QUALITY OF LIFE, FUNCTIONAL OUTCOMES, AND DEPRESSION: 3 YEARS FOLLOWING THE ONSET OF BIPOLAR DISORDER

by

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Abstract

*Background:* Quality of Life (QoL) and functional outcomes appear to be markers of mental health but little is known about their trajectory in the early stages of Bipolar Disorder Type I (BD I). Early phase depression appears to have a significant influence on such outcomes. This study observed the trajectory of QoL and functional outcomes and examined if (a) number of prodromal depressive episodes (prior to the first episode of mania) (b) the total number of episodes of depression experienced by 3 years, and (c) severity of ongoing depressive symptomatology, impacted QoL and functioning, across the first 3 years following the first episode of mania in a cohort of individuals with BD I.

*Methods:* 40 individuals diagnosed with BD I and recovering from their first episode of mania were recruited from an overarching clinical program based in a hospital setting. Participants completed assessments for QoL (the Quality of Life Enjoyment and Satisfaction Questionnaire), functionality (the Multidimensional Scale of Independent Functioning), and depressive symptomatology (Hamilton Depression Rating Scale) annually from baseline to year 3. Any history of prodromal and recurrent depressive episodes was also recorded.

*Results:* QoL and functionality were observed to improve between baseline and year 1, and then stabilize up to year 3. OLS regression was utilized to assess the predictors of QoL and functional outcomes. Higher severity of depressive symptomatology at baseline and year 3 were found to be predictive of lower QoL at 3 years following the onset of illness. No depression variables were significantly related to QoL or functionality difference scores between year 3 and baseline.

*Conclusion:* This is the first longitudinal study to (a) examine the trajectory of QoL and functionality in the first 3 years of illness in a First Episode Mania (FEM) sample of individuals...
with BD I and (b) examine the relationship of multiple depression variables to QoL at year 3 as well as change in QoL and functionality from baseline to year 3. The findings support the need for treatment to focus on the management of depressive symptomology in the early stages of BD I, which in turn may enhance QoL.
Lay summary

This study examined wellbeing and everyday functioning in the early stages of Bipolar Disorder Type 1 (BD I). Wellbeing and functionality were assessed right after diagnosis and then annually for 3 years. Depressive episodes experienced before and since onset of BD I, as well as the severity of depressive symptoms each year since diagnosis were collected. Results showed that wellbeing and functionality improved initially and then stabilized in the 3 years following the onset of BD I. Depressive symptoms that were experienced immediately after the onset of BD I and at year 3 were related to lower wellbeing at year 3, but depression was not related to changes in wellbeing or functionality over time. Depression appears to have a long-term influence on wellbeing and needs to be treated more thoroughly. Mental health therapies may help individuals with BD I develop skills to manage depression and improve wellbeing.
Preface

This thesis uses data from the STOP_EM project, approved by the University of British Columbia’s Research Ethics Board (certificate: H04-70169). None of the text from this thesis was directly taken from any previously published or collaborative articles.

Chapter 3. The medical data for this study were collected by psychiatrists in the Mood Disorders Centre at the University of British Columbia, Point Grey campus. All other data were collected by the research team and myself in the Mood Disorders Centre at the University of British Columbia, Point Grey campus. I was responsible for collecting data on demographics, quality of life, functionality, recurrent mood episodes and symptomology among other elements of the research protocol.

I was primarily responsible for the identification and design of the research project for this thesis. All (other) chapters of this thesis were completed by me with guidance from my supervisor and committee members. All analysis of the data for this thesis was completed by me with guidance from my supervisor and committee members.
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Chapter 1: Introduction

The Problem

The World Health Organisation has noted the global impact of Bipolar Disorder (BD) to have the fifth highest burden of disease with respect to mental illness (Ferrari et al., 2016). BD is characterized by a combination of clinical depression and extremely elevated mood states known as mania (Bipolar Disorder Type 1; BD I) and/or (milder) hypomanic episodes (Bipolar Disorder Type 2; BD II). It can be a severe, recurrent and progressive mental health condition, associated with high morbidity (Mitchell, 2013). Symptomatic remission has been a prominent focus for therapeutic interventions and research (Yatham, Lecrubier, Fieve, Davis & Harris et al., 2004; Yatham et al., 2009). However, there is a growing recognition and interest in the importance of achieving well-being beyond symptomatic improvement in mental illness (Keyes, 2002). In particular, the positive psychology movement (Seligman & Csikszentmihalyi, 2000) asserts well-being may be crucial to achieving mental health.

Well-being has often been described as Quality of Life (QoL) in BD (Lent, 2004; Michalak, Torres, Bond, Lam & Yatham, 2013; Morton et al., 2017; Morton, Michalak & Murray, 2017; Murray & Michalak, 2012). QoL has been described as a more comprehensive and specific conceptualization of well-being that has been commonly used in medical contexts (Lent, 2004). Subjective QoL is defined as an individual’s perception of their position in life within the context of culture and value systems and how it relates to their goals, expectations, standards and concerns (World Health Organisation, 1998, as cited in Murray and Michalak, 2012; World Health Organisation, 2018). However, lower QoL has been found to persist even in cases where symptomatic improvement has been achieved with medical treatment of BD (Michalak, Yatham, Kolesar, & Lam, 2006). This implies that the current focus of clinical
treatment in BD seems to miss attending to the role of subjective QoL in attaining mental health. Murray et al. (2017) report a growing interest in subjective QoL as a recovery-oriented outcome for BD.

It has been suggested that subjective well-being may be crucial to functioning well in everyday life (Keyes, 2002). It is unclear how lowered QoL observed to persist beyond symptomatic remission in BD (Michalak et al. 2006) may be contributing to functionality. However, BD has been found to be related to impairments in everyday functioning beyond symptomatic relief (Aydemir, 2016; MacQueen, Young & Joffe, 2001; Kauer-Sant’Anna, Bond, Lam & Yatham, 2009; Shipee et al., 2016; Grande, Berk, Birmaher & Vieta, 2016). Individuals with BD have been found to experience functional difficulties in occupational, social, household, and cognitive domains, to name a few. Furthermore, high levels of disability have been seen in BD (Grande et al., 2016). An expanding breadth of research in functionality and QoL in BD continues to demonstrate that traditional symptomatic and syndromal markers of treatment success in BD appear to fall short of capturing the full extent of the illness and improvement within it (Aydemir, 2016; Martin et al., 2013).

The examination of QoL as well as functional outcomes has allowed for a deeper and more holistic approach to understanding the impact of BD on individuals (Deckersbach et al., 2016; Michalak et al., 2013; Rosa et al., 2010). Thus, QoL and functioning are being recognized as important markers for prognosis and treatment success (Morton et al., 2017; Murray & Michalak, 2012) and are being promoted as key target outcomes for recovery to mental health in BD (Deckersbach et al., 2016; Morton et al., 2017). Furthermore, it has been suggested that QoL and functioning may have a bidirectional relationship with the profile of BD (Morton et al., 2017; Murray & Michalak, 2012), meaning that improvements in both well-being and
functioning may, in turn, regulate symptoms of BD.

It has been proposed that illness progression in BD does not have to be the only outcome as it may potentially be reversed with treatment and support (Murray et al., 2017). Studies of the trajectory of illness have provided some support for this (Morton et al., 2017). In a longitudinal study, QoL was found to improve over a 5-year period for individuals living with different types of BD for varying lengths of time with guideline-driven treatment (Morton et al., 2017). Similar findings have been reported for the early stages of the illness (Michalak, et al., 2013; Oldis et al., 2016). QoL and functional outcomes have been seen to decline following the onset of the first criterion episode of BD I (i.e., first episode of mania; FEM), but then improve within 12-18 months following the first episode of mania (Michalak, 2013; Oldis et al., 2016). However, there is very little information on the trajectory of QoL beyond the first 18 months following the onset of BD. It has been hypothesised that, with illness progression and as individuals spend more days in mood episodes, hope can wane and, in turn, QoL can deteriorate (Michalak et al., 2013). Further research is needed to determine the trajectory of in BD to explore how it may change and what factors may be contributing to it.

As staging models in BD I would suggest, it is apparent that earlier intervention may impact the course of illness (Murray et al., 2017; Vieta, Reinare & Rosa et al., 2011) and hence QoL and functionality. This, in turn, warrants a closer look at factors influencing QoL and functionality following onset of BD I. However, there is a dearth of research examining possible determinants of QoL and functionality in the early stages of the illness. Identifying possible predictors of QoL and functionality in the early stages of BD I may be helpful in optimizing personal and functional well-being. Some negative predictors of QoL in BD I have been identified to be the duration of illness (Elghonemy, Omar, Essa, & Morsy, 2011; Gutiérrez-
Rojas, Gurpegui, Ayuso-Mateos, Gutiérrez-Ariza, Veguilla, & Jurado, 2008) and the presence of psychotic symptoms (Cotton et al., 2017; Elghonemy et al., 2011). Poor premorbid adjustment has also been noted to be a predictor of lower QoL in the early stages of illness (Oldis et al., 2016).

It has been suggested that all of the different mood states in BD I are predictive of lowered QoL (Vojta, Kinosian, Glick, Altshuler, & Bauer, 2001) and functionality (Harvey, 2011). In particular, depressive symptomology has consistently been reported to be a significant predictor of QoL in BD I (Amini & Sharifi, 2012; Cotrena, Damiani, Kochhann, Milman, & Paz, 2016; Michalak et al. 2013; Vojta et al., 2001; Zhang, Wisniewski, Bauer, Sachs, & Thase, 2006). Depression has also been shown to negatively impact everyday functioning (Harvey, 2011; Bowie et al., 2010; Chacko, Dayal Narayan & Prabhavathy, 2011). Furthermore, depressive symptoms, including those of low intensity, have also been found to be strong predictors of QoL (Dias, Brissos, Frey, & Kapczinski, 2008). Even the few studies examining the trajectory of illness, QoL, and functioning following the first episode of mania (Michalak et al. 2013; Oldis et al., 2016) have found the presence and severity of depressive symptoms to be associated with lower QoL.

A notable finding is that QoL and functional impairments have been reported to be sustained beyond symptomatic remission in BD I (Rosa et al., 2010; Thomas, Nisha, & Varghese, 2016). Individuals with BD I have reported experiencing greater functional impairments and lower levels of well-being in interpersonal and work domains when compared to individuals with recurrent depressive disorder (RDD), even during periods of remission from a mood episode in both RDD and BD (Chacko et al., 2011). Furthermore, Chacko et al. (2011) found a higher number of mood episodes and longer length of illness to lead to lower well-being
and functionality. There appears to be a possibility that depressive episodes could have some sustained impact beyond symptomatic remission, although Gutiérrez-Rojas et al. (2008) did not find a prolonged impact of remitted episodes of depression on QoL and functionality.

A higher number of depressive episodes have been found to be predictive of lower functional and QoL related outcomes during inter-episodic periods of euthymia (MacQueen et al., 2000; Özer, Uluşahin, Batur, Kabakçi & Saka, 2002; Pilar, Lorenzo & Luis, 2005). This, in turn, supports the notion that symptomatic remission may not equate to mental health. However, a more recent study of QoL during euthymic phases has found it to not be influenced by relapses of depressive episodes (Shabani et al., 2013). It is important to note that although Shabani et al. (2013) used different measures for their study variables, the evidence appears to be contradictory. Such evidence points toward a complex and inconsistent relationship between the potentially prolonged impact of depressive episodes on QoL and functionality. Given the importance of intervention in the earlier stages of the illness in BD I, it becomes crucial to consider the potential effects of depressive symptomology on QoL and functionality at this stage.

Research has shown the depressive polarity of the first mood episode to be correlated with a worse clinical prognosis (Perugi et al., 2000). In contrast to this, an examination of the depressive polarity of the first mood episode and its relationship with health-related QoL showed no association (Gutiérrez-Rojas et al., 2008). However, there is little information on how the polarity of the first episode may impact subjective QoL and functionality. To the best of my knowledge, there is only one study that has reported the number of previous depressive episodes at baseline to have a marked impact on QoL in the early stages of the illness (Michalak et al., 2013). Despite the lack of clarity over the longitudinal impact of prodromal depressive symptomology and recurrent depressive episodes, there appears to be sufficient evidence to
support further examination. Early phase depression, characterized by prodromal episodes, recurrent episodes and severity of ongoing symptomology, appears to influence QoL in the early stages of BD I. In particular, there is a need to explore the impact of prodromal depressive symptomology and recurrent depression in the early stages of BD I. Given that this is a time when individuals are learning to adapt to the illness and develop appropriate coping skills, understanding the predictors of QoL and functionality may assist in optimizing mental health.

The present study

Given the emerging importance of QoL and functionality as measures and target outcomes of achieving good mental health in BD I, observations of their trajectory from the onset of illness is important. Previous research has only examined QoL across the first 18 months following the onset of illness in FEM cohorts (Michalak et al. 2013; Oldis et al. 2016). Another longitudinal study has focused on examining medical, mental or physical components of QoL (Morton et al. 2017) in a mixed sample of BD participants. To my knowledge, this is the first study to observe the trajectory of subjective QoL and functionality using wellbeing and life satisfaction-centric measures in the 3 years following the onset of BD I. Furthermore, this study examined the impact of early phase depression – i.e., prodromal depressive symptomology, recurrent depressive episodes, and severity of ongoing depressive symptomology as potential predictors of QoL and functional outcomes in BD I in the first 3 years following the onset of BD I. Specifically, the potentially prolonged impact of the number of depressive episodes that occurred before the onset of BD I (i.e., before the first criterion episode of mania) on QoL and functionality was assessed as well as the impact of the number and severity of recurrent depressive episodes on longitudinal QoL and functional outcomes.
Chapter 2: Literature Review

Bipolar Disorder

Bipolar Disorder (BD), formerly known as manic-depressive illness has prominently been classified as a group of major affective/mood disorders (Phillips & Kupfer, 2013). BD is characterized by a combination of clinical depression and extremely elevated mood states known as mania and (milder) hypomanic episodes. The different combinations of these episodes define four types of bipolar disorder. The Diagnostic Statistical Manual of mental disorders fifth edition (DSM-V, American Psychiatric Association, 2013) notes these to be Bipolar disorder type I (BD I), Bipolar disorder type II (BD II), Bipolar Disorder Not Otherwise Specified (BD-NOS) and Cyclothymic disorder or Cyclothymia.

The DSM-V (American Psychiatric Association, 2013) classifies BD based on the presence of a range of symptoms as described next. BD I is characterized by episodes of depression and mania, whereas BD II is a combination of hypomania and depression. BD-NOS presents where the symptoms do not meet the criteria for BD I or BD II but there is a clear overlap of affective features that have impacted behaviour. Prolonged periods (of at least 2 years) of hypomania and depression that do not meet any of the other diagnostic categories are diagnosed as Cyclothymia. It is possible for both manic and depressive features to present together as a mixed episode.

A mood episode is defined by a significant deviation from an individual’s normal mood or behaviour that lasts for a sustained period. Symptoms of clinical depression are similar to those that mark bipolar depressive episodes. These include, but are not limited to; low mood, feelings of sadness and hopelessness that are present for a minimum of two weeks. A loss of interest in activities that were previously enjoyable, difficulties in concentrating, changes in
eating and/or sleeping habits, and suicidal ideation or planning can also define depressive symptomology.

Symptoms of mania can be considered to be on the ‘polar opposite’ end of the mood spectrum. Mania is marked by elevated mood, feelings of happiness, excitement, increased energy and extreme irritability lasting for several days. Other symptoms of mania can include restlessness, reduced sleep, increased goal-directed activity, increased sexual activity, risk-taking behaviour, racing thoughts and/or speech. Symptoms of psychosis such as delusions of grandiosity, or auditory or visual hallucinations can also be present in mania and often lead to hospitalization. Hypomania is characterized by similar symptoms of mania but with lower intensity and lasting for 4 or more days DSM-V (American Psychiatric Association, 2013). Hypomanic episodes typically have longer periods of depression in BD II. The Diagnostic Guidelines from the Task Force of the International Society for Bipolar Disorders (ISBD) note that bipolar illness has significant overlaps with other mental disorders (Ghaemi et al., 2008), such as psychotic, anxiety, and personality disorders (Culver, Arnow and Ketter, 2007).

BD has been noted to be one of the most prevalent and severe mental illnesses present today (Clemente et al., 2015; Perron et al., 2009). A recent meta-analysis of 25 community-based studies from 15 countries, which included 276,221 participants, showed the pooled lifetime prevalence is 1.06% for BD I and 1.57 % for BD II (Clemente et al., 2015). It is evident that the diagnosis of BD is not only consistent across cultures but can also have a significant impact across the life span. Being diagnosed with BD can have a significant effect on various life domains, including the self, family, peer, and romantic relationships with others (Inder et al., 2011).
The age of onset for BD has been seen to be typically between the ages of 15 and 24 years (Bellivier et al., 2011). Another research team pooled and analyzed data for 1566 patient-participants from six international sites and found the mean age for onset of BD to be between 23 and 28 years. Males and females have been found to have a similar age of onset in BD (Kawa et al., 2005). An in-depth literature review has found an equal prevalence of bipolar disorder in males and females (Diflorio & Jones, 2010). Individuals with BD have been reported to have similar levels of education (approximately 12.6 years) to that of the general population (Schoeyen et al., 2011).

BD can have profoundly negative effects on individuals, families, and society. BD has been reported to be associated with cognitive and functional impairment and is one of the leading causes of disability among youth and young adults (Grande et al., 2016). Given the young and economically active segment of society that BD affects, there is a high cost to society associated with the condition (Gardner et al., 2006). Furthermore, BD has been found to be associated with increased mortality, in particular, the risk of suicide has been reported to be 20-30 times higher in BD compared to the general population (Pompili, et al., 2013).

The prevailing classification of BD that is most commonly acknowledged in clinical and research settings is that of a chronic mood disorder. However, there appears to be a growing interest in exploring the condition from a range of different perspectives. Traditionally, motor activity, such as body movement and speech related activity, has been considered to be a marker of BD. For example, elevated motor activity such as accelerated pace of speech has been found to occur in manic mood states. Research in motor activity suggests that BD may be a disorder of activity (Maxhuni et al., 2015). In a naturalistic study that spanned across 12 weeks, Maxhuni et al. (2015) were able to use everyday activity information such as motor activity and features of
speech to classify mood episode types in BD. Voice parameters were analysed for telephone recordings provided by participants in this study. As a result, the course of relapse could be classified by computer software which in turn was found to closely follow psychiatric assessments.

Biomedical research has been trying to solve the mysteries of BD. To date, there are no specific biomarkers that can be used to classify the condition but research in the field is expanding. Studies of brain derived neurotrophic factors have identified them to be state-markers of episodes in BD (Fernandes et al., 2011). Other research has tried to classify BD by evaluating inflammatory immune response and gene expression (Fillman, Sinclair, Fung, Webster & Weikert, 2014). Strakowski et al. (2010) suggested that behavioural traits such as impulsivity may be key markers for BD. Specific cognitive subtypes have also been identified for BD (Sparding et al. 2017). Although, there appears to be several ways to classify BD, this study will utilize the traditional classification of BD as a mood disorder.

The severity of bipolar illness can increase if left untreated (Medeiros, Senço, Lafer, & Almeida, 2016). However, staging models (Vieta et al., 2011) of BD I purport stability of diagnosis and better prognosis for individuals who undergo early intervention. Although BD I can have lasting detrimental effects, it is highly treatable with medication and a number of therapies (Yatham et al., 2004; 2009), resulting in better chances for clinical improvement (e.g., reduced symptomatology). Treatment has predominantly focused on clinical improvement.

Randomized controlled trials have attempted to examine the role of psychosocial therapies in BD. Most psychosocial therapies for BD focus on helping an individual achieve reduced relapse rates, increased quality of life (QoL), improved functioning, and better symptomatic outcomes (Schöttle, Huber, Bock, & Meyer, 2011). Unfortunately, treatment
adherence is low in BD I. Psychosocial therapies adjunctly used to assist medical treatment (e.g., psychoeducation and Cognitive Behavioural Therapy) only show some success (Gaudiano, Weinstock & Miller, 2008). The low-moderate levels of success reported in randomized controlled trials examining psychosocial therapy in BD may be due to methodological challenges. Schöttle et al. (2011) reported that it can be difficult to compare the success of psychosocial therapies due to the inclusion of a range of patient populations and varying periods of follow-up offered in studies. Despite these challenges, research has shown psychosocial therapies to be related to positive outcomes in BD.

Keyes (2002) has argued that the treatment of mental illness (i.e., clinical improvement) may not necessarily equate to mental health. It can be argued that mental health is a multi-dimensional experience. Literature from rehabilitation work in mental illness has asserted that subjective variables – such as hope for change, social support, QoL, life satisfaction, and well-being – have a significant role to play in achieving mental health (Mancini, Hardiman, and Lawson, 2005).

**Positive Psychology and Well-being**

Health has long been defined as not merely the absence of disease but a state of complete physical, mental, and social well-being (The World Health Organisation, 2018). This definition expands the conceptualization of health and gives well-being a central role. Seligman and Csikszentmihalyi (2000) argued that positive psychological strengths, such as well-being, have an important role in achieving psychological health. Keyes (2002), however, suggested that the absence of symptoms of mental illness or the presence of high levels of subjective well-being do not indicate mental health. He proposed the complete state model of mental health, which suggests that mental health is defined by the concurrent presence of a combination of symptoms
of both mental illness and mental health. This model asserts that mental illness is often more than the sole presence or absence of emotional symptoms. Mental health has also been described as a complex state. Keyes (2002) has suggested that mental health sits on a continuum where the absence of mental health has been characterized as ‘languishing’ in life and the presence of mental health signifies ‘flourishing’ in life.

Languishing in life has been described as an experience of low well-being and low functioning. Meanwhile, flourishing has been characterized to encompass high levels of well-being and functioning. Keyes and Lopez (2002) further expanded the model to include states of ‘struggling and floundering’. They noted that individuals may be ‘struggling’ as they experience high well-being and significant symptoms of mental illness. On the other hand, ‘floundering’ may be experienced when an individual encounters low wellbeing and high levels of mental illness. Although individuals may achieve some symptomatic remission in mental illness (i.e., reduction in mood symptoms or severity), it is unclear if they are experiencing mental health. Keyes (2002) has described this to be a state of 'languishing' that is associated with poor emotional health as well as psychosocial and functional impairment. Keyes (2002) noted this to be the case for individuals who had experienced a depressive episode in the past 12 months in his study.

Keyes (2002) further emphasized the importance of emotional well-being in achieving mental health. He asserted that emotional well-being is associated with the presence of positive affect (i.e., being in good spirits), the absence of negative affect (e.g., hopelessness) and perceived satisfaction with life (Keyes, 2002). Traditional measures of emotional well-being have focused on an individual’s satisfaction with life overall but fail to recognize the social
Subjective well-being, however, is based upon an individual’s perception of their affective states, as well as psychological and social functioning.

Subjective well-being emphasizes the importance of functioning, wherein positive functioning has been described as consisting of six dimensions of psychological well-being: self-acceptance, positive relations with others, personal growth, purpose in life, environmental mastery, and autonomy (Keyes, 2002). Furthermore, Keyes (2002) has argued that psychological well-being may only be one piece to functioning well in life. The social dimension consisting of an individual’s perception of social coherence, social integration, social acceptance, and social contribution is another important piece to functioning well. It is thus evident that the construct of well-being is complex, consisting of several dimensions that appear to have significant implications for achieving good mental health. The examination of well-being may be key to understanding why some individuals flourish in life more than others, despite some similar challenges associated with BD.

A growing body of research has demonstrated the importance of well-being in achieving mental health. Manicavasagar et al. (2014) showed that positive psychological interventions decrease symptoms of depression and anxiety whilst also increasing well-being in youth. In a meta-analysis of randomized controlled studies of positive psychological interventions, Bolier et al. (2013) found evidence for the success of such interventions in clinical populations. Positive psychological interventions were identified to be effective in reducing depressive symptomatology and enhancing subjective and psychological well-being in participants. Hence, it seems clear that well-being has a central role in managing mental illness.

There have been strong academic debates, however, about how to define the concept of well-being. Two theoretical traditions have conceptualized well-being as either a hedonic or a
eudaimonic construct. The hedonic conceptualization of well-being has been focused on pleasure and happiness, based on a tripartite model composed of satisfaction with life, absence of negative affect, and presence of positive affect (Cooke, Melchert, & Connor, 2016). Given that both positive and negative affect are key components in this model, it becomes difficult to apply this model to BD I. For example, the positive affect experienced in a manic state can lead to significantly disruptive and risky behaviours in BD and which in turn may reduce well-being. In particular, it would be difficult to assess hedonic well-being in BD I given that manic and depressed mood episodes characterize the illness.

The eudaimonic conceptualization of well-being focuses on fulfilling one's potential and functioning at an optimal level (Lent, 2004). In Ryan and Deci's (2001) model of eudaimonic well-being, they suggested that the three psychological needs of autonomy, competence, and relatedness need to be fulfilled in order to achieve well-being. The eudaimonic conceptualization of well-being indicates that functioning at an optimal level can serve as a key indicator of well-being. However, it does not fully define what an ‘optimal’ level of functioning is. Given the higher functioning that can be seen in hypomanic mood states in BD, for example, it can be difficult to define when an individual is functioning optimally, particularly from a subjective standpoint. Furthermore, the eudaimonic model limits itself in that it only asserts the importance of psychological needs. Both the hedonic and eudaimonic models put forward some important conceptual elements for defining well-being. However, research suggests that each of these conceptualizations alone fall short of fully capturing well-being (Cooke et al., 2016; Lent, 2004; Ryan & Deci, 2001), particularly for individuals with BD I.

**Quality of Life**

There is a recognized third conceptualization of well-being, which is QoL (Michalak et al
Cooke et al. (2016) note that QoL is often used interchangeably with life satisfaction and subjective well-being in research. In this light, the QoL conceptualization of well-being may be more broad and comprehensive than both hedonic and eudaimonic conceptualizations. QoL can encompass physical, psychological, and social domains of functioning and has been employed frequently in medical contexts (Lent, 2004). Much research has focused on QoL in relation to BD I. Although a lack of consensus over the definitions of well-being and QoL has been reported in BD literature (Michalak, Yatham, & Lam, 2005), the two have been found to be closely related (Morton et al., 2017). Morton et al. (2017) found the concepts of functioning, health, subjective experience, and well-being to be related to QoL in BD, in a thematic analysis of 275 papers.

Research on QoL has allowed for the examination of physical, emotional, social, occupational, and spiritual well-being (Michalak et al., 2005). BD can have significant adverse effects on QoL (IsHak et al., 2012). In a qualitative study that explored a patient-centred perspective of the impact of BD on QoL, 52 interviews with patients, caregivers, and healthcare professionals identified several themes to be central to QoL: routine, independence, stigma and disclosure, identity, social support, and spirituality (Michalak et al., 2006). Participants reported that BD had an immense negative impact on their QoL. The areas most impacted were noted to be education, vocation, financial functioning, and social and intimate relationships. Hence, the QoL construct involves a highly subjective perception of personal well-being and functionality.

Most clinical research has traditionally focused on symptom ratings as a measure of outcomes (Strejilevich et al., 2013). However, the QoL construct has been proposed to be a measure of clinical change that is also complementary to traditionally used clinical tools (Michalak & Murray, 2010). In a large study comparing 108 participants who had been
diagnosed with BD to a 1,200 control participant group recruited from the general public, BD was found to be associated with lower scores on the mental and physical measures of QoL (Gutiérrez-Rojas et al., 2008). This association between BD and lowered levels of well-being was prevalent, irrespective of mood state. However, the authors noted that low mental QoL was related to early age of onset of the illness and depressive symptoms.

**First Episode Mania and Trajectory of QoL**

Since the peak age of onset of BD I has been identified to be during adolescence and early adulthood, the developmental impact of this disorder has also been of interest. In particular, longer duration of the disorder and higher number of depressive episodes has been found to be associated with a higher self-exploration and self-acceptance in youth and young adults (Inder et al., 2010). These elements can be considered to form key cognitive evaluations of life experience and its emotions, which have been viewed as components of well-being (Arthaud-Day, Rode, Mooney, & Near, 2005). Such cognitive evaluations have considerable implications for QoL and mental health for youth and young adults diagnosed with BD I.

Given the unique challenges that can be associated with a younger age of onset of BD I, the role of well-being in a sample of participants recovering from their first episode of mania (FEM) has been examined (Michalak, et al., 2013). They assessed the QoL of participants in remission from the first episode (baseline) and then at 6-month intervals up to 18 months. Perceived QoL was found to be high amongst this group of newly diagnosed participants at baseline, but also improved at months 12 and 18. The authors proposed that this may be due to participants potentially being able to retain hope early in the course of the disorder. However, an increased number of depressive episodes and depressive symptoms experienced during the course of the study predicted lower QoL. It was suggested that, as BD progresses and a higher
number of mood episodes are experienced, individuals may become aware of the ongoing struggles associated with the disorder and hope could possibly abate. As a result, QoL could also be negatively impacted over a longer time period.

Oldis et al. (2016) also explored the trajectory of QoL across 18 months following the first episode of psychotic mania in sample of 60 participants with BD I. They also found QoL to improve within 12-18 months of the onset of illness and depressive symptoms at 18 months following the FEM were associated with lower QoL. Oldis et al. (2016) further explored premorbid adjustment as a predictor of QoL in the early stages of BD I. They defined premorbid adjustment as the degree to which an individual achieves developmental goals as expected for his/her sex and age group before the onset of illness. Poor premorbid adjustment is demonstrated by a failure to achieve developmental milestones prior to the onset of illness or a delay in achieving expected milestones. Oldis et al. (2016) found poor premorbid adjustment to be associated with lower QoL 18 months following the onset of illness in BD I. It is unclear if the participants in this study had experienced depressive symptoms prior to enrolment in the study and if such a history may have influenced the results. However, it would appear that both depressive symptoms and developmental factors influence well-being in the early stages of BD I.

Qualitative research has further illustrated the difficulties associated with BD and its impact on various domains of life in the early stages of the illness (Delmas, Proudfoot, Parker, & Manicavasagar, 2011). An exploration of the subjective experiences of individuals and their families adjusting to the diagnosis of BD I in the first 12 months and then 3-5 years’ post diagnosis was conducted by Delmas and colleagues (2011). It was noted that individuals with BD felt that the illness had a negative impact on their families, jobs, homes and relationships. A prime concern with accepting the illness in the early stages was the chronic nature of BD I and
the long-term treatment and/or lifestyle changes needed to manage it. With the experience of further mood episodes, there was a growing realization that the individuals needed assistance. The authors reported that, for some individuals with BD, time was a key feature to accepting the diagnosis and that they had to undergo certain life experiences in order to fully accept the illness and its implications to their QoL.

It is evident that the length of time following the diagnosis of BD has important implications for QoL. Although QoL improvements have been reported to occur in the first 18 months of being diagnosed with BD (Michalak et al., 2013), trajectory and acceptance of the illness also have considerable implications for QoL and vice versa. Longer periods of time (3-5 years) following the diagnosis of BD seem to be connected with greater experience and acceptance of the illness. However, it is unclear how QoL may change within the first few years of being diagnosed with BD and how the illness is integrated into the various domains of life. A longitudinal observation of QoL across 3 years following the onset of BD I may shed light on whether it continues to improve, remains stable, or deteriorates during this early period.

**Functionality**

With the growing interest in the QoL construct and subjective well-being, it has become evident that symptomatic and syndromal remission in BD may not encompass complete recovery to mental health (Martin et al., 2013). Whilst QoL assessments offer a comprehensive measure of well-being in several life domains, they may not be able to fully capture functionality within those domains. Functionality appears to be a key component of mental health and hence warrants a closer examination. Keyes (2002) has suggested that achieving subjective well-being may be a critical factor to functioning well in life. Functional impairment has thus become the focus of both subjective and objective well-being. Aydemir (2016) reported on a FEM study in
which only 43% of participants achieved functional recovery over a two-year period. This finding is in contrast to almost 98% of participants achieving syndromal recovery and 72% experiencing symptomatic recovery (Tohen et al., 2003).

The study of functional outcomes has explored the impact of BD on everyday functionality. This includes an examination of functionality in work, social, household, and cognitive domains, to name a few. A review of functional outcomes in BD research has shown that 30-60 % of individuals with BD experience poor psychosocial functioning, particularly in occupational and social domains (MacQueen et al., 2001). Most strikingly, individuals with BD have been described to be a distinctly vulnerable group who experience greater disability and have fewer resources compared to individuals with major depression (Shipee et al., 2011). In particular, Shipee et al. (2011) identified BD to be associated with higher rates of non-employment and spending missed work days in bed.

Given that BD is associated with significant functional impairment and disability (Grande, et al., 2016), it comes with high personal and social costs. Understanding the factors that may be contributing to functional impairments may be crucial to developing translational knowledge that may assist in remediating it and helping individuals achieve better mental health. Mood symptoms, particularly depression, have been shown to impact everyday functioning (Harvey, 2011). In a study evaluating functional outcomes in a sample of 130 participants with BD, occupational and interpersonal functional deficits were found to be associated with depression (Bowie et al. 2010).

Furthermore, Kauer-Sant’Anna et al., (2009) noted that functional deterioration might be enduring in BD. In a study of participants following their FEM, the authors found depressive symptoms to have a profoundly negative effect on functional outcomes in BD. Michalak et al.
also examined psychosocial functioning and found some improvement at six months after the FEM. However, better functional outcomes were noted to be related to remission of depressive symptoms. This, in turn, has implications for personal well-being. Deckersbach et al. (2016) noted that functional and QoL outcomes should be considered to be important markers of improvement to mental health in BD.

**Depression, Quality of Life, and Functionality**

Research in schizophrenia and schizoaffective disorder has found depressive symptoms to be predictors of QoL, and the severity of depressive symptoms seems to be negatively correlated with QoL (Kao, Liu, Chou, & Cheng, 2012). When compared with major depression, BD I has been found to have a greater negative impact on QoL and functioning (Cotrena et al., 2016). This result has been attributed to the more severe clinical symptomology associated with BD I. In a large study (N = 958) examining QoL in individuals with BD experiencing an acute depressive episode, milder depressive symptoms were found to be correlated with better QoL (Yatham et al., 2004). Furthermore, Zhang et al. (2006) identified depression to be a strong predictor of QoL in BD where the presence of depressive symptomatology was noted to be strongly associated with reduced QoL.

Calabrese, Hirschfeld, Frye, and Reed (2004) found that depressive symptoms were experienced more frequently and perceived to be more debilitating when compared to manic symptoms in BD I. Participants in this study also perceived the presence of depressive symptoms in the past four weeks to have a greater impact on occupational, familial, and social domains, which are key components of QoL (Calabrese et al., 2004). They also reported depressive symptoms to affect functioning. Simon, Bauer, Ludman, Oepskalski, and Unützer
also found severity of depressive symptoms to be strongly associated with functional impairment and disability.

Rosa et al. (2010) examined functional outcomes for several life domains across different mood states in BD. The greatest impairment in functional outcomes was found to be for those individuals experiencing depression. Because depressive symptomology has been found to be a strong determinant of perceived QoL, it has been suggested that associated functional deficits may also drive QoL (Vojta et al., 2001). Furthermore, depression has been found to predict clinical improvement for individuals with poor baseline functioning (Deckersbach et al., 2016). Most notable though is that QoL and functional impairments have been seen to persist in euthymic mood states (Rosa et al., 2010).

One possible explanation for the impact of depression on QoL in BD has been offered by Morris et al. (2005). They suggested that hopelessness is often experienced in depression and some cyclical illnesses such as BD, and thus orienting oneself to think about a future where well-being is restored may be difficult to achieve. This may be the case when a higher number or longer lengths of depressive episodes are experienced in BD. Moreover, it is important to note that depressive episodes have been reported to predominate over manic mood states in BD (Michalak, Murray, Young, & Lam, 2008). Given this clinical feature of BD, it is evident that depressive symptomology has a complex relationship with QoL and functionality. Therefore, examination of this relationship is imperative, particularly in the early stages of the illness in order to maximize chances for achieving better mental health. A longitudinal observation of QoL, functionality, and their relationship with depression in the FEM BD I population offers a unique opportunity to do this.
Clinical guidelines and research make it very clear that clinical variables play a large role in the experience and prognosis of BD, particularly in its early stages. However, most research has predominantly focused on the disease model of BD and is primarily concerned with its pathology and how to optimise clinical improvement. There is very little focus on the examination of variables such as well-being that could contribute to good mental health. Keyes (2005) noted that research needs to focus on bridging salutogenesis (i.e., study of the nature and causes of health) and pathogenesis (i.e., study of the factors that cause disease) in helping individuals.

This study attempted to bridge salutogenesis and pathogenesis by examining how clinical features of BD, particularly depression, may be interacting with subjective well-being and functionality in the early stages of BD I. QoL has been shown to deteriorate significantly following the FEM, but it can recover by 18 months with appropriate treatment (Michalak et al., 2013). It is unclear, however, whether this level of QoL can be sustained beyond this period. Previously, it has been hypothesised that, with illness progression and as individuals spend more days in mood episodes, hope can wane and, in turn QoL, can deteriorate (Michalak et al. 2013). To be able to assess such a hypothesis, QoL and functional outcomes would need to be observed for a longer period of time in a FEM sample of BD I participants.

The present study observed if QoL and functionality improved, was maintained, or declined over a 3-year period in a sample of newly diagnosed participants with BD I. In addition, this study explored how (a) number of prodromal depressive episodes (prior to the FEM) (b) the total number of episodes of depression experienced by 3 years, and (c) severity of ongoing depressive symptomatology, impact QoL and functioning in BD I over 3 years following the
onset of illness. Such an examination may shed more light on whether depressive episodes can have a prolonged impact on QoL and functionality in BD I.
Chapter 3: Manuscript and Method

A longitudinal examination of quality of life, functional outcomes and depression in the first 3 years following the first episode of mania in bipolar disorder

Introduction

The World Health Organisation reported that Bipolar Disorder (BD) has the fifth highest burden of disease with respect to mental illness (Ferrari et al., 2016). BD is characterized by a combination of clinical depression and extremely elevated mood states known as mania (Bipolar Disorder Type 1; BD I) and/or (milder) hypomanic episodes (Bipolar Disorder Type 2; BD II). It can be a severe, recurrent, and progressive mental health condition that is associated with high morbidity (Mitchell, 2013). BD has been reported to be one of the leading causes of disability among youth and young adults (Grande, Berk, Birmaher & Vieta, 2016). Given the young and economically active segment of society that BD affects, there is a high cost to society associated with the condition (Gardner et al., 2006).

Well-being, quality of life, and functionality in BD. Symptomatic remission has been the main focus for therapeutic interventions and research (Yatham, Lecrubier, Fieve, Davis & Harris et al., 2004; Yatham et al. 2009). However, there is growing recognition and interest in the importance of achieving well-being and improved functionality beyond symptomatic improvement in mental illness (Keyes, 2002). This research has shown that traditional symptomatic and syndromal markers of treatment success in BD appear to fall short of capturing the full extent of the illness and improvement within it (Aydemir, 2016; Martin et al., 2013). For example, poorer quality of life (QoL) and functional impairments have been reported to be sustained beyond symptomatic remission in BD I (Michalak, Yatham, Kolesar, & Lam, 2006; Rosa et al., 2010; Thomas, Nisha, & Varghese, 2016). Such research has shown that everyday
functionality in work, social, household and cognitive domains, for example, is negatively impacted in BD. Individuals with BD I have reported experiencing greater functional impairments and lower levels of well-being in interpersonal and work domains when compared to individuals with recurrent depressive disorder (RDD) even during periods of remission from a mood episode in both RDD and BD (Chacko, Dayal Narayan, & Prabhavathy, 2011).

Recent reviews have shown that BD can have significant adverse effects on functional outcomes (MacQueen, Young, & Joffe, 2001) and QoL (IsHak et al., 2012). MacQueen et al., (2001) showed that 30-60% of individuals with BD experience poor psychosocial functioning, particularly in occupational and social domains. Most strikingly, individuals with BD have been described as a distinctly vulnerable group who experience greater disability and have fewer resources, as compared to individuals with major depression (Shipee et al., 2011). Furthermore, Kauer-Sant’Anna, Bond, Lam & Yatham (2009) noted that functional deterioration might be enduring in BD. In a study of participants following their FEM, the authors found depressive symptoms to have a profoundly negative effect on functional outcomes in BD. Michalak et al. (2013) also examined psychosocial functioning and found some improvement at six months after the FEM. However, better functional outcomes were noted to be related to remission of depressive symptoms.

In terms of QoL, longitudinal studies have found QoL to somewhat improve over time with guideline-driven treatment. Morton et al. (2017) reported QoL to improve with guideline-driven treatment over a 5-year period for individuals living with different types of BD for varying lengths of time. Similar findings have been reported for the early stages of the illness (Michalak, Torres, Bond, Lam & Yatham, 2013; Oldis et al., 2016). That is, QoL and functional outcomes have been found to decline following the onset of the first criterion episode of BD I.
(i.e., first episode of mania; FEM), but then improve within 12-18 months (Michalak, 2013; Oldis et al., 2016). However, there is very limited information on the trajectory of QoL beyond the first 18 months following the onset of BD. It has been hypothesised that hope can wane and, in turn, QoL can deteriorate with illness progression and as individuals spend more days experiencing mood episodes (Michalak et al., 2013). Further research is needed to examine the trajectory of QoL and functioning in BD to explore how these trajectories may change and what factors may be contributing to these patterns.

The examination of QoL as well as functional outcomes, has allowed for a deeper and more holistic approach to understanding the impact of BD (Deckersbach et al., 2016; Michalak et al., 2013; Rosa et al., 2010). As a result, QoL and functionality have been promoted as key target outcomes for mental health in BD (Deckersbach et al., 2016; Morton et al., 2017). Furthermore, it has been suggested that QoL and functioning may have a bidirectional relationship with the profile of BD (Morton et al., 2017; Murray & Michalak, 2012), meaning that not only does BD impact QoL and functioning but that improvements in both well-being and functioning may regulate symptoms of BD.

As staging models in BD I would suggest, it is apparent that earlier intervention may impact the course of illness (Murray et al., 2017; Vieta, Reinares, & Rosa, 2011) and hence, both QoL and functionality. This, in turn, warrants a closer look at factors influencing QoL and functionality following the onset of BD I. However, there is a dearth of research examining possible determinants of QoL in the early stages of the illness. Identifying possible predictors of QoL in the early stages of BD I may be helpful in optimizing personal and functional well-being. Some predictors of QoL in BD I have been identified to be the duration of illness (Elghonemy, Omar, Essa, & Morsy, 2011; Gutiérrez-Rojas, Gurpegui, Ayuso-Mateos, Gutiérrez-Ariza,
Veguilla & Jurado, 2008) and the presence of psychotic symptoms (Cotton et al., 2010; Elghonemy et al., 2011). Poor premorbid adjustment has also been noted to be a predictor of lower QoL in the early stages of illness (Oldis et al., 2016).

**Depression, QoL, and functionality.** It has been suggested that manic and depressive mood states in BD I are predictive of lowered QoL (Vojta, Kinosian, Glick, Altshuler, & Bauer, 2001) and functionality (Harvey, 2011). Depressive symptomology has consistently been reported to be a significant predictor of QoL in BD I (Amini & Sharifi, 2012; Cotrena Damiani, Kochhann, Milman & Paz., 2016; Michalak et al. 2013; Oldis et al., 2016; Vojta et al., 2001; Zhang, Wisniewski, Bauer, Sachs, & Thase, 2006), even when it is of low intensity (Dias, Brissos, Frey, & Kapczinski, 2008). Depression has also been shown to impact everyday functioning (Bowie et al., 2010; Chacko et al., 2011; Harvey, 2011).

Chacko et al. (2011) found a higher number of mood episodes and longer length of illness were related to lower well-being and functionality. A higher number of depressive episodes has also been found to be predictive of lower functionality and QoL related outcomes during inter-episodic periods of euthymia (MacQueen et al., 2000; Özer, Uluşahin, Batur, Kabakçi & Saka, 2002; Pilar, Lorenzo & Luis, 2005). This, in turn, supports the notion that symptomatic remission may not equate to mental health. While this suggests that depressive episodes could have some sustained impact beyond symptomatic remission, it is worth noting that Gutiérrez-Rojas et al. (2008) did not find prolonged impact of remitted episodes of depression on QoL and functionality in BD. A more recent study of QoL during euthymic phases also did not find QoL to be influenced by relapses of depressive episodes (Shabani et al., 2013). Although the evidence appears to be contradictory, it points towards a complex and inconsistent relationship between the potentially prolonged impact of depressive episodes on QoL and functionality. Given the
importance of intervention in the earlier stages of the illness in BD I, it becomes crucial to consider the potential effects of depressive symptomology on QoL and functionality at this stage.

Research has shown the depressive polarity of the first mood episode to be correlated with a worse clinical prognosis (Perugi et al., 2000) but to have no association with health-related QoL (Gutiérrez-Rojas et al., 2008). There is little information on how the polarity of the first episode may impact subjective QoL and functionality. To my knowledge, there is only one study that has examined this and they reported that the number of previous depressive episodes at baseline had a marked negative impact on QoL in the early stages of the illness (Michalak et al., 2013). Given the lack of clarity over the longitudinal impact of prodromal depressive symptomology and recurrent depressive episodes on QoL and functionality, further research is needed. In particular, there is a need to explore the impact of prodromal depressive symptomology and recurrent depression in the early stages of BD I. Given that this is a time when individuals are learning to adapt to the illness and develop appropriate coping skills, understanding the predictors of QoL may assist in optimizing mental health.

The present study

It is evident that symptomatic and syndromal remission in BD may not encompass complete mental health (Keyes, 2006). Research has shown functional impairments and lowered QoL to persist beyond clinical recovery in BD I (Michalak, et al. 2013). However, only a couple of studies have examined the trajectory and predictors of QoL and functional outcomes up to 18 months following the FEM in BD I (Michalak et al., 2013; Oldis et al., 2016). Thus, the purpose of the present study was to examine the trajectory of subjective QoL and functionality for the first three years following the onset of BD I. Furthermore, this study examined the relationship of early phase depression – specifically, prodromal depressive symptomology (i.e., before the
FEM), number of depressive episodes across the three years, and severity of ongoing depressive symptomology at each time point – to QoL at year 3, as well as to differences between year 3 and baseline in QoL and functional outcomes in a sample of FEM BD I patients in remission. To my knowledge, this is the first study to examine this longitudinally across three years.

**Research Questions and Hypotheses**

The following three research questions and hypotheses were explored in this study:

1) *What is the observed trajectory of (a) perceived QoL and (b) functional outcomes at baseline, 1 year, 2 years, and 3 years following the onset of illness in a FEM sample of individuals with BD I? Is the difference between these variables at baseline and year 3 significantly different from 0?*

   I hypothesised that QoL and functional outcomes would improve between baseline and 3 years in this sample primarily because staging models in BD have shown better prognosis for individuals with BD who receive early intervention (Vieta et al., 2011), as was the case for this sample. It is difficult to predict whether QoL will continue to improve beyond 18 months in a FEM sample of individuals with BD I as this has not been examined previously. Although Michalak et al. (2013) proposed that individuals could experience more mood episodes, lose some hope about the effectiveness of treatments, and experience reductions in QoL, I did not expect that to be the case with this sample. Moreover, Morton et al. (2017) found QoL to improve over 5 years under a guideline-driven treatment in a mixed sample of individuals with BD (Type I, Type II, BD-Not Otherwise Specified), although the rate of improvement slowed down considerably over time and declines were observed for the physical functioning components of QoL. Similar improvements in QoL have been reported in studies examining QoL across the 18 months that followed the FEM (Michalak et al.,
2013; Oldis et al., 2016). The most improvement in QoL has been found to occur in the first 12 months following the onset of illness.

Everyday functionality has been found to improve in the first six months following the FEM in BD I (Kauer-Sant’Anna et al., 2009; Michalak et al. 2013). However, it is unclear if functionality will continue to improve beyond this as very few studies have examined this. Functional deficits have been seen to persist beyond symptomatic improvements in BD (Ayedemir, 2016; Kauer-Sant’Anna et al., 2009; Rosa et al., 2010). As the FEM sample of participants recruited for this study have received medical intervention from the onset of illness, I hypothesized that functionality will to continue to improve in the first 3 years following the FEM.

Notably, however, only a handful of studies have looked at the trajectory of QoL and functional outcomes in BD I and none have looked at this across the first 3 years following the onset of illness in a FEM sample of participants with BD I. To my knowledge, only one study has examined the 5-year trajectory of QoL in BD (Morton et al., 2017), but this longitudinal study was focused on QoL as being comprised of psychosocial and physical functioning in a sample of participants diagnosed with different types of BD living with the illness for varying lengths of time. Morton et al. (2017) noted the need for future studies to examine the relationship between symptomology and measures of QoL with a life satisfaction or well-being focus.

2) Are there significant bivariate relationships between the dependent variables of QoL and functional outcomes and each of: (a) key demographic variables (i.e., age, sex, years of education), (b) prodromal depressive symptomology (number of depressive episodes prior to FEM), (c) total number of depressive episodes experienced in BD I between baseline and
year 3, and (d) severity of ongoing depressive symptomology at baseline, year 1, year 2, and year 3 time of data collection?

Based on findings from previous research (Michalak et al., 2013; Oldis et al., 2016), I hypothesized that the key demographic variables will not be correlated with QoL and functional outcomes. I hypothesized that the presence of prodromal depressive symptomology, a higher total number of depressive episodes, and that severity of ongoing depressive symptomology at baseline, year 1, year 2, and year 3 time of data collection would each be negatively correlated with QoL and functional outcomes. Michalak et al., (2013) reported the presence of depressive episodes that occurred before the onset of illness to be predictive of QoL 12 months following FEM.

Impairments in both QoL and functioning have been reported to be sustained beyond symptomatic remission in BD (Rosa et al., 2010; Thomas et al., 2016; Chacko et al., 2011; Michalak et al. 2013). It is possible that depressive episodes that occurred prior to FEM may have a lasting negative relationship with QoL. Depressive episodes have been found to be negatively associated with QoL (Amini & Sharifi, 2012; Cotrena et al., 2016; Michalak et al. 2013; Vojta et al., 2001; Zhang et al., 2006) and functional outcomes in BD I (Kauer-Sant’Anna et al., 2009; Calabrese, Hirschfeld, Frye & Reed et al., 2004; Deckersbach et al., 2016; Rosa et al., 2010). Previous research has identified severity of ongoing depressive symptomology in the earlier stages of the illness to have a longitudinal influence on QoL (Michalak et al., 2013). Severity of depression during the earlier phases of the illness (i.e., baseline and 12 months) has been found to be predictive of poorer QoL at 12 and 18 months (respectively) following the onset of illness in an FEM sample of participants (Michalak et
The presence of subsyndromal depression has been found to be associated with poor functional outcomes in a FEM sample of participants (Kauer-Sant’Anna et al., 2009).

3) Of the observed significant bivariate relationships between the dependent variables of QoL and functional outcomes and the independent variables (i.e., age, sex, years of education, prodromal depressive symptomology, total number of depressive episodes between baseline and 3 years, and severity of ongoing depressive symptomology at baseline, year 1, year 2, and year 3 time of data collection), which ones still show a significant relationship with the dependent variables when considered together?

None of the sociodemographic variables (i.e., age, sex, and years of education) were hypothesized to have significant bivariate relationships with QoL or functional outcomes. Previous research has also not found such sociodemographic variables to be correlated with QoL and functionality (Michalak et al., 2013; Oldis et al., 2016). The literature review revealed prodromal depressive episodes (Michalak et al., 2013), a higher number of depressive episodes (Chacko et al., 2011; Pilar, Lorenzo & Luis, 2005; MacQueen et al., 2000; Özer et al., 2002), and severity of ongoing depressive symptomology in BD I (Bowie et al., 2010; Calabrese et al., 2004; Cotrena et al., 2016; Harvey, 2011; Kao, Liu, Chou & Cheng et al., 2011; Kauer-Sant’Anna et al., 2009; Michalak et al., 2013; Rosa et al., 2010; Simon et al., 2007; Yatham et al., 2004; Zhang et al., 2004) to be correlated with reduced QoL and functionality. It is difficult to predict what will be found when all of these variables are examined together as this has not be examined before and is a novel contribution to the literature.
Method

The data for this study were derived from a larger data pool collected as part of the Systematic Treatment Optimization Program for Early Mania (STOP-EM) at the University of British Columbia and in collaboration with Vancouver General Hospital. This is a comprehensive clinical program providing medical and psychological follow-up for individuals who have recently been diagnosed with BD. Individuals participating in the program are offered clinical follow-up, optional pharmacological treatment, and psychoeducation. The STOP-EM project also has a large longitudinal research component focused on evaluating the clinical, functional, neurocognitive, neuroanatomical, and biochemical trajectories of the early stages of BD I. The project was initiated in 2004 and has been recruiting participants who are in remission from their first episode of mania.

Enrolment into STOP-EM has been completed but the program continues to provide naturalistic follow-up to currently-enrolled participants. A team of psychiatrists provide ongoing outpatient medical management based on the guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT; Yatham et al., 2009) and clinical expertise. The research component of STOP-EM invites participants to attend study visits every six months. At the baseline visit, comprehensive clinical interviews were conducted to collect information on sociodemographic variables, symptomology, medication use, psychiatric and physical medical history, family medical history, QoL, and functionality. Magnetic resonance imaging of the brain and neurocognitive assessments were also completed. Follow-up assessments of mood and other psychiatric features are conducted at the six-month visits of the STOP-EM program and as needed.

Participants. Forty participants aged between 14-35 years, diagnosed with BD I and in
remission from a manic episode that was experienced in the preceding 3 months were selected from the STOP-EM project. The data for participants that had attended every study visit were examined to identify the largest amount of data available for a longitudinal examination. The following study visits were identified to have the most data available: baseline, year 1, year 2, and year 3. Participants were selected based on their consecutive attendance of the baseline, year 1, year 2, and year 3 study visits. Participants were recruited from UBC Hospital and Vancouver General hospital, along with other affiliated sites. Recruitment was also conducted through referrals received from family physicians and psychiatrists. Medical diagnoses of mania and BD I were confirmed by psychiatrists as per the Diagnostic Statistical Manual 4th edition, text revised (DSM-IV-TR, American Psychiatric Association, 2000), Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998) and clinical expertise.

As per the DSM-IV-TR, BD I can be diagnosed under a broad range of clinical presentations. These include symptoms of pure or mixed mania, which can present with or without psychotic features and/or co-morbidities including substance use. The STOP-EM study inclusion criteria were based on the above to ensure a representative sample of participants was recruited in this naturalistic study. All study procedures were approved by the UBC Clinical Research Ethics Board (CREB) and all participants provided written informed consent prior to participation in any study procedures. The parents or legal guardians of participants who were under 19 years of age provided written informed consent. In addition to this, participants under the age of 19 years also signed assent forms prior to participation in any study procedures.

1 The participant sample in the study conducted by Michalak et al. (2013) were also recruited from the STOP-EM project at UBC. Thus, there may be overlap in the data at baseline and year 1 for some of the participants.
**Procedure.** The STOP-EM project has maintained a rolling recruitment model since 2004. As a result, participants have received follow-up for varying lengths of time. Some participants are in the first year of follow-up whereas others have reached the 14th year of follow-up visit. At each of their visits, participants complete clinical, functional, and QoL measures among other assessments. In the current study, clinical, functional and QoL outcome data from baseline, and each of 1, 2, and 3 years follow-up were examined. The baseline-year 3 time frame was selected for a longitudinal analysis as the largest amount of data was available for this period. Many participants have recently been enrolled in the study and have not reached the year 3 study visit and so their data could not be examined longitudinally. Clinical data for the number of depressive episodes experienced by each participant prior to the onset of the illness and since the FEM were examined in this study. Demographic data (age, sex, and years of education) were examined in this study to describe the sample and determine if they were related to QoL or functional outcomes.

**Variables and Measures.** This study observed the trajectory of QoL and functional outcomes across the 3 years following onset of illness in a FEM sample of participants with BD I. This study also examined the potential burden of depression on QoL and functional outcomes. There were three dependent variables (DVs) of interest in this study: (1) a measure of QoL at 3 years, (2) the difference in QoL between baseline and year 3, and (3) the difference in functional outcomes between baseline and year 3. In addition to the demographic variables of age, sex, and years of education, there were six independent variables (IVs) providing measures of number of depressive episodes and severity of symptoms. Each variable and its measure are described in alphabetical order below.
Depression. Depressive symptomology was assessed using the 29-item Hamilton Depression Rating Scale (HDRS-29; Williams, 1988), which assesses both typical and atypical symptoms of depression. Clinicians make ratings using anchors that provide a measure of severity from either 0 (absent) to 2 (severe) or 0 (absent) to 4 (most severe). The total score can range from 0 to 89, with higher scores indicating higher severity of symptoms. Interrater reliability for the total score has been reported to be 0.97 and the scale has been validated for use with individuals diagnosed with BD (Iannuzzo, Jaeger, Goldberg, Kafantaris, & Sublette, 2006). HDRS scores were obtained at baseline, year 1, year 2, and year 3 and serve as continuous IVs in this study. The HDRS scores were used in conjunction with clinical interviews conducted by psychiatrists to create a continuous IV of the number of depressive episodes that a participant experienced between baseline and 3 years. Finally, the continuous IV of prodromal depressive history (i.e., the number of depressive episodes prior to the FEM) was retrospectively assessed through clinical interviews conducted by psychiatrists at the baseline visit.

Functional Outcomes. Functional outcomes in the month preceding the study visit were assessed using the Multidimensional Scale of Independent Functioning (MSIF; Jaeger, Berns, & Czobor, 2003). The MSIF explores functionality in work, education, and residential environments. Assessments for domain levels of role responsibility, support, and performance in the three environments were made using independent ratings. The following 7-point role functioning response format was used to devise ratings on the MSIF: (1) essentially normal, (2) very mild disability or low end of normal range, (3) somewhat disabled, (4) moderately disabled, (5) significantly disabled, (6) extremely disabled, and (7) totally disabled. Each role domain was then assigned a global score to note the overall level of role responsibility, support, or performance across the three environments. An overall global rating for functionality was
derived using these domain global scores. This was done by examining the global score assigned to each environment. The rating for work role is weighted most heavily, followed by the ratings for education and residential roles. However, education roles may be weighted more strongly than work roles for young adults, for whom school attendance is an expected role. The overall global score provides a measure of the total level of disability as compared to the expected roles for that individual's peer group. The MSIF data were reverse coded to ensure higher values represented higher levels of functioning.

The MSIF provides a comprehensive measure of functional outcomes. The MSIF allows for the examination of functionality for individuals living in specialized environments such as hospitals. It also explores the level of support an individual may be receiving. As many of the participants were either in hospital or under medical leave at the time of enrolment into the study, the MSIF is able to provide information on functionality within this framework. The MSIF scale has been validated for use with individuals with BD (Berns, Uzelac, Gonzalez & Jaeger, 2007). Interrater reliability for overall rating has been found to have an alpha value of 0.90 (Jaeger, Berns, & Czobor, 2003).

Functional outcomes were obtained at baseline, 1, 2, and 3 years so the observed trajectory could be examined. However, MSIF scores at year 1, 2 and 3 showed skewness values more extreme than -1 and hence were not appropriate for use in subsequent regression analyses. A global MSIF simple difference score for overall global functioning between baseline and year 3 (i.e., year 3 minus baseline) was calculated and found to be fairly normally distributed, with a skewness value of 0.77 (SE = 0.37) and kurtosis value of -0.39 (SE = 0.73), and thus was used as a continuous DV. A high positive MSIF difference score would indicate a greater improvement between baseline and year 3.
**Quality of Life (QoL).** QoL was evaluated using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison & Blumenthal, 1993). The Q-LES-Q scale is a comprehensive self-report questionnaire that assesses a wide spectrum of QoL domains. The scale is comprised of 93 non-disorder-specific items which assess the following 10 domains: physical health, mood, leisure time activities, social relationships, general activities, medication satisfaction, life satisfaction and enjoyment, work (if applicable), household duties (if applicable), and school/coursework (if applicable). Responses are made by reflecting on the past week and using the following 5-point Likert-type response format: (1) not at all or never, (2) rarely, (3) sometimes, (4) often or most of the time, and (5) frequently or all of the time. Total scores for each domain can be generated.

As three of the Q-LES-Q domains (work, household duties and school/coursework) are only completed if applicable, they were not included here because many of the participants were enrolled into the program when they were hospitalized or had recently been discharged and were under medical leave following the first episode of mania. The perceived QoL index (PQoL; Ritsner et al., 2000) was used to provide a measure of QoL in this study. The PQoL index is calculated by averaging across the 60 items that make up the seven other domains of the Q-LES-Q. The Q-LES-Q has been validated for use in mood disorders, and particularly for BD (Michalak et al., 2010). A higher PQoL score means a higher level of perceived QoL and satisfaction reported by an individual. Scores were obtained at baseline, 1, 2, and 3 years so the observed trajectory could be examined.

The year 3 PQoL scores presented with a fairly normal distribution. However, a simple difference score was calculated for the perceived QoL index score to provide a measure of change between baseline and year 3, similar to the global MSIF difference score. The PQoL
difference score also demonstrated a relatively normal distribution. Specifically, the year 3 PQoL index scores showed a skewness value of -0.55 (SE = 0.37) and kurtosis value of -0.17 (SE: 0.73) and the PQoL index difference scores showed a skewness value of 0.66 (SE = 0.37) and kurtosis value of 1.40 (SE: 0.73). A high positive PQoL difference score indicates that greater improvement in perceived QoL was experienced by an individual between baseline and year 3. The year 3 PQoL index score, as well as the difference score between baseline and year 3 (i.e., year 3 minus baseline), served as continuous DVs in the regression analyses.

**Data Analysis**

Descriptive statistics were computed to provide a summary of the sociodemographic variables (age, sex, years of education and ethnicity) of the sample. Descriptive data were also computed for the number of prodromal depressive episodes, and the total number of depressive episodes (baseline to year 3). Preliminary data analyses were completed to examine any missing data and outliers. The Expectation Maximization algorithm was used to replace missing data. As described above, the distributions of the DVs were examined to determine if they are normal (e.g., using histograms, measures of skewness and kurtosis) as this is an assumption of many statistical analyses (e.g., regression).

Reliability estimates were calculated for any scale scores used in the analysis. Internal consistency estimates of reliability were examined for the year 3 PQoL index score, perceived QoL difference score, and total HDRS scores at baseline, 1, 2, and 3 years using Cronbach’s alpha. The difference score was calculated by first subtracting each item of the baseline PQoL index from the respective year 3 PQoL index score for each participant. A Cronbach’s alpha was calculated for the resulting PQoL difference scores. Reliability estimates were not calculated for
the global MSIF difference score as the item scores are not directly used to calculate the global score.

Descriptive data were then examined for PQoL index score and MSIF scores at baseline, 1, 2, 3 years, as well as their respective difference scores. HDRS (severity) scores at baseline, 1, 2, and 3 years were also examined.

Bivariate Pearson’s $r$ correlational analyses were conducted to assess the degree of association among the DVs and IVs. The correlations among the HDRS scores or among the various IVs were then examined to ensure there is no evidence of multicollinearity. Additional bivariate Pearson’s $r$ correlations were then computed between the sociodemographic variables of age and years of education with the DVs. An independent samples t-test was performed to assess if there are any statistically significant sex differences in the DVs; Cohen’s $d$ was calculated to identify the effect size of any differences. Correlations between each of the DVs and IVs were used to determine which IVs would be included in the subsequent regression analyses.

Three separate univariate regression analyses were conducted - one for each DV (i.e., the year 3 PQoL index score, the PQoL index difference score, and the global MSIF difference score). IVs found to be significantly correlated to each of the DVs were included in the respective regression analysis. Pratt’s measure was calculated using the $D_p = \hat{\beta}_p \hat{\rho}_p / R^2$ formula for each of the IVs found to be significant in the regression model. This provided a measure of the proportion of the explained variance in the DV that each significant IV accounted for relative to other IVs in the model. Thus, Pratt’s measure indicated the relative importance of each variable in the regression model. One sample t-tests were performed to examine if the PQoL and MSIF difference scores were significantly different from zero. Additional follow-up analyses...
were conducted using paired-sample t-tests between PQoL scores collected at baseline, year 1, year, 2 and year 3 to assess whether the changes between the time points were significant. Similar analyses were performed for the MSIF data collected at the various time points. All analyses used a statistical significance level of p < 0.05.

Results

Participant demographics and clinical summary. The sample consisted of 40 individuals ranging in age from 14-34 years (M = 22.5, SD = 4.96). Sixty percent of the sample was female and the majority of participants were Caucasian (72.5%) or Asian (22.5%). Years of education for the sample ranged from 9 to 20 (M = 14.1, SD = 2.54). Approximately 28% of the participants had experienced at least one episode of prodromal depression (before the onset of the FEM); the number of prodromal episodes in the sample ranged from 0 to 7 (M = 1.15, SD = 1.86). With respect to recurrence of depressive episodes across the three years, 30% of the sample had experienced at least one episode since the FEM; the number of recurrent depressive episodes in the sample ranged from 0 to 6 (M = 1.28, SD = 1.36). Although mania per se was not a variable of interest in this study, only 22.5% of participants had experienced a recurrent manic episode in the 3 years following the FEM; the number of manic episodes in the sample ranged from 0 to 3 (M = 0.28, SD = 0.60).

Missing data. Missing data analysis was performed on the individual items from the PQoL index score and HDRS for the baseline, year 1, 2, and 3 time points. Missing data for each PQoL index score item ranged across the 40 study participants as follows: baseline – between 2.5 and 15.0%; year 1 – 2.5 and 12.5%; year 2 – 2.5 and 10.5%; year 3 – 2.5 and 7.5%. Missing data for each HDRS item ranged across the 40 study participants as follows: baseline – 2.5%, year 1 –

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2 It is also worth noting that the total number of recurrent manic episodes did not correlate significantly with any of the DVs.
0%, year 2 – between 5.0 and 7.0%, and year 3 – between 2.5 and 5.0%. Information on the
number of prodromal depressive episodes was not available for one participant. The patterns of
missing data were examined and the Expectation Maximization algorithm was selected as the
appropriate strategy to replace missing data.

**Reliability.** Internal consistency estimates of reliability were calculated using Cronbach’s
alpha for each of the time points at which PQoL data were collected. The following Cronbach’s
alphas were produced for the PQoL index scores: baseline = 0.97, year 1 = 0.98, year 2 = 0.98,
and year 3 = 0.98. A Cronbach’s alpha of 0.93 was calculated for the PQoL index difference
score. The following Cronbach’s alpha internal consistency estimates of reliability were
produced for the HDRS scores at: baseline = 0.90, year 1 = 0.79, year 2 = 0.80, and year 3 =
0.87. Recall that reliability estimates could not be calculated for the global MSIF difference
score as the item scores are not directly used to calculate the global score.

**Observed trajectory of QoL and functionality across 3 years.** The mean data for the
PQoL index and MSIF scores across the four time-points in the study have been provided in
Table 1. The mean scores for the PQoL index were observed to improve between baseline and
year 3. Specifically, the PQoL index difference score shows a mean increase of 0.52 points (SD
= 0.50) in PQoL between baseline and year 3, which is statistically significantly different from 0,
t (39) = 6.52, p = 0.001, d = 1.03, 95% CI [0.36, 0.68]. However, the biggest improvement
appears to have occurred between baseline and year 1 whereas the mean PQoL index scores
appear to remain stable after year 1.

Follow-up analyses were performed to explore the differences between PQoL scores
collected at the various time-points. A paired-samples t-test showed a statistically significant
improvement in the PQoL scores from baseline to year 1 (t(39) = 5.73, p = 0.00, d = 0.92, 95%
Paired-samples t-tests conducted showed no statistically significant differences in the scores for PQoL scores from year 1 to year 2 ($t(39) = 0.44, p = 0.66, d = 0.08, 95\% \text{ CI } [0.13, 0.20]$) or from year 2 to year 3 ($t(39) = 0.26, p = 0.80, d = 0.04, 95\% \text{ CI } [0.16, 0.20]$). This suggests that PQoL remained somewhat stable beyond year 1 and up to year 3.

Table 1

*Mean PQoL index, MSIF, and HDRS scores across time*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Mean (SD)</th>
<th>Year 1 Mean (SD)</th>
<th>Year 2 Mean (SD)</th>
<th>Year 3 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PQoL</td>
<td>3.47 (0.58)</td>
<td>3.93 (0.61)</td>
<td>3.96 (0.67)</td>
<td>3.98 (0.57)</td>
</tr>
<tr>
<td>MSIF</td>
<td>4.38 (2.20)</td>
<td>6.00 (1.24)</td>
<td>5.88 (1.44)</td>
<td>6.01 (1.02)</td>
</tr>
<tr>
<td>HDRS</td>
<td>7.38 (8.64)</td>
<td>2.63 (3.82)</td>
<td>4.90 (5.42)</td>
<td>4.75 (6.75)</td>
</tr>
</tbody>
</table>

Note. PQoL = Perceived Quality of life index score; MSIF = Multi-dimensional Scale of Independent Functioning; HDRS = Hamilton Depression Rating Scale; SD = Standard deviation.

The mean scores for the MSIF also improved between baseline and year 3. The MSIF difference score indicates a mean increase of 1.7 points ($SD = 2.20$) in functionality between baseline and year 3, which was found to be significantly different from 0, $t(39) = 4.89, p = 0.001, d = 0.77, 95\% \text{ CI } [1.00, 2.40]$. The biggest improvement, however, seems to have occurred between baseline and year 1, much like the pattern seen for PQoL index scores. The mean MSIF score then seems to drop slightly at year 2 before improving again at year 3.

A paired-samples t-test showed a statistically significant improvement in the MSIF scores from baseline to year 1; $t(39) = 4.00, p = 0.00, d = 0.63, 95\% \text{ CI } [0.80, 2.45]$. Paired-samples t-tests showed no statistically significant differences in the scores for MSIF scores from year 1 to
year 2 ($t(39) = -0.45, p = 0.66, d = -0.07, 95\% CI [-0.69, 0.44]$) or from year 2 to year 3 ($t(39) = 0.88, p = 0.38, d = 0.14, 95\% CI [-0.26, 0.66]$).

For comparison purposes, mean HDRS scores are also provided in Table 1 at each of the four time points. The mean HDRS score at baseline was the highest of all the time points, reflecting participants’ relatively higher average severity of depression following the onset of the FEM. The mean HDRS score decreased considerably at year 1, indicating that the participants were experiencing fewer symptoms of depression on average. The mean HDRS increased by year 2 and remained at a similar level at year 3.

**Correlational analysis.** Bivariate correlational analyses between the DVs and the sociodemographic variables of age and years of education did not produce any statistically significant correlations as can be seen in Table 2.

Table 2

*Correlations between QoL and functional outcome variables and age and years of education.*

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Age</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years</td>
<td>Years</td>
</tr>
<tr>
<td>Year 3 PQoL scores</td>
<td>-.09</td>
<td>-.17</td>
</tr>
<tr>
<td>PQoL difference score</td>
<td>.24</td>
<td>.14</td>
</tr>
<tr>
<td>MSIF difference scores</td>
<td>.12</td>
<td>.14</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Note. PQoL = Perceived Quality of life index score; MSIF = Multi-dimensional Scale of Independent Functioning; HDRS = Hamilton Depression Rating Scale
Independent-samples t-tests were conducted to determine if there were any significant sex differences in the year 3 PQoL index scores, PQoL index difference scores, or MSIF difference scores. There were no significant differences in the year 3 PQoL index scores for males ($M = 3.95$, $SD = 0.53$) and females ($M = 4.00$, $SD = 0.61$); $t (38) = -0.31$, $p = 0.76$, $d = -0.09$, 95% CI [-0.53, 0.35], the PQoL index difference scores for males ($M = 0.40$, $SD = 0.34$) and females ($M = 0.59$, $SD = 0.58$); $t (38) = -1.20$, $p = 0.24$, $d = 0.40$, 95% CI [-0.84, 0.05], or the MSIF difference scores for males ($M = 2.19$, $SD = 2.29$) and females ($M = 1.36$, $SD = 2.12$); $t (38) = 1.15$, $p = 0.26$, $d = 0.38$, 95% CI [-0.07, 0.81].

Table 3 shows the bivariate correlations between all DVs and IVs. Bivariate correlational analysis revealed year 3 PQoL index scores to be statistically significantly and negatively correlated with the total number of depressive episodes that occurred between baseline and year 3, baseline depressive symptomology, year 1 depressive symptomatology, and year 3 depressive symptomatology.
Table 3

**Correlations between PQoL and functional outcome variables and depression.**

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Prodromal depressive episodes</th>
<th>Total depressive episodes up to year 3</th>
<th>Baseline HDRS</th>
<th>Year 1 HDRS</th>
<th>Year 2 HDRS</th>
<th>Year 3 HDRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 3 PQoL</td>
<td>-.15</td>
<td>-.53**</td>
<td>-.52**</td>
<td>-.34*</td>
<td>-.20</td>
<td>-.56**</td>
</tr>
<tr>
<td>Difference Scores PQoL</td>
<td>-.08</td>
<td>.01</td>
<td>.23</td>
<td>-.24</td>
<td>.03</td>
<td>-.30</td>
</tr>
<tr>
<td>Difference scores MSIF</td>
<td>-.03</td>
<td>-.22</td>
<td>.09</td>
<td>-.27</td>
<td>-.17</td>
<td>-.07</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Note. PQoL = Perceived Quality of life index score; MSIF = Multi-dimensional Scale of Independent Functioning; HDRS = Hamilton Depression Rating Scale

The PQoL index difference scores and the MSIF difference scores between baseline and year 3 did not correlate statistically significantly with any of the IVs. Multicollinearity was examined among the HDRS scores for each time point, the number of prodromal depressive episodes, and the total number of depressive episodes that occurred between baseline and year 3. None of these correlations exceeded $r = 0.40$, so there was no evidence of problematic multicollinearity.

**Predictors of year 3 PQoL index scores.** Prior to conducting an OLS multiple regression, the assumptions and diagnostics were assessed. The scatterplot between the residuals and year-3 PQoL index predicted scores is presented in Figure 1, which demonstrated that individuals’ error scores (residuals) were randomly scattered. There did not appear to be any
curve-like or fan shaped pattern. The assumptions of linearity and homoscedascity appeared to have been met for this model.

Figure 1

*Scatterplot of individuals’ error scores (residuals)*

The participant sample for this study was recruited from various hospitals and referrals from community-based psychiatrists across the Lower Mainland area of British Columbia. The sample was not clustered and thus the assumption of independence has been met for this regression model. Based on the histogram in Figure 2 and the Q-Q plot in Figure 3, the residuals of the model appear to follow a near normal distribution. The OLS regression model assumes that residual scores are normally distributed and this assumption appears to have been met.
As the total number of depressive episodes between baseline and year 3, as well as baseline, year 1, and year 3 HDRS depressive symptomology scores were statistically significant
correlates of year 3 PQoL index scores, they were retained for further analysis. An OLS multiple
linear regression was performed to predict year 3 PQoL index scores based on the four possible
predictor variables. Table 4 presents the results from this analysis. A statistically significant
equation was found for the model \( F (4, 35) = 11.239, p < 0.001 \). The regression model
accounted for 56% of the variance. Only depressive symptomology at baseline and year 3 were
found to be significant predictors of year-3 PQoL index scores in the presence of the other
variables. Pratt’s analysis further showed that depressive symptomology at baseline and year 3
accounted for almost 33% and 41% of the variance, respectively. Variance inflation factor (VIF)
statistics were produced for the model to examine any multicollinearity between predictors.
None of the predictor values produced a VIF greater than 1.5 and hence there was no evidence of
multicollinearity. The data were examined for any multivariate outliers with a Cook’s distance
greater than 1. There was no evidence of any multivariate outliers.

An examination of influential cases, however, showed that the data from one of the
participants had a leverage value of 0.50, which could be unduly influential. The data for this
participant were removed and a new model was produced. The OLS multiple linear regression
was re-run. A significant equation was found for the model \( F (4, 34) = 8.820, p < 0.001 \). The
new regression model accounted for 51% of the variance. Again, only HDRS depressive
symptomology at baseline and year 3 were found to be significant predictors of year 3 PQoL
index scores. Removing the unduly influential outlier reduced the \( R^2 \) value by 5%. Notably, the
same predictors were found to be significant predictors and the individual regression coefficients
did not change very much.
Table 4

OLS regression results for year 3 PQoL

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Significance</th>
<th>Pearson’s r</th>
<th>Pratt's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B Standard Error Beta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>4.477 0.099 -0.172</td>
<td>45.173</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence Depression (total # of episodes up to year 3)</td>
<td>-0.073 0.058 -0.172</td>
<td>-1.250 0.220</td>
<td>-0.527 0.161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HDRS</td>
<td>-0.024 0.008 -0.359</td>
<td>-3.023 0.005*</td>
<td>-0.523 0.334</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1 HDRS</td>
<td>-0.025 0.018 -0.164</td>
<td>-1.338 0.190</td>
<td>-0.339 0.099</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3 HDRS</td>
<td>-0.034 0.011 -0.406</td>
<td>-3.240 0.003*</td>
<td>-0.562 0.406</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.01 level

Regression analyses for the PQoL index difference scores and MSIF difference scores between baseline and year 3 were not performed as they did not correlate with any of the possible predictors in the bivariate analyses.

Discussion

The purpose of the present study was to examine the trajectory of QoL and functionality for the first 3 years following the onset of BD I. The relationship of prodromal depressive symptomology, number of depressive episodes, and severity of ongoing depressive symptomology across 3 years to QoL at year 3, as well as to differences in QoL and functional
outcomes between year 3 and baseline in a sample of FEM BD I patients in remission was explored. This is the first study to observe the trajectory of QoL and functionality for as long as 3 years following FEM in BD I patients.

**The observed trajectory of QoL and functional outcomes.** The year 3 PQoL index scores and PQoL difference scores were found to be highly reliable (alpha = .98). Consistent with previous findings in FEM samples (Michalak et al., 2013; Oldis et al., 2016), QoL outcomes were observed to improve between baseline and 1 year after the onset of illness. This observation was found to be statistically significant and produced a fairly large effect size. However, the level of QoL was basically stable from year 1 to year 3 following FEM. This pattern of stability seen in the study is a novel finding. Previous researchers (Michalak et al., 2013; Oldis et al., 2016) have suggested that QoL could potentially decline over time. The results from this study indicate that it may be possible to retain improvements in QoL gained in the first year following the FEM for at least another two years. This finding may serve as good news for individuals who have recently experienced their FEM, in that initial deficits in QoL do not have to be permanent. Such a finding may further orient individuals with BD I and their health care professionals to the importance of improving QoL in the early stages of the illness.

The observed trajectory for functional outcomes also displayed a similar pattern of improvement. A one-sample t-test confirmed that the change in functionality between baseline and year 3 was significantly different from zero. Consistent with findings from previous research in FEM samples (Kauer-Sant’Anna et al., 2009; Michalak et al., 2013), functional outcomes were seen to improve the most between baseline and one year following the FEM. Again, this was found to be statistically significant and demonstrated a moderate effect size. While functionality appeared to have declined two years after the onset of illness before improving...
again by year 3, these were not statistically significant differences. It is worth noting that depressive symptomology at year 2 was observed to be relatively more severe, on average, relative to years 1 and 3. It is possible that the small decline in functionality may correspond to the small increase in severity of depressive symptoms at this time point. This trend appears to be consistent with previous research that has shown functionality to be reduced in the presence of depression (Bowie et al., 2010; Calabrese et al., 2004; Harvey et al., 2011; Kauer-Sant’Anna et al., 2009; Michalak et al., 2013; Rosa et al., 2010; Simon et al., 2007). Interestingly, as depressive symptomology slightly improved at the year 3 time point, functionality also improved to a comparable level to that observed at year 1. Again, these changes were small and not statistically significant.

The trajectory of functionality observed in this study offers another novel finding which may be further explored in future research. This finding suggests that functionality may be somewhat fluid in the early stages of BD I. The observed improvement in functionality following FEM may offer hope to individuals with BD I in that the functionality can improve as depressive symptoms are reduced. This, in turn, could potentially serve as an incentive to individuals to seek treatment of depressive symptoms sooner in order to restore or improve functionality. Again, further research is needed to verify the observations of this study.

**Early phase depression, QoL and functionality.** The relationship of early phase depression with QoL and functional outcomes in the 3 years following the onset of BD I was a key focus of this study. Three DVs were used: QoL at year 3, difference in QoL from baseline to year 3, and difference in functionality from baseline to year 3. Early phase depression was explored by evaluating the impact of prodromal depressive episodes, total number of depressive episodes in the 3 years post FEM, and severity of ongoing depressive symptomology at each
time point. To my knowledge, this is the first study to explore these variables of depression together along with their potential longitudinal relationship with QoL and functional outcomes.

**Early phase depression and QoL at 3 years following FEM.** QoL at year 3 showed statistically significant bivariate relationships with the total number of depressive episodes over the three years ($r = -.53$) as well as severity of depressive symptomatology at baseline ($r = -.52$), year 1 ($r = -.34$), and year 3 ($r = -.56$). Prodromal depressive episodes ($r = -.15$) and year 2 depressive symptomatology ($r = -.20$) were not significantly related to QoL at year 3. Sociodemographic variables (i.e., sex, age, years of education) were also not related to QoL at year 3. An OLS regression found that only baseline and year 3 depressive symptomatology remained as significant predictors of QoL at year 3, when in the presence of other predictors significant at the bivariate level.

Previous research found prodromal depressive episodes to be predictive of lower levels of QoL in the first year of the illness (Michalak et al., 2013). As this study found no significant relationship between prodromal depressive episodes and QoL 3 years post FEM, it is quite possible that prodromal depressive episodes have a stronger relationship with QoL only in the very early stages of the illness and any negative impact of these episodes is remediated over time. If this is indeed the case, then it may offer hope to clinicians and patients. Such a finding could mean that the experience of prodromal depressive episodes does not necessarily have long-term debilitating effects - at least over the initial 3 years in a sample receiving treatment. This supports the notion that individual resilience may be fairly high in (at least in some) young individuals who have recently been diagnosed with BD I, as previously identified by Michalak et al. (2013) and Oldis et al. (2016).
It is also important to note that only 28% of the sample had experienced any prodromal depressive episodes. As the data on prodromal depressive history were collected retrospectively through clinical interviews, the accuracy of such data is susceptible to range of influences. For example, it may be the case that the participants that opted to participate in this study were not able to fully recall the details of their mental health history. As a result, it is possible that the sample may not have been fully representative of the larger BD I FEM population and the analysis was unable to pick up any effects.

Another possible reason for the lack of relationship seen between prodromal depression and QoL at 3 years may be due to treatment success following the FEM. It may be the case that intensive and regular treatment, such as that offered in the STOP-EM program, may reduce the longitudinal impact of prodromal depressive episodes. As some research has provided evidence for a possible relationship between prodromal depressive episodes and QoL post FEM (Michalak et al., 2013), future research should be conducted to see if the findings can be replicated or to examine them from a different perspective. For example, a prospective study with a sample of participants at high-risk for developing BD I may be able to provide more information on the possible impact of prodromal depressive episodes on QoL later on in life. Alternatively, future research may need to incorporate other means of data collection such as gathering collateral information from families or a review of medical charts.

The correlational relationship between recurrence of depression (between baseline and the year-3 time-point) and QoL at 3 years following the onset of the illness observed in this study appears to be consistent with previous literature (Amini & Sharifi, 2012; Cotrena et al., 2016; Michalak et al., 2013; Vojta et al., 2001; Zhang et al., 2006). This finding suggests that a higher total number of depressive episodes may be associated with a lower level of QoL at the 3-year
time point. However, this result was not reproduced in the regression analysis given the presence of other variables.

**Early phase depression and the PQoL difference score (baseline -year 3).** None of the sociodemographic or depression variables examined in the study showed significant bivariate relationships with the PQoL difference score between baseline and year 3; although baseline \( r = 0.23^{3} \), year 1 \( r = -0.24 \), and year 3 \( r = -0.30 \) depressive symptomatology showed correlations of some notable magnitude, because these were relatively small and nonsignificant, no regression analysis was conducted. It is important to note that the difference score (year 3 minus baseline) for the PQoL was utilised in this study to examine the change in QoL in the first 3 years following the FEM. The results from the one-sample t-test confirmed that the difference observed in the PQoL scores between baseline and year 3 were indeed significantly different from zero. Previous research has not examined the PQoL difference score so it is difficult to interpret the results with respect to previous findings. As the PQoL difference score may be considered to be a measure of change in QoL, other literature (Michalak et al. 2013; Oldis et al. 2016) that has examined the longitudinal relationship between QoL (although not the difference score specifically) and each of sociodemographic variables and severity of ongoing depressive symptomology may shed more light on the findings from this study as discussed below.

It was hypothesised that age and years of education would not correlate with the PQoL difference score. Previous research has not found any significant correlations between QoL and such demographic factors and the findings from this study are consistent with it (Michalak et al., 2013; Oldis et al., 2016). Although the correlations between severity of ongoing depressive symptomology and the PQoL difference scores were non-significant, they showed a trend

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3 This correlation was indeed positive in sign; thus, higher depressive symptomatology at baseline was associated with more improved quality of life from baseline to year 3. This may reflect the greater impact of treatment on QoL for patients with initially worse depressive symptomatology.
towards the presence of a negative relationship between them. These findings are partially consistent with previous literature that has shown severity ongoing depressive symptomology to be associated with reduced QoL (Calabrese et al., 2004, Cotrena et al., 2016; Kao et al., 2011, Michalak et al., 2005; 2008; 2013; Oldis et al., 2016; Zhang et al., 2006).

This study also examined the bivariate correlation between prodromal depressive episodes and the PQoL difference score (representing the change between baseline and year 3), which was found to be nonsignificant. Again, it is possible that as successful treatment of BD I in the early stages of the illness reduces mood symptoms, it may also help improve QoL. This in turn may remove any long-term impact of prodromal depression after the first year following the FEM. It is important to note that the volunteer sample of participants used in the study could have unique characteristics which may not allow the sample to be fully representative of the larger FEM BD I population. A larger sample size of participants may produce a dataset with more variability and statistical power that may be able to better describe the relationship, if one exists, between prodromal depressive episodes and QoL in the early stages of BD I.

The PQoL difference score was found to show a trend towards a positive correlation with severity of ongoing depressive symptomology at baseline but as a non-significant finding, which is not consistent with previous research (Calabrese et al., 2004, Cotrena et al., 2016; Kao et al., 2011, Michalak et al., 2005; 2013; Oldis et al., 2016; Zhang et al., 2006). Notably, previous research did not use a difference score for QoL or extend its exploration over a 3-year period of time in a FEM sample of individuals with BD I. Such differences may be the reason why this study was not able to find a statistically significant relationship between the PQoL difference score and severity of ongoing depressive symptomology. It may be the case that there was something unique about the participant sample in this study and that it may not be fully
representative of the larger BD I FEM population. Only further research with a greater sample size with more variability may be able to shed more light on the trend-level correlations seen in this study.

**Early phase depression and functionality difference score (baseline – year 3).** None of the sociodemographic or depression variables examined in the study showed significant bivariate relationships with the difference score between baseline and year 3 functionality. The variables of age and years of education were predicted to have a nonsignificant relationship with the functionality difference score. The findings from this study are consistent with previous literature (Michalak et al. 2013). At the bivariate level, only total number of depressive episodes over the 3 years \( r = -.22 \) and year 1 \( r = -.27 \) depressive symptomatology showed correlations of any notable magnitude but, as these were relatively small and nonsignificant, no regression analysis was conducted. These findings should be interpreted with caution due to the nature of the measurement tool (MSIF) used to assess functionality. It was not possible to estimate internal consistency for this tool as it not a scaled measure. Hence, there is no way of knowing to what degree reliability may have influenced the statistical results. However, given the format of the tool used in this study, it produced objective ratings of functionality as made by health care professionals and has been reported to have high inter-rater reliability (Jaeger et al., 2003).

The lack of a significant correlation \( r = -.03 \) observed between the presence of prodromal depressive episodes and change in functionality between baseline and year 3 following the FEM is not consistent with previous research that has indicated that depression can have a longitudinal effect on functionality (Chacko et al., 2010; Michalak et al., 2006; Rosa et al., 2010; Thomas et al., 2016). However, other research has shown remission of depressive symptoms to be related to improvements in functional outcomes (Kauer-Sant’Anna et al., 2009),
which seems consistent with the findings of this study. It is possible that remission of prodromal depressive episodes allowed for functionality to be restored or improved and hence prodromal depression did not have a longitudinal influence. It is also important to note that data regarding prodromal depressive episodes were collected retrospectively and thus are susceptible to bias. It is difficult to determine if, and how often, the participants in this study experienced clinical depression prior to their FEM. Only prospective studies would be able to examine this with higher empirical sensitivity.

The findings from this study are consistent with research that has demonstrated that remitted episodes of depression do not have a prolonged impact on functionality in BD I (Gutiérrez-Rojas et al., 2008; Shabani et al., 2013). The lack of a relationship between prodromal depressive episodes and the difference in functionality from baseline to year 3 following the FEM is encouraging for researchers, clinicians, and individuals with BD I. It may be the case that that depression experienced prior to the onset of illness in BD I does not necessarily have a longitudinal detrimental impact on functionality. Such results again provide support for the notion that resilience may be high in individuals who have recently experienced their FEM and received clinical follow-up.

The lack of relationship observed between prodromal depressive episodes and functional outcomes in the early stages of BD is a novel finding as this relationship has not been previously examined with a FEM BD I sample. It is notable, however, that functional outcomes were measured using a difference score. This was necessary due to the lack of normality in the year 3 scores. Had it been possible to use those year 3 scores, a similar pattern of findings may have been found with functionality as was found with year 3 PQoL scores vs. PQoL difference scores.
Future research may have to examine this possibility further, perhaps with a different measure of functionality.

Previous research has shown severity of ongoing depressive symptomology to be associated with lower functionality (Bowie et al., 2010; Calabrese et al., 2004; Harvey et al., 2011; Kauer-Sant’Anna et al., 2009; Michalak et al., 2013; Rosa et al., 2010; Simon et al., 2007). A statistically significant correlation between severity of ongoing depressive symptomology and the functionality difference score was not produced in this study. However, consistent with previous research, severity of ongoing depressive symptomology at year 1 demonstrated a trend-level correlation with the functionality difference score in this study. Albeit, it is difficult to draw any firm conclusions based on trends seen in the study data. Further research with a larger sample size and greater variability in functional outcomes scores would be able provide more information on the correlational trends seen in this study. Perhaps, functional outcome scores collected at individual time points may serve to be more sensitive variables of functionality than a difference score.

It is important to note that both the PQoL and MSIF difference scores represented change in QoL and functional outcomes over 3 years from the onset of illness. None of the depression variables were found to explain this change. Challenges related to the methodology used, variability in scores, and score reliability may have contributed to the lack of relationship seen between the depression variables and change in QoL and functional outcomes over the 3 years. It may also be the case that other factors may have contributed to positive trajectories seen for both QoL and functional outcomes. It is unclear what these may be; it is recommended that this be explored further in future research.
**Predictors of QoL at 3 years following the FEM.** Severity of ongoing depressive symptomology at the year 3 time-point was found to be predictive of QoL at 3 years following the FEM. This finding demonstrates that actively experiencing depressive symptoms can have negative consequences for QoL. This finding supports previous research which has consistently reported severity of ongoing depressive symptomology to be a strong predictor of QoL (Amini & Sharifi, 2012; Cotrena et al., 2016; Michalak et al., 2013; Morton et al., 2017; Oldis et al., Vojta et al., 2001; Zhang et al., 2006). Examining the severity of ongoing depressive symptomology allowed for the inclusion of both syndromal and sub-syndromal levels of depression in this study. This makes it a more sensitive measure of the impact of depression. The differences between the impact of syndromal and sub-syndromal symptoms of depression were not examined as this was beyond the scope of the study. However, the findings from this study indicate that depressive symptoms (whether syndromal or sub-syndromal) can have significant ramifications for QoL and both need to be closely monitored and treated.

This is the first study to explore the longitudinal relationship of depression and QoL 3 years following the FEM. One of the most critical findings of this study was that higher severity of depression at the onset of illness (baseline) was found to be predictive of lower QoL 3 years later. This finding is consistent with literature which has demonstrated depressive symptomology to have longitudinal ramifications for QoL (Michalak et al., 2013; Rosa et al., 2010; Thomas et al., 2016). Similarly, Michalak et al. (2013) reported severity of depression during the earlier phases of the illness (i.e., baseline and 12 months) to be predictive of poorer QoL at 12 and 18 months (respectively) in a FEM study.

It is unclear how depression at the onset of the illness may be impacting QoL after 3 years. There may be something unique about the experience of depression which closely follows
the onset of illness in BD I. For example, the mean baseline HDRS depression score recorded in
the study was observed to be the highest in comparison to the other time-points. It is possible that
the higher severity of depression in the early stages of the illness may lead to the development of
poorer coping skills or even hamper the development of effective coping skills for depressive
symptoms later on in the illness. Morris et al. (2005) have suggested that hopelessness is often
experienced with depression. It is also possible that experiencing depression and lower QoL
immediately following the onset of illness may be associated with some feelings of hopelessness
that may be sustained in the first 3 years of the illness.

Previous qualitative research has suggested that BD can negatively impact personal
identity (Michalak et al., 2006; Inder et al., 2011), which is closely related to the 'self' domain of
QoL. It is possible that the experience of depression following the onset of illness in BD I could
have a significant effect on an individual’s sense of identity. Individuals may feel less confident
in themselves and their abilities as they question their life experiences within mood episodes. As
a result, depression may have a lingering influence on an individual’s self-esteem and their
beliefs about their ability to achieve a good QoL. This, in turn, may lead to lower QoL in the
early stages of BD I. It would seem that experiencing depression following the onset of illness
may prime individuals for poorer QoL in the future. Additional qualitative and quantitative
research would need to examine the relationship between early phase depression, personal
identity, and QoL.

Although, severity of depressive symptomology at baseline and year 3 were found to
predict QoL at 3 years following the FEM in a sample of individuals with BD I, all hope is not
lost. This study does offer some hopeful findings in that the trajectories of QoL and functional
outcomes were observed to improve over the first year following the FEM and stabilise for
another 2 years beyond that in a sample of individuals with BD I receiving treatment. Despite the challenges resulting from the experience of depressive symptoms immediately following the FEM, individuals can experience an overall improvement in QoL in the early phase of BD I (up to 3 years).

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Chapter 4: Conclusion

The purposes of this study were to (a) examine the trajectory of QoL and functional outcomes across the first 3 years following the onset of BD I, and (b) explore the relationship between QoL and functional outcomes with early phase depression. The number of prodromal depressive episodes, total number of depressive episodes to recur and severity of ongoing depressive symptomology across the first 3 years following the onset of illness in BD I were examined as components of early phase depression. The findings from this study suggest that QoL and functional outcomes may be able to improve in the first year following the onset of illness in BD I and such gains may be sustained up to 3 years. These findings are consistent with, but extend, previous literature that only focused on QoL and functional outcomes in the 6-18 month period following the onset of BD I (Michalak et al., 2013; Oldis et al., 2016; Kauer-Sant'Anna et al., 2009).

Although only observational data were presented in this study, the findings have important implications for individuals living with BD I and for further research. Firstly, the improvement and subsequent stabilisation seen in QoL and functional outcomes in this study may offer hope to individuals who have recently been diagnosed with BD I and for those who are treating these individuals. Such observations suggest that QoL and functional deficits do not have to be permanent. Secondly, these findings support the notion that early intervention in BD I may change the course of illness progression and its potential impact on QoL and functionality (Murray et al., 2017; Vieta et al., 2011).

This study found that year 3 PQoL showed significant correlations with the total number of depressive episodes between baseline and year 3, as well as baseline, year 1, and year 3 HDRS depressive symptomology. However, the regressions analysis found that only depressive
symptomology at baseline and year 3 were found to be significant predictors of year-3 PQoL in the presence of the other variables. Both PQoL and MSIF difference scores did not show significant or sizeable (r<.30) correlations with any of the variables in this study. The lack of correlations seen with the PQoL and MSIF difference score variable could be due to smaller variability in the scores. This may be the case more so for the PQoL difference score as it had a smaller range, notably between -0.41 and 2.10 (mean = .52, standard deviation = .51), whereas the MSIF difference score ranged between -1.00 and 6.00 (mean of .52, standard deviation = 2.21. However, it is important to note that reliability was found to be high for the PQoL difference score. With respect to the MSIF difference score, there may have been some challenges arising from potentially lower reliability for this score, which could not be examined due to the nature of the tool and available data.

However, the findings from this study reassert that QoL outcomes can suffer as a result of the severity of ongoing depressive symptomology even 3 years following the FEM. Again, these findings are consistent with previous research (Amini & Sharifi, 2012; Cotrena et al., 2016; Michalak et al., 2013; Morton et al., 2017; Oldis et al., 2016; Vojta et al., 2001; Zhang et al., 2006) which have shown the severity of ongoing depressive symptomology to influence QoL, even after some time has passed. Furthermore, this is the first study to find that depressive symptomology experienced immediately following the onset of illness in BD I can negatively influence QoL outcomes 3 years later. Identifying such predictors of QoL in the early stages of BD I may be helpful in optimizing good mental health in this condition. This information may bring more awareness to the influence of early phase depression and, as a result, may fuel further research to explore meaningful ways to remediate its effects. The findings from this study further
reinforce the notion that depression needs to be aggressively treated in the earlier stages of the illness (Michalak et al., 2013, Oldis et al., 2016).

**Implications for counselling psychology**

This study proposes some implications for the role of psychotherapy for BD I. As psychotherapies have been found to only find some success in BD I (Gudiano et al., 2008), it may be important to go back to the drawing board to continue to find the strengths within these therapies. Many of the individuals with BD I in clinical settings receive effective guideline-driven treatment which has been shown to improve clinical prognosis (Vieta et al., 2011; Yatham et al., 2005; 2009). However, the challenges experienced with QoL can be quite subjective. The optimisation of psychotherapies with a focus on enhancing QoL and functional well-being would be beneficial. For example, it may be helpful to augment medical care with psychosocial therapies to assist individuals in developing skills to manage depressive symptomology in the early stages of BD I.

Counselling and psychotherapy may be able to provide individuals with BD I with a subjective workspace to empower themselves with skills to cope with the difficult subjective experience of reduced wellbeing. Individuals with BD I may benefit from skills training for the recognition and management of depressive symptoms in the very early stages of the illness. It may also be helpful to assist individuals process their understanding of BD I and what it means for their personal identity. This may give individuals the opportunity to enhance their self-confidence and clarify their beliefs for the future.

Although this study did not find a relationship between everyday functioning (as measured by the MSIF) and early phase depression variables, it remains unclear how individuals with BD I may subjectively experience functional changes, if any. Further research exploring the
subjective experience of functionality and how it may be influenced by early phase depression in the FEM BD I population is needed. Interestingly, research has shown that psychoeducation can significantly improve functioning in individuals with BD (Kurdal, Tanriverdi & Savaş, 2014). In particular, Kurdal et al., (2014) noted that psychoeducation was more effective at improving functioning than medical treatment alone.

It has been suggested that QoL may moderate symptoms of BD I (Ishak et al., 2012; Morton et al., 2017; Murray & Michalak, 2012) and so psychotherapeutic services may need to focus on this goal. This, in turn, may impact clinical prognosis for individuals with BD I. The traditional clinical model of treatment has prevailed but it falls short of fully capturing the complex relationship between the clinical features of BD I and the subjective nature of QoL. Perhaps, treatment models with components of both clinical and subjective approaches may be able optimise wellbeing in BD I.

Study strengths

Some of the key strengths of this study come from the type and nature of the data that were collected. Previous research has called for a longitudinal examination of QoL defined as life satisfaction (Morton et al., 2017), which this study was able to offer. In particular, a naturalistic longitudinal data set was used to explore this gap in the literature. This offered a unique opportunity to explore changes across time. Furthermore, such data may be able to model real-world applicable findings for FEM populations in clinical settings.

The data for this study were derived from a very specific subsection (i.e., FEM) of the BD I population, which allowed for the examination of well-being from the onset of the illness. This, in turn, permitted a closer examination of the factors that may influence prognosis and the possibility to manage these earlier in the illness. As the sample population was recruited from a
wide range of naturalistic clinical settings, the results from this study may generalise across other Canadian FEM populations. Caution should be exercised when generalising these results, however, as the participant sample in this study was found to have an above average level of education (Michalak et al., 2013) and were volunteer participants. It is important to note that Michalak et al., (2013) were able to retain a higher number of FEM participants over the 18 months of their study. As this study was also longitudinal in design, retention of participants became increasingly difficult beyond the first 18 months. This was mainly due to the fact that the study sample was composed of adolescents and young adults who were fairly geographically mobile. Many moved away for further education and for occupational reasons.

**Study limitations**

There are some limitations to this study that must be considered. From a research perspective, the observational data from this study provides some preliminary evidence that could be further explored. However, it is important to note that the collection of observational data also comes with its limitations. It is not possible to make inferences of causality from observational data and such data are subject to the influence of a range of external factors. Although, it can be argued that there appears to be a temporal order between the IVs and DVs, the data for this study were not collected in a controlled experimental design. It is difficult to determine if depression experienced following the FEM came before the reduced QoL or resulted from it. Perhaps, another extraneous variable such as financial difficulty may explain why QoL may have been lower prior to the onset of illness. Furthermore, it was not possible to examine QoL prior to the onset of illness in this study. This makes it difficult to determine the direction of causality unless a non-spurious relationship exists between the IV and DV.
Despite some of the challenges with the data, it is important to note that this study explored QoL in a naturalistic setting which can be considered to be a key strength. The participants of this study received medical care as usual in an outpatient setting and did not undergo any experimental control. Such a research design allows for some real-world applicability of this data. Furthermore, the current state of research exploring QoL and functional outcomes in the FEM population is limited. For the first time in the QoL field of study, the findings of this study offer a longitudinal (3 years) insight into QoL and how it may be related to early phase depression that is experienced following the FEM in BD I. These data, although limited in some ways, may attract more interest to this crucial topic inviting further longitudinal research with the FEM population.

One of the challenges for this study comes from the fact that participants were recruited into the study over a 12 year period of time, following the onset of their FEM. Pharmacological and psychosocial treatments for BD, as well the social context around the acceptance of mental illness have undergone some changes over this period of time. Although it can be argued that the lifetime prevalence of BD has remained somewhat stable, the potential impact of pharmacological, psychotherapeutic, and social changes on QoL and functional outcomes cannot be ignored. It is also important to note that some individuals in this study had opted out of receiving pharmacological or psychosocial treatments offered to them at different time points throughout the study period; thus, the sample is not strictly one that has consistently received treatment and may be somewhat more representative of the larger FEM population.

It is possible that the MSIF may not have been sensitive enough to pick up on subtle changes for this participant sample. Also, this tool only examined functionality in three domains (work, school and household) and may have omitted picking up important information in other
domains of life. Future research should consider using additional measures of objective and subjective functionality to discern whether the findings from this study are true to the FEM population in clinical settings.

Depressive symptoms that were experienced immediately following the onset of illness (i.e., baseline) and severity of ongoing depressive symptomology (at year 3) were found to predict QoL at 3 years following the onset of illness in BD I in this study. It is possible that other factors may also be contributing to this relationship. For example, Michalak et al. (2013) have noted that several psychosocial factors such as social support or life events could also be predictive of QoL. The data for such factors have not been collected as part of the clinical program from which the data for this study were derived and so could not be examined. However, the relationship between depression and QoL found in this study invites quantitative and qualitative studies to explore this further.

One of the key challenges of this study was related to the exploration of recurrent depression in a sample of participants who were receiving some form of guideline-driven treatment. Participants in this study received frequent monitoring of their symptoms, psychoeducation, support from mental health staff and optional medical treatment. As a result, it is quite possible that this sample of participants may have experienced fewer relapses as compared with the general population of individuals with BD I. This renders the applicability of these findings as somewhat limited. At the same time, it can be argued that participants in this study are receiving medical follow-up in a naturalistic setting, making the findings more generalizable. It is also important to note that it can be difficult to examine longitudinal QoL and functionality in the early stages of BD I without the involvement of a medically monitored
participant sample. From a clinical and ethical perspective, experimentally manipulating access to medical treatment to explore longitudinal outcomes in an FEM population is inappropriate.

Mania is a key feature of BD I but it was not explored in this study as the participants had not experienced much relapse into manic mood and thus the sample size would have been a problem. In general, the sample size was a challenge to this study and it limited the options for statistical analysis. Only the data for individuals who had attended all four time points in the study were included in the analysis. It can be argued that this approach may limit the generalisability of the data as it may not have been fully representative of the participants who were not included in the study. At the same time, it is important to note that, despite challenges to retention in longitudinal research, this study was able to collect valuable data in a very selective FEM BD I sample of participants receiving consistent medical follow-up.

Implications for future research

This study focused on overall perceived QoL which collectively considers various aspects of life such as the home, work, and social domains of QoL. Domain level analysis for QoL may have been able to provide more details on the experiences of individuals with BD I. In particular, the use of a BD specific measure may have been more appropriate. Michalak and Murray (2010) developed the Quality of Life in Bipolar Disorder scale, which measures specific domains known to be impacted in BD (e.g., sleep, finances). It was not possible to use this scale as much of the data for this study had been collected prior to the development of it. In line with this, the addition of a subjective measure of functionality may have provided additional information for functional outcomes. Further research is needed to explore longitudinal QoL at the domain level as well as the subjective sense of functionality in FEM samples.
Finally, this study examined only three facets of depression (the number of prodromal and recurrent episodes, and severity of ongoing symptomology). The length of depressive episodes could also have been explored as this has previously been found to be a predictor of lower QoL and functionality (Chacko et al. 2011). It was not possible to collect information on the length of prodromal episodes in this study as these data were retroactively collected. The potential impact of comorbidities, such as anxiety or substance use, should be included in future research as they have also been found to be predictive of QoL (Michalak et al., 2013). Finally, because mania is a key characteristic of BD I, future research may be able to explore the longitudinal relationship between QoL, functionality and mania.

**Concluding Statement**

This longitudinal study is the first to find QoL and everyday functionality to improve and remain stable in the first 3 years of illness in an FEM sample of individuals with BD I. It further identified depressive symptoms that were experienced immediately following the onset of illness and severity of ongoing depressive symptomology (at year 3) to predict QoL at 3 years following the FEM. The findings from this study reassert the need to aggressively treat depression in BD I. Furthermore, such findings may encourage individuals to remain medically and clinically compliant with the treatment offered to them to prevent relapses of depression which may have long term consequences for QoL in at least, the first 3 years following the FEM in BD I. Finally, this study supports an expansion of counselling and psychoeducation services to individuals with BD I to help them manage the condition, prevent relapse and improve QoL.
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