doi.org/10.1016/j.jad.2019.08.049

Cardoso, G., Xavier, M., Vilagut, G., Petukhova, M., Alonso, J., Kessler, R. C., & Caldas-de-Almeida, J. M. (2017). Days out of role due to common physical and mental conditions in Portugal: Results from the WHO world mental health survey. *BJPsych Open*, *3*(1), 15–21. https://doi.org/10.1192/bjpo.bp.115.002402

Carpenter, J. K., Andrews, L. A., Witcraft, S. M., Powers, M. B., Smits, J. A. J., & Hofmann, S. G. (2018). Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of Randomized placebo-controlled Trials. *Depression and Anxiety*, *35*(6), 502–514. https://doi.org/10.1002/da.22728

Cerdá, M., Sagdeo, A., Johnson, J., & Galea, S. (2010). Genetic and environmental influences on psychiatric comorbidity: A systematic review. *Journal of Affective Disorders*, *126*(1-2), 14–38. https://doi.org/10.1016/j.jad.2009.11.006

Çevik, B., Mançe-Çalışır, Ö., Atbaşoğlu, E. C., Saka, M. C., Alptekin, K., Üçok, A., Sırmatel, B., Gülöksüz, S., Tükün, A., van Os, J., & Gümüş-Akay, G. (2019). Psychometric liability to psychosis and childhood adversities are associated with shorter telomere length: A study on schizophrenia patients, unaffected siblings, and non-clinical controls. *Journal of Psychiatric Research*, *111*, 169–185. https://doi.org/10.1016/j.jpsychires.2019.01.022

Chakrabarty, T., Harkness, K. L., McInerney, S. J., Quilty, L. C., Milev, R. V., Kennedy, S. H., Frey, B. N., MacQueen, G. M., Müller, D. J., Rotzinger, S., Uher, R., & Lam, R. W. (2020). Childhood maltreatment and cognitive functioning in patients with major depressive disorder: a CAN-BIND-1 report. *Psychological Medicine*, *50*(15), 2536–2547. https://doi.org/10.1017/S003329171900268X

Coplan, J. D. (2015). Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches. *World Journal of Psychiatry*, *5*(4), 366. https://doi.org/10.5498/wjp.v5.i4.366

Costello, E. Jane., Pine, D. S., Hammen, C., March, J. S., Plotsky, P. M., Weissman, M. M., Biederman, J., Goldsmith, H. Hill., Kaufman, J., Lewinsohn, P. M., Hellander, M., Hoagwood, K., Koretz, D. S., Nelson, C. A., & Leckman, J. F. (2002). Development and natural history of mood disorders. *Biological Psychiatry*, *52*(6), 529–542. https://doi.org/10.1016/s0006-3223(02)01372-0

Danese, A., & Widom, C. S. (2020). Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nature Human Behaviour*, *4*(8), 811–818. https://doi.org/10.1038/s41562-020-0880-3

Davidson, J. R. T. (2010). Major depressive disorder treatment guidelines in America and Europe. *The Journal of Clinical Psychiatry*, *71*(suppl E1). https://doi.org/10.4088/jcp.9058se1c.04gry

DeRubeis, R. J., & Strunk, D. R. (2017). The Oxford Handbook of Mood Disorders. In *Google Books*. Oxford University Press. https://books.google.ca/books?hl=en&lr=&id=Ukq1DgAAQBAJ&oi=fnd&pg=PA313&dq=why+are+anxiety+and+mood+disorders+so+often+comorbid&ots=F7oOoohrR8&sig=WqlcmNLwYr8ny3jZnru4pjNM0Ug&redir_esc=y#v=onepage&q=why%20are%20anxiety%20and%20mood%20disorders%20so%20often%20comorbid&f=false

De Venter, M., Van Den Eede, F., Pattyn, T., Wouters, K., Veltman, D. J., Penninx, B. W. J. H., & Sabbe, B. G. (2017). Impact of childhood trauma on course of panic disorder: contribution of clinical and personality characteristics. *Acta Psychiatrica Scandinavica*, *135*(6), 554–563. https://doi.org/10.1111/acps.12726

Dvir, Y., Ford, J. D., Hill, M., & Frazier, J. A. (2014). Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. *Harvard Review of Psychiatry*, *22*(3), 149–161. https://doi.org/10.1097/hrp.0000000000000014

Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. *American Journal of Psychiatry*, *160*(8), 1453–1460. https://doi.org/10.1176/appi.ajp.160.8.1453

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/brm.41.4.1149

Fava, M., Rankin, M. A., Wright, E. C., Alpert, J. E., Nierenberg, A. A., Pava, J., & Rosenbaum, J. F. (2000). Anxiety disorders in major depression. *Comprehensive Psychiatry*, *41*(2), 97–102. https://doi.org/10.1016/s0010-440x(00)90140-8

First, M. B. (2015). Structured Clinical Interview for theDSM(SCID). *The Encyclopedia of Clinical Psychology*, 1–6. https://doi.org/10.1002/9781118625392.wbecp351

Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. *The Lancet*, *381*(9878), 1672–1682. https://doi.org/10.1016/s0140-6736(13)60857-0

Gobin, R. L., & Freyd, J. J. (2014). The impact of betrayal trauma on the tendency to trust. *Psychological Trauma: Theory, Research, Practice, and Policy*, *6*(5), 505–511. https://doi.org/10.1037/a0032452

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I. *Archives of General Psychiatry*, *67*(2), 113. https://doi.org/10.1001/archgenpsychiatry.2009.186

Gross, J. J. (2015). Emotion regulation: current status and future prospects. *Psychological Inquiry*, *26*(1), 1–26.

Haroz, E. E., Ritchey, M., Bass, J. K., Kohrt, B. A., Augustinavicius, J., Michalopoulos, L., Burkey, M. D., & Bolton, P. (2017). How is depression experienced around the world? A systematic review of qualitative literature. *Social Science & Medicine*, *183*, 151–162. https://doi.org/10.1016/j.socscimed.2016.12.030

Hayward, L. E., Vartanian, L. R., Kwok, C., & Newby, J. M. (2020). How might childhood adversity predict adult psychological distress? Applying the identity disruption model to

understanding depression and anxiety disorders. *Journal of Affective Disorders*, *265*, 112–119. https://doi.org/10.1016/j.jad.2020.01.036

Hirschfeld, R. M. A. (2001). The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(6), 244–254. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181193/#:~:text=The%20presence%20of%20depressive%2Fanxiety%20comorbidity%20substantially%20increases%20medical

Hovenkamp-Hermelink, A. (2020). *The long-term course of anxiety disorders: An epidemiological perspective*. https://doi.org/10.33612/diss.147431929

Hovens, J. G. F. M., Giltay, E. J., Wiersma, J. E., Spinhoven, P., Penninx, B. W. J. H., & Zitman, F. G. (2012). Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatrica Scandinavica*, *126*(3), 198–207. https://doi.org/10.1111/j.1600-0447.2011.01828.x

Jaworska-Andryszewska, P., & Rybakowski, J. K. (2018). Childhood trauma in mood disorders: neurobiological mechanisms and implications for treatment. *Pharmacological Reports*, *116*. https://doi.org/10.1016/j.pharep.2018.10.004

Judd, L. L. (1995). Mood disorders in the general population represent an important and worldwide public health problem. *International Clinical Psychopharmacology*, *10*(Supplement 4), 5–10. https://doi.org/10.1097/00004850-199512004-00002

Judd, L. L., Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., Paulus, M. P., Kunovac, J. L., Leon, A. C., Mueller, T. I., Rice, J. A., & Keller, M. B. (1998). A prospective 12-year study of subsyndromal and syndromal depressive symptoms in

unipolar major depressive disorders. *Archives of General Psychiatry*, *55*(8), 694. https://doi.org/10.1001/archpsyc.55.8.694

Kaiser, T., Herzog, P., Voderholzer, U., & Brakemeier, E. (2021). Unraveling the comorbidity of depression and anxiety in a large inpatient sample: Network analysis to examine bridge symptoms. *Depression and Anxiety*. https://doi.org/10.1002/da.23136

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., & Van Ameringen, M. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, *14*(Suppl 1), S1. https://doi.org/10.1186/1471-244x-14-s1-s1

Kaufman, J., & Charney, D. (2000). Comorbidity of mood and anxiety disorders. *Depression and Anxiety*, *12*(S1), 69–76. https://doi.org/10.1002/1520-6394(2000)12:1+%3C69::aid-da9%3E3.0.co;2-k

Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott PA. The longitudinal interval follow-up evaluation: A comprehensive method for assessing outcome in prospective longitudinal studies. *Archives of General Psychiatry.* 1987;44:540–548. doi:10.1001/archpsyc.1987.01800180050009.

Kendler, K. S. (1996). Major depression and generalised anxiety disorder. *British Journal of Psychiatry*, *168*(S30), 68–75. https://doi.org/10.1192/s0007125000298437

Kendler, K. S., Eaves, L. J., Loken, E. K., Pedersen, N. L., Middeldorp, C. M., Reynolds, C., Boomsma, D., Lichtenstein, P., Silberg, J., & Gardner, C. O. (2011). The Impact of environmental experiences on symptoms of anxiety and depression across the life span. *Psychological Science*, *22*(10), 1343–1352. https://doi.org/10.1177/0956797611417255

Kennedy, S. H., Milev, R., Giacobbe, P., Ramasubbu, R., Lam, R. W., Parikh, S. V., Patten, S. B., & Ravindran, A. V. (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. *Journal of Affective Disorders*, *117*, S44–S53. https://doi.org/10.1016/j.jad.2009.06.039

Kuuire, V. Z. (2019). Childhood adversity and psychosocial health outcomes in later life among Immigrants in Canada. *Journal of Immigrant and Minority Health*, *22*(2), 383–391. https://doi.org/10.1007/s10903-019-00884-8

Lähdepuro, A., Savolainen, K., Lahti-Pulkkinen, M., Eriksson, J. G., Lahti, J., Tuovinen, S., Kajantie, E., Pesonen, A.-K., Heinonen, K., & Räikkönen, K. (2019). The impact of early life stress on anxiety symptoms in late adulthood. *Scientific Reports*, *9*(1), 1–13. https://doi.org/10.1038/s41598-019-40698-0

LaNoue, M., Graeber, D., de Hernandez, B. U., Warner, T. D., & Helitzer, D. L. (2010). Direct and indirect effects of childhood adversity on adult depression. *Community Mental Health Journal*, *48*(2), 187–192. https://doi.org/10.1007/s10597-010-9369-2

Layde, P. M., Broste, S. K., Desbiens, N., Follen, M., Lynn, J., Reding, D., & Vidaillet, H. (1996). Generalizability of clinical studies conducted at tertiary care medical centers: A population-based analysis. *Journal of Clinical Epidemiology*, *49*(8), 835–841. https://doi.org/10.1016/0895-4356(96)00006-6

Lewis, P. A., & Critchley, H. D. (2003). Mood-dependent memory. *Trends in Cognitive Sciences*, *7*(10), 431–433. https://doi.org/10.1016/j.tics.2003.08.005

Li, W., Lai, W., Guo, L., Wang, W., Li, X., Zhu, L., Shi, J., Teopiz, K. M., McIntyre, R. S., & Lu, C. (2023). Childhood maltreatment and subsequent depressive symptoms: a

prospective study of the sequential mediating role of self-esteem and internalizing/externalizing problems. *BMC Psychiatry*, *23*(1). https://doi.org/10.1186/s12888-023-04654-7

Lima Osório, F., Loureiro, S. R., Hallak, J. E. C., Machado-de-Sousa, J. P., Ushirohira, J. M., Baes, C. V. V., Apolinário, T. D., Donadon, M. F., Bolsoni, L., Guimarães, T., Fracon, V. S., Casagrande, A. P., Pizzeta, F., Mascarenhas, R., Sanches, R. F., Santos, R. G., Martin-Santos, R. L., & Crippa, J. A. S. (2019). Clinical validity and intrarater and test-retest reliability of the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV). *Psychiatry and Clinical Neurosciences*, *73*(12). https://doi.org/10.1111/pcn.12931

Mandelli, L., Serretti, A., Marino, E., Pirovano, A., Calati, R., & Colombo, C. (2006). Interaction between serotonin transporter gene, catechol-O-methyltransferase gene and stressful life events in mood disorders. *The International Journal of Neuropsychopharmacology*, *10*(04), 437. https://doi.org/10.1017/s1461145706006882

Mantere, O., Isometsä, E., Ketokivi, M., Kiviruusu, O., Suominen, K., Valtonen, H. M., Arvilommi, P., & Leppämäki, S. (2010). A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. *Bipolar Disorders*, *12*(3), 271–284. https://doi.org/10.1111/j.1399-5618.2010.00810.x

Marangoni, C., Hernandez, M., & Faedda, G. L. (2016). The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. *Journal of Affective Disorders*, *193*(1), 165–174. https://doi.org/10.1016/j.jad.2015.12.055

Martin-Key, N. A., Olmert, T., Barton-Owen, G., Han, S. Y. S., Cooper, J. D., Eljasz, P., Farrag, L. P., Friend, L. V., Bell, E., Cowell, D., Tomasik, J., & Bahn, S. (2021). The Delta

Study – Prevalence and characteristics of mood disorders in 924 individuals with low mood: Results of the of the World Health Organization Composite International Diagnostic Interview (CIDI). *Brain and Behavior*, *11*(6). https://doi.org/10.1002/brb3.2167

McIntyre, R. S., Berk, M., Brietzke, E., Goldstein, B. I., López-Jaramillo, C., Kessing, L. V., Malhi, G. S., Nierenberg, A. A., Rosenblat, J. D., Majeed, A., Vieta, E., Vinberg, M., Young, A. H., & Mansur, R. B. (2020). Bipolar disorders. *The Lancet*, *396*(10265), 1841–1856. https://doi.org/10.1016/s0140-6736(20)31544-0

McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P., Healy, C., O'Donnell, L., & Clarke, M. C. (2021). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatrica Scandinavica*, *143*(3), 189–205. https://doi.org/10.1111/acps.13268

Meier, S. M., & Deckert, J. (2019). Genetics of Anxiety Disorders. *Current Psychiatry Reports*, *21*(3). https://doi.org/10.1007/s11920-019-1002-7

Miklowitz, D. J., & Johnson, S. L. (2006). The psychopathology and treatment of bipolar disorder. *Annual Review of Clinical Psychology*, *2*(1), 199–235. https://doi.org/10.1146/annurev.clinpsy.2.022305.095332

Moffitt, T. E., Caspi, A., Taylor, A., Kokaua, J., Milne, B. J., Polanczyk, G., & Poulton, R. (2009). How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychological Medicine*, *40*(6), 899–909. https://doi.org/10.1017/s0033291709991036

Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., & Poulton, R. (2007). Depression and generalized anxiety disorder. *Archives of General Psychiatry*, *64*(6), 651. https://doi.org/10.1001/archpsyc.64.6.651

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A Meta-Analysis. *American Journal of Psychiatry*, *169*(2), 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335

Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders. *American Journal of Human Genetics*, *57*(4), 935–953. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1801512/

Nelson, J., Klumparendt, A., Doebler, P., & Ehring, T. (2017). Childhood maltreatment and characteristics of adult depression: Meta-analysis. *British Journal of Psychiatry*, *210*(2), 96–104. https://doi.org/10.1192/bjp.bp.115.180752

Newbury, J. B., Arseneault, L., Moffitt, T. E., Caspi, A., Danese, A., Baldwin, J. R., & Fisher, H. L. (2018). Measuring childhood maltreatment to predict early-adult psychopathology: Comparison of prospective informant-reports and retrospective self-reports. *Journal of Psychiatric Research*, *96*(1), 57–64. https://doi.org/10.1016/j.jpsychires.2017.09.020

NICE. (2009). *Recommendations | Depression in adults: recognition and management | Guidance | NICE*. Www.nice.org.uk. https://www.nice.org.uk/guidance/cg90/chapter/Recommendations#care-of-all-people-with-depression

NICE. (2021). *NATIONAL INSTITUTE FOR HEALTH AND CARE 1*. https://www.nice.org.uk/guidance/gid-cgwave0725/documents/draft-guideline-4

Olatunji, B. O., & Wolitzky-Taylor, K. B. (2009). *Anxiety sensitivity and the anxiety disorders: A meta-analytic review and synthesis.* Psycnet.apa.org. https://psycnet.apa.org/record/2009-19763-008

Ott, C. A. (2018). Treatment of anxiety disorders in patients with comorbid bipolar disorder. *Mental Health Clinician*, *8*(6), 256–263. https://doi.org/10.9740/mhc.2018.11.256

Otte, C. (2011). Cognitive behavioral therapy in anxiety disorders: current state of the evidence. *Anxiety*, *13*(4), 413–421. https://doi.org/10.31887/dcns.2011.13.4/cotte

Öztaş Ayhan, H., & Işiksal, S. (2005). Memory recall errors in retrospective surveys: A reverse record check study. *Quality & Quantity*, *38*(5), 475–493. https://doi.org/10.1007/s11135-005-2643-7

Palmier-Claus, J. E., Berry, K., Bucci, S., Mansell, W., & Varese, F. (2016). Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. *British Journal of Psychiatry*, *209*(06), 454–459. https://doi.org/10.1192/bjp.bp.115.179655

Parikh, S. V., Quilty, L. C., Ravitz, P., Rosenbluth, M., Pavlova, B., Grigoriadis, S., Velyvis, V., Kennedy, S. H., Lam, R. W., MacQueen, G. M., Milev, R. V., Ravindran, A. V., & Uher, R. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical guidelines for the management of adults with major depressive disorder. *The Canadian Journal of Psychiatry*, *61*(9), 524–539. https://doi.org/10.1177/0706743716659418

Patten, S. B. (2016). Updated CANMAT guidelines for treatment of major depressive disorder. *The Canadian Journal of Psychiatry*, *61*(9), 504–505. https://doi.org/10.1177/0706743716660034

Pavlova, B., Perlis, R. H., Alda, M., & Uher, R. (2015). Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry*, *2*(8), 710–717. https://doi.org/10.1016/s2215-0366(15)00112-1

Pavlova, B., Perroud, N., Cordera, P., Uher, R., Alda, M., Dayer, A., & Aubry, J.-M. (2018). Anxiety disorders and childhood maltreatment as predictors of outcome in bipolar disorder. *Journal of Affective Disorders*, *225*, 337–341. https://doi.org/10.1016/j.jad.2017.08.048

Pavlova, B., Perroud, N., Cordera, P., Uher, R., Dayer, A., & Aubry, J.-M. (2016). Childhood maltreatment and comorbid anxiety in people with bipolar disorder. *Journal of Affective Disorders*, *192*, 22–27. https://doi.org/10.1016/j.jad.2015.12.002

R Core Team. (2019). *R: The R Project for Statistical Computing*. R-Project.org. https://www.r-project.org/

Roy, M-A., Neale, M. C., Pedersen, N. L., Mathé, A. A., & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine*, *25*(5), 1037–1049. https://doi.org/10.1017/s0033291700037533

Saha, S., Lim, C. C. W., Cannon, D. L., Burton, L., Bremner, M., Cosgrove, P., Huo, Y., & McGrath, J. (2020). Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis. *Depression and Anxiety*, *38*(3), 286–306. https://doi.org/10.1002/da.23113

Shao, J., Dai, Z., Zhu, R., Wang, X., Tao, S., Bi, K., Tian, S., Wang, H., Sun, Y., Yao, Z., & Lu, Q. (2019). Early identification of bipolar from unipolar depression before manic episode: Evidence from dynamic rfMRI. *Bipolar Disorders*, *21*(8), 774–784. https://doi.org/10.1111/bdi.12819

Simon, G. E. (2003). Social and economic burden of mood disorders. *Biological Psychiatry*, *54*(3), 208–215. https://doi.org/10.1016/s0006-3223(03)00420-7

Sokal, R. R., & F James Rohlf. (2012). *Biometry : the principles and practice of statistics in biological research*. W.H. Freeman.

Taylor, S., Koch, W. J., & McNally, R. J. (1992). How does anxiety sensitivity vary across the anxiety disorders? *Journal of Anxiety Disorders*, *6*(3), 249–259. https://doi.org/10.1016/0887-6185(92)90037-8

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychological Medicine*, *45*(12), 2481–2498. https://doi.org/10.1017/s0033291715000574

Tyrer, P., & Baldwin, D. (2006). Generalised anxiety disorder. *The Lancet*, *368*(9553), 2156–2166. https://doi.org/10.1016/s0140-6736(06)69865-6

Warshaw, M. G., Dyck, I., Allsworth, J., Stout, R. L., & Keller, M. B. (2001). Maintaining reliability in a long-term psychiatric study: an ongoing inter-rater reliability monitoring program using the longitudinal interval follow-up evaluation. *Journal of Psychiatric Research*, *35*(5), 297–305. https://doi.org/10.1016/s0022-3956(01)00030-9

Warshaw, M. G., Keller, M. B., & Stout, R. L. (1994). Reliability and validity of the longitudinal interval follow-up evaluation for assessing outcome of anxiety disorders. *Journal of Psychiatric Research*, *28*(6), 531–545. https://doi.org/10.1016/0022-3956(94)90043-4

Yap, M. B. H., Pilkington, P. D., Ryan, S. M., & Jorm, A. F. (2014). Parental factors associated with depression and anxiety in young people: A systematic review and meta-analysis. *Journal of Affective Disorders*, *156*(1), 8–23. https://doi.org/10.1016/j.jad.2013.11.007

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Beaulieu, S., Alda, M., O'Donovan, C., MacQueen, G., McIntyre, R. S., Sharma, V., Ravindran, A., Young, L. T., Milev, R., Bond, D. J., Frey, B. N., Goldstein, B. I., Lafer, B., Birmaher, B., Ha, K., & Nolen, W. A. (2012). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disorders*, *15*(1), 1–44. https://doi.org/10.1111/bdi.12025

Yonkers, K. A., Bruce, S. E., Dyck, I. R., & Keller, M. B. (2003). Chronicity, relapse, and illness?course of panic disorder, social phobia, and generalized anxiety disorder: Findings in men and women from 8 years of follow-up. *Depression and Anxiety*, *17*(3), 173–179. https://doi.org/10.1002/da.10106

Young, E. A., Abelson, J. L., Curtis, G. C., & Nesse, R. M. (1997). Childhood adversity and vulnerability to mood and anxiety disorders. *Depression and Anxiety*, *5*(2), 66–72. https://doi.org/10.1002/(sici)1520-6394(1997)5:2%3C66::aid-da2%3E3.0.co;2-3