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Examining the Relationship between Duration of Untreated Psychosis and Self-Perceived Recovery in Clients of an Early Intervention Program in London, Canada: A 10-Year Prospective Cohort Study

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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Abstract

Background: The duration of untreated psychosis (DUP) is negatively associated with objective recovery among people with first-episode psychosis (FEP). However, the association between DUP and subjective recovery is not known. **Objectives:** To investigate whether DUP is statistically associated with self-perceived recovery scores (subjective recovery) and occupational activity (objective recovery) 10-years after the first episode of psychosis. **Methods:** A cohort of 65 clients from an early intervention program completed a battery of outcome measures 10-years following initial treatment for FEP (March 1997 to February 2002). Multiple linear or logistic regression analyses were used to estimate the association between DUP and both measures of recovery, adjusting for potential confounding factors. **Results:** We did not find a statistically significant association between DUP and either weeks of occupational activity (OR = 1.26, 95%CI: 0.81 to 1.95) or self-perceived recovery score ($\beta = -0.73$, 95%CI: -2.42 to 0.97), adjusting for 10-year confounding factors. However, we found a negative association between negative symptoms at 10-year follow-up and occupational activity (OR = 0.69, 95%CI: 0.57 to 0.84), as well a positive association between perceived social support score at 10-year follow-up and self-perceived recovery score ($\beta = 0.94$, 95%CI: 0.45 to 1.42), adjusting for 10-year confounding factors. **Conclusions:** Our findings suggest that factors other than DUP have an impact on objective and subjective recovery at 10-year follow-up. Further research examining factors associated with self-perceived recovery after a first episode of psychosis is warranted.

Keywords

First-Episode Psychosis, Duration of Untreated Psychosis, Recovery.

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List of Abbreviations

CI = Confidence Interval

CORS = Course of Onset or Relapse Schedule

DAST-20 = Drug Abuse Screening Test, 20-items

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DUI = Duration of Untreated Illness

DUP = Duration of Untreated Psychosis

ICC = Intraclass Correlation Coefficient

LHSC = London Health Sciences Centre

MAR = Missing At Random

MARS = Maryland Assessment of Recovery in People with Serious Mental Illness Scale

MI = Multiple Imputation

MNAR = Missing Not At Random

OR = Odds Ratio

PAS = Premorbid Adjustment Scale

PEPP = Prevention and Early Intervention Program for Psychoses

SAMHSA = Substance Abuse Mental Health Services Administration

SANS = Scale for the Assessment of Negative Symptoms

SAPS = Scale for the Assessment of Positive Symptoms

SCID-CV = Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version

SD = Standard Deviation

VIF = Variance Inflation Factor

Chapter 1

1 Background & Introduction

In this chapter, the overall purpose of this thesis is provided in Section 1.1, followed by background information about psychosis, first-episode psychosis, and early intervention programs in Sections 1.2, 1.3, and 1.4, respectively. Thereafter in Section 1.5, the rationale for this thesis is provided, followed by a brief description of our thesis objectives in Section 1.6. Next in Section 1.7, the data source is described. Subsequently in Section 1.8, the contributions to this thesis are outlined. Lastly, an overview of the chapters in this manuscript is provided in Section 1.9.

1.1 Overall Purpose

The overall purpose of this thesis is to investigate whether the length of time psychosis is left untreated is associated with a person's judgement of his or her recovery from first-episode psychosis at 10-year follow-up.

1.2 Background Information: Psychosis

1.2.1 Psychosis Overview

Psychosis is a syndrome or a set of symptoms; it is not a mental health diagnosis or disease (Keks & Blashki, 2006). A range of symptoms characterize psychosis, and these symptoms are typically categorized as either “positive” (present or added on) or “negative” (absent or reduced), and are often referred to as “psychotic symptoms” or “symptoms of psychosis” (Jones, Hacker, Cormac, Meaden, & Irving, 2012; Minas et al., 1992). Examples of positive symptoms include delusions, which are false, unjustified beliefs and judgments, and hallucinations which involves seeing, hearing, tasting, or smelling something that is not actually present (American Psychiatric Association, 2013). Examples of negative symptoms include reduction in speech and difficulty in thinking (American Psychiatric Association, 2013). In general, these symptoms change a person's state of mind in which he or she is unable to differentiate what is real (American Psychiatric Association, 2013), and the person is often described as being “out of touch

with reality” or having a “distorted perception of reality.” The number, type, and severity of psychotic symptoms can vary from person to person depending on the underlying cause of psychosis.

There are a number of potential causes of psychosis. These include, but are not limited to alcohol and drug (e.g., cocaine) use or withdrawal, brain injury, other health conditions (e.g., epilepsy), intense stress, or an underlying mental illness (American Psychiatric Association, 2013). In this thesis, psychosis as a consequence of a mental illness will be considered, which may occur in the context of several different psychiatric disorders, including schizophrenia, delusional disorder, bipolar disorder, or depression with psychotic features. These are typically classified as either non-affective (e.g., schizophrenia) versus affective (e.g., bipolar disorder) (e.g., ElTayeban, ElGamal, Roshdy, & Al-Khadary, 2014; Salvatore et al., 2007) or as schizophrenia-spectrum versus other psychotic disorder (American Psychiatric Association, 2013).

It has been estimated that approximately 3% of the general population will experience psychosis at some point over the course of their lifetime (Perala et al., 2007). Typically, people experience their first episode of psychosis in their late teens and early twenties (Kessler et al., 2007). During this period of late adolescence and early adulthood, personal and professional development and growth occurs (Harris et al., 2005; Mackrell & Lavender, 2004), which can potentially be disrupted by the onset of psychosis, consequently having a negative impact on the person and his or her family (Reed, 2008).

Fortunately, psychosis can be treated, with earlier treatment resulting in better outcomes (Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). In addition, some people will never experience psychosis (i.e., psychotic episode) again and do recover, whereas others suffer a relapse and may or may not recover (Robinson et al., 1999).

1.2.2 Phases of Psychosis

An episode of psychosis typically occurs in three phases, beginning with the *prodrome* (or *prodromal*) phase, followed by the *acute* phase, and ending with the *recovery* phase (Figure 1.1). The duration of each phase varies from person to person. During the

prodrome, the person experiences gradual non-specific changes in thoughts, feelings, and behaviours such as sleep disturbance, depressed mood, irritability, reduced concentration, drive, and motivation (Yung & McGorry, 1996). During the *acute* phase, a person experiences hallucinations, delusions, or other symptoms of psychosis for which treatment should be sought immediately to prevent any further interference in the different domains of a person's life. During the final phase, the *recovery* phase, symptoms of psychosis alleviate or disappear completely, allowing the person to better cope with daily life and resume roles or activities that he or she was engaged in prior to the psychotic episode (Davidson, O'Connell, Tondara, Lawless, & Evans, 2005).

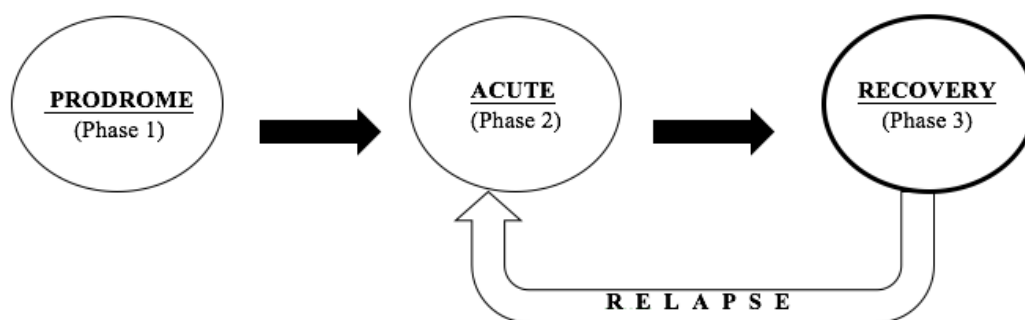


Figure 1.1: Phases of Psychosis.

Importantly, the last phase highlights that recovery after a psychotic episode is possible; however, it is highly variable (de Koning et al., 2009; Marshall & Rathbone, 2011). While some may recover after a psychotic episode, others do not. Even among those that do recover, some may suffer one or more relapses, and may or may not recover again.

It is also important to highlight that the elimination or reduction of psychotic symptoms does not directly equate with a person being in the recovery phase. Although remission of symptoms is seen as a sign of recovery for some, for others it is either not acknowledged as a sign of recovery or it is one of many signs of recovery that have yet to be attained such as regaining previous social functions, cognitive functions, or trust in others (Eisenstadt, Monteiro, Diniz, & Chaves, 2012; Lam et al., 2010; Windell, Norman, & Malla, 2012).

1.3 Background Information: First-Episode Psychosis

1.3.1 Definition

First-episode psychosis has garnered increased research and clinical interest over the past two decades, although significant heterogeneity exists in how it is operationalized. Typically, it is operationalized based on one of the following three definitional categories: (i) the first treatment contact for a psychotic disorder; (ii) antipsychotic medication use for a specified length of time; (iii) the duration of psychotic symptoms (Breitborde, Srihari, & Woods, 2009).

Regardless of the definitional category that is used, *first-episode psychosis*, in general, refers to a person who is in the early stage of a psychotic illness and who has received minimal or no prior treatment (Breitborde, Srihari, & Woods, 2009).

1.3.2 Incidence

A recent study conducted by Anderson and colleagues (2012) estimated the age and gender standardized annual incidence of first-episode schizophrenia-spectrum psychosis in Quebec among people aged 14 to 25 years to be 82.9 per 100 000 for males and 32.2 per 100 000 for females. A 3-year period (2004-2006) was used to identify people with first-episode schizophrenia (Anderson, Fuhrer, Abrahamowicz, & Malla, 2012). Approximately 65% of people with first-episode psychosis present with schizophrenia-spectrum, which includes diagnoses such as schizophrenia, schizophreniform disorder, schizoaffective disorder, or delusional disorder (Kirkbridge et al., 2006; Proctor, Mitford, & Praxton, 2004; Reay, Mitford, McCabe, Paxton, & Turkington, 2010).

1.4 Background Information: Early Intervention Programs

Over the past 20 years, an increasing number of specialized early intervention programs have been developed and implemented in countries around the world, including Canada (Edwards & McGorry, 2002; McGorry, Killackey, & Yung, 2008), which has at least one such program in each of the 10 provinces, with more than 60 programs across the province of Ontario. The proliferation of these programs may in part be attributed to the growing interest in improving outcomes through early detection of positive symptoms

and the use of pharmacological, psychosocial, and/or vocational interventions targeting the first two to five years after the onset of a first episode of psychosis, a critical period (Birchwood, Todd, & Jackson, 1998; McGorry et al., 2007).

During the initial critical period, trajectories of outcomes are generally defined (Harrison et al., 2001) and rates of relapse are relatively high (i.e., approximately 80%) (Bergé et al., 2015; Robinson et al., 1999). It is therefore not surprising that two of the primary objectives of these programs are to alter the negative trajectory of outcomes by reducing the duration of untreated psychosis through early detection and prompt initiation of treatment (Singh & Fisher, 2005), and by preventing relapse (Alvarez-Jimenez et al., 2012; Robinson et al., 1999; Schooler et al., 2005).

1.4.1 Shorten the Duration of Untreated Psychosis

A long duration of untreated psychosis is associated with a range of poor outcomes (Norman & Malla, 2001; Norman et al., 2005; Marshall et al., 2005; Perkins et al., 2005); however, it is one of the few modifiable prognostic factors of poor outcome (Chang et al., 2012b; Singh & Fisher, 2005). Therefore, the primary aim of specialized early intervention programs is to improve outcomes in people with a first episode of psychosis by shortening the duration of untreated psychosis through early detection and treatment (Chang et al., 2012b; Singh & Fisher, 2005).

There does appear to be some uncertainty as to whether the effects of shortening the duration of untreated psychosis are sustained over the long-term, which may in part be attributed to the limited number of prospective outcome studies with follow-up periods of 10-years or more. There also appears to be some emerging interest in the association between the duration of untreated illness and poor outcome, which is the length of time between the onset of any earlier non-psychotic signs of illness and initiation of treatment (Crumlish et al., 2009), which has been found to be more consistently associated with poor outcome than the duration of untreated psychosis (e.g., Crumlish et al., 2009; Dell’Osso, Glick, Baldwin, & Altamura, 2012; Harris et al., 2005; Keshavan et al., 2003; Norman et al., 2012). As a result, many specialized early intervention programs are also

now targeting people believed to be in the prodromal phase of psychosis, or at an ultra-high risk for developing a psychotic disorder (de Koning et al., 2009).

1.4.2 Relapse Prevention

Vulnerability to relapse is high during the first 5-years following initial onset (Bergé et al., 2015), with most people experiencing a relapse at least once during the two to five-year period (Gitlin et al., 2001; Robinson et al., 1999). Moreover, the cumulative incidence is 80% at 5-year follow-up (Robinson et al., 1999).

Prevention of relapse is important because experiencing a relapse can potentially result in disengagement from meaningful activities (e.g., school or work) and from family or friends, which can adversely impact a person's psychosocial and vocational development (Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005), and may impede recovery. Clinically, prevention of relapse is important because a future response to treatment such as antipsychotic medication may potentially be reduced after each relapse (Tibbo, Malla, Manchanda, Williams, & Joobar, 2014), and progressive gray matter loss may occur based on the durations of relapses (Andreasen, Liu, Ziebell, Vora, & Ho, 2013).

Targeting modifiable risk factors (e.g., duration of untreated psychosis) has been suggested to contribute to the relatively lower relapse rates observed among people treated and followed-up in an early intervention program for psychosis, compared to those in routine care (Malla, Norman, Bechard-Evanc, Schmitz, Manchanda, & Cassidy, 2008). Despite the lower rates (i.e., 20% to 30% during 2-years), risk of relapse continues to be a barrier to recovery (Malla et al., 2008; Tibbo, Malla, Manchanda, Williams, & Joobar, 2014). Moreover, identification of factors associated with relapse has been suggested to facilitate the development of effective prevention strategies (Hui et al., 2013).

1.5 Study Rationale

With emerging clinical and research interest in the assessment of recovery as an outcome among people with first-episode psychosis, identification of factors that may impede recovery is important to promote, as well as sustain recovery. Given that the duration of

untreated psychosis has been identified as one of the few modifiable risk factors of poor outcome in people with first-episode psychosis, its relationship to recovery is of interest. However, the existing literature on the relationship between duration of untreated psychosis and recovery has focused on one dimension of recovery, objective recovery, and this relationship has been assessed over a short period of time (< 10-years). To address the current gaps in the literature, we investigated whether the duration of untreated psychosis is associated with the other dimension of recovery, subjective recovery, and we assessed this relationship over a 10-year follow-up period.

1.6 Thesis Objectives

Using data from 65 clients of an early intervention program who received initial treatment for a first episode of psychosis at least 10-years ago, the four objectives of this thesis were:

1. To examine the association between objective and subjective measures of recovery at 10-year follow-up.
2. To investigate whether the duration of untreated psychosis is associated with objective recovery, adjusting for potential confounding variables.
3. To examine whether the duration of untreated psychosis is associated with subjective recovery, adjusting for potential confounding variables.
4. To investigate whether relapse mediates the relationship between the duration of untreated psychosis and subjective recovery, adjusting for potential confounding variables.

A detailed description of each of these four objectives and hypotheses will be provided in Chapter 2, with reference to our conceptual framework.

1.7 Data Source: PEPP Data Set

The data used in this thesis came from a prospective cohort study (i.e., source study) titled, “*Assessment of 10 Year Outcomes for Clients of the Prevention and Early Intervention Program for Psychoses (PEPP)*.” The purpose of this study was to assess outcomes of clients 10-years following initial treatment for a first episode of psychosis at

PEPP (London, Canada). Primary outcomes assessed were levels of positive and negative symptoms, level of functioning, and self-perceived recovery. Secondary outcomes assessed were dysfunctional attitudes, neurocognition, self-stigma, and self-efficacy.

The five main objectives of this study included:

1. Compare 10-year outcomes with those at 5-year follow-up.
2. Identify early predictors of 10-year outcomes.
3. Examine outcomes not previously assessed in earlier follow-up assessments with the same cohort of clients.
4. Assess the degree of correspondence between symptomatic, functional, and subjective measures of outcome.
5. Examine in greater detail the nature of negative symptoms at 10-years, and examine the correlates/predictors of variation in these symptoms.

Objectives 1 to 3 of this thesis aligned with two of the five main objectives of the source study, specifically objectives 2 and 4.

1.8 Contributions to Current Study

My contribution to the current study began with selecting our exposure and outcome variables of interest in collaboration with Dr. Kelly Anderson, my thesis supervisor, and Dr. Ross Norman, the primary investigator of the source study. I then formulated the thesis objectives and corresponding hypotheses in collaboration with Drs. Anderson and Norman. Thereafter, I proposed a statistical analysis plan for each of the objectives with consultation from Dr. Anderson. The statistical analysis plan included adjustment of potential confounding variables in our preplanned statistical analyses, which were identified as such from a conceptual framework that Dr. Anderson and I created, based on available data. The objectives and statistical analysis plan were reviewed by Dr. Norman to ensure that we did not miss anything from a clinical perspective. Dr. Neil Klar, a member of my thesis supervisory committee, also reviewed the objectives and statistical analysis plan to check for feasibility and to ensure that we did not miss anything from a statistical perspective. Upon approval from Drs. Norman and Klar, I submitted a request for access to a subset of the variables. After I received the data set from Dr. Norman, I ‘cleaned’ the data (Chapter 3), examined the amount of missing data using several

approaches (Chapter 3), selected a method to handle missing data (i.e., multiple imputation) with consultation from Drs. Anderson and Klar, and then assessed for multicollinearity. Thereafter, I conducted all analyses and interpreted findings with consultation from Dr. Anderson. Lastly, my contribution ended with the writing of this manuscript. The critical revision of this manuscript for content, structure, writing clarity and quality was an on-going process that involved Drs. Anderson and Klar.

1.9 Overview of Thesis Chapters

The current study will be described in greater detail in the next four chapters:

Chapter 2 provides a detailed description of the duration of untreated psychosis, our exposure variable of interest, and recovery (i.e., objective and subjective recovery), our outcome variable of interest. It also summarizes the existing literature assessing the association between these variables in people who were initially treated at an early intervention program for either a first episode of psychosis or a first episode of schizophrenia.

Chapter 3 describes the study procedures of the source study, along with the variables and measures included in the data set. It then provides an overview of the multiple imputation method used to handle missing data, and it outlines our statistical analysis plan comprised of a point biserial correlation, a multiple logistic regression analysis, a multiple linear regression analysis, and a mediation analysis for objectives 1, 2, 3, and 4, respectively.

Chapter 4 presents findings from the main analyses that included data from a cohort of 65 clients of PEPP, which were analyzed using Stata (version 14). It then presents findings from the two sets of sensitivity analyses that involved the use of complete data, as well as the use of imputed data with the duration of untreated illness as the exposure variable in place of the duration of untreated psychosis.

Chapter 5 discusses key findings, including the following statistically significant findings: (i) duration of untreated psychosis is not associated with both measures of recovery, whereas the duration of untreated psychosis is associated with both measures of

recovery; (ii) perceived social support is positively associated with subjective recovery; (ii) negative symptoms are negatively associated with objective recovery. It then highlights that in a clinical context, a more comprehensive overview of a person's recovery after a first episode of psychosis is attained by assessing different dimensions of recovery, and factors other than the duration of untreated psychosis need to be targeted to enhance a person's subjective and objective recovery from a first episode of psychosis.

Chapter 2

2 Literature Review

In this chapter, a detailed description of the duration of untreated psychosis and recovery is provided in Sections 2.1 and 2.2, respectively. In Section 2.3, the existing literature on the association between the duration of untreated psychosis and recovery is summarized. In Section 2.4, gaps in the existing literature are discussed. Thereafter, in Section 2.5, our conceptual framework is presented. Lastly, a detailed description of the thesis objectives and hypotheses with reference to the conceptual framework is provided in Section 2.6.

2.1 Duration of Untreated Psychosis

2.1.1 Definition, Components, & Measurement

Definition

The duration of untreated psychosis (DUP) or treatment delay is generally defined as the time interval ($t_1 \leq \text{DUP} \leq t_2$) between the onset of psychotic symptoms (e.g., positive symptoms such as hallucinations and delusions; t_1) and the initiation of adequate treatment (e.g., antipsychotic medication for a period of 1 month; t_2) (Compton et al., 2007; Ienciu, Romoşan, Bredicean, & Romoşan, 2010; Malla, Norman, Scholten, & Manchanda, 2005; McGlashan, 1999; Tang et al., 2014). Essentially, the duration of untreated psychosis measures ‘delay in treatment’ for psychosis (Malla, Norman, Scholten, & Manchanda, 2005). Thus, the terms ‘duration of untreated psychosis’ and ‘treatment delay’ are often used interchangeably. A list of other synonyms is provided in Appendix A.

Components

The duration of untreated psychosis can be conceptualized as being comprised of three temporally separate components: 1) A ***help-seeking*** component (i.e., Help-Seeking Delay), defined as the time interval between the onset of psychotic symptoms and first contact with health services (e.g., general practitioner); 2) A ***referral*** component (i.e., Referral Delay), defined as the time interval between first contact with health services

and referral to mental health care services; and 3) A *mental health care services* component (i.e., Delay in Mental Health Care Service), defined as the time interval between referral to mental health care services and initiation of adequate treatment (Figure 2.1) (Boonstra, Sterk, Wunderink, Sytma, De Haan, & Wiersma, 2012; Brunet, K., Birchwood, M., Lester, H., & Thornhill, 2007). A recent review of the multifaceted determinants of the duration of untreated psychosis suggests that patient-, illness-, and family level factors are more likely to influence the help-seeking component of the duration of untreated psychosis, whereas system-level factors are more likely to influence the referral component of the duration of untreated psychosis (Compton & Broussard, 2011). Some of these factors are modifiable, whereas others are not. Factors that influence and/or are more likely to influence the mental health care services component of the duration of untreated psychosis have not readily been investigated. However, Boonstra and colleagues (2012) reported that delay in mental health care service was significantly longer for people with first-episode psychosis who not only already received treatment for other diagnoses from a mental health care service, but also for those living in rural areas compared to those living in urban areas.

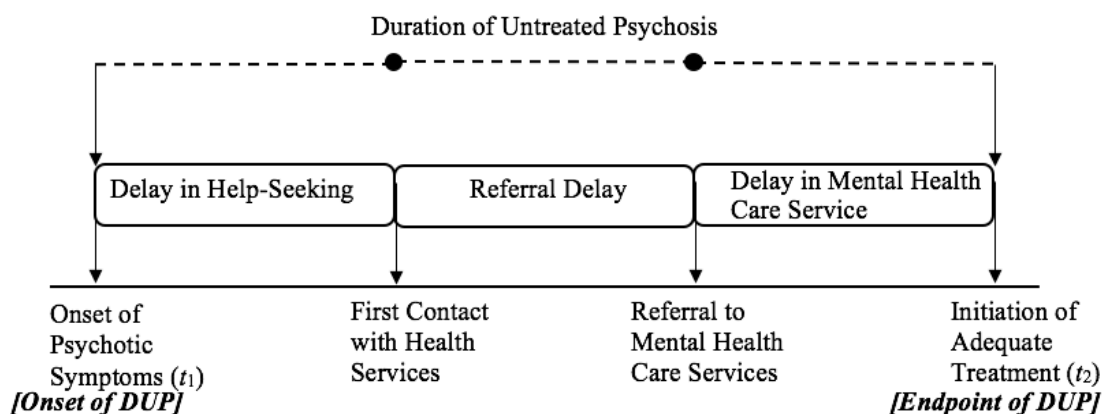


Figure 2.1: Components of DUP. Note: This figure is modified from French, Smith, Shiers, Reed, & Rayne (2010). DUP = Duration of Untreated Psychosis; t_1 = time-point one, which corresponds to the *onset* of DUP; t_2 = time-point two, which corresponds to the *endpoint* of DUP.

Measurement

Measurement of the duration of untreated psychosis ($t_1 \leq \text{DUP} \leq t_2$) involves estimating the length of time (e.g., weeks) that has elapsed between the *onset* of the duration of untreated psychosis (t_1) and the *endpoint* of the duration of untreated psychosis (t_2) (Compton, 2007; Norman & Malla, 2001) (Figure 2.1). The duration of untreated psychosis estimates obtained will vary depending on how the *onset* (t_1) and the *endpoint* (t_2) are operationalized (Compton, 2007; Norman & Malla, 2001). Variation in the operationalization of the *onset* and *endpoint* of the duration of untreated psychosis is apparent in studies included in Table 2.1. For instance, operationalization of the *onset* of the duration of untreated psychosis included the onset of first positive psychotic symptoms or psychosis onset (Evensen et al., 2012; Friis et al., 2015). Operationalization of the *endpoint* of the duration of untreated psychosis included initiation of antipsychotic medication or hospitalization (Compton, 2007; Friis et al., 2015; Jaracz et al., 2015). Variation in the operationalization of the onset and endpoint of the duration of untreated psychosis makes comparison across studies difficult.

Definition of DUP in this Thesis

We defined the duration of untreated psychosis as the length of time in weeks between the date of onset of positive psychotic symptoms (e.g., hallucination) to the date of initiation of adequate treatment. Adequate treatment referred to treatment with antipsychotic medication for 1-month (or until symptoms have resolved) or psychosocial treatment (i.e., assertive case management) for 1-month. These dates were extracted from select items from the Course of Onset or Relapse Schedule (CORS; Norman & Malla, 2002).

2.1.2 Influence of DUP on Outcomes

There have been two systematic reviews of the literature specifically investigating the link between the duration of untreated psychosis and outcome in people with either first-episode psychosis or first-episode schizophrenia (Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). With the exception of one study, both reviews consisted of

studies with follow-up periods of two-years or less. The conclusions of each review were consistent: A *longer* duration of untreated psychosis is associated with *poorer* short-term outcomes (Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). It remains unclear whether the duration of untreated psychosis is associated with long-term (≥ 10 -years) outcomes, attributed in part to the limited number of empirical studies with follow-up periods of 10-years or more.

We conducted a literature search of studies examining the association between the duration of untreated psychosis and long-term (≥ 10 -years) outcomes in people with first-episode psychosis or first-episode schizophrenia. Table 2.1 summarizes study characteristics and main findings of studies identified by our literature search.

All studies ($n = 12$) were conducted in countries other than Canada and were published between 2005 and 2016. Of all the studies, half of the studies ($n = 6$) had a length of follow-up of 10-years (Austin et al., 2015; Evensen et al., 2012; Friis et al., 2016; Rund et al., 2015; Shrivastava et al., 2010; White et al., 2009), while a majority of the remaining studies ($n = 4$) had a length of follow-up of more than 10-years (Hill et al., 2012; Ichinose et al., 2010; Röpcke & Eggers, 2005; Tang et al., 2014), and the remaining few studies ($n = 2$) had lengths of follow-up of both 10 and more than 10-years (Jaracz et al., 2015; Kinoshita et al., 2005). The rate of follow-up ranged from 29% (Ichinose et al., 2010) to 87% (Rund et al., 2015), and the sample size ranged from 31 (Ichinose et al., 2010) to 304 (Austin et al., 2015). The mean duration of untreated psychosis ranged from 6 to 88 weeks (Evensen et al., 2012; Hill et al., 2012).

Table 2.1: Summary of Studies ($n = 12$) Examining the Relationship between DUP and Long-Term (≥ 10 -years) Outcomes in People with First-Episode Psychosis or First-Episode Schizophrenia.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Rate of Follow-up n/total (%)	Measurement of DUP		DUP Categorization	Mean DUP	Outcome(s)/ Outcome Measures	Relationship between DUP & Outcome(s) [Yes/No]
						Onset	Endpoint				
Kinoshita et al. (2005)	Japan	Psychiatric Care Organizations (Private mental hospitals, Prefectural mental hospital, Private Psychiatry Clinics, Public General Hospitals, and Health Centers)	10 & 15 years	52 Patients with First-Episode Schizophrenia	52/97 (54%)	Onset of illness	Initial visit at a medical facility		9.9 months	Good Outcome = Complete remission with or without relapse Poor Outcome = Incomplete remission with or without relapse or continuous psychotic illness	A long DUP was significantly associated with poor outcome at 10-year follow-up, but not at 15-year follow-up.
Röpcke & Eggers (2005)	Germany	Outpatient Clinic for Child & Adolescent Psychiatry	15.4 years+	39 Patients with a diagnosis of Early Onset Schizophrenia	39/55 (71%)	Onset of first psychotic symptoms	First antipsychotic treatment		Not provided	<u>Psychopathological and Social Outcome</u> Clinical Global Impression (CGI), Psychosocial functioning (Global Assessment of Social Function, Negative Symptoms, Positive Symptoms, and General Psychopathology (PANSS))	DUP was not significantly associated with any of the outcomes at follow-up.
White et al. (2009)	United Kingdom	National Health Service Psychiatric Units	10 years	69 Patients with First-Episode Psychosis	69/109 (63%)	Onset of first positive psychotic symptoms	Index admission		24.68 weeks	Functional Outcome, Service Contact/ Dependency, & Outcome Symptom Burden	DUP was independently associated with poor outcome symptom burden at 10-year follow-up. [Yes]

Note: DUP = Duration of Untreated Psychosis; + = Mean length of follow-up (10.2-21.2 years); n = count; PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impression; & = and; % = Percentage.

(Continued)

Table 2.1: Summary of Studies ($n = 12$) Examining the Relationship between DUP and Long-Term (≥ 10 -years) Outcome in People with First-Episode Psychosis or First-Episode Schizophrenia.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Rate of Follow-up n /total (%)	Measurement of DUP		DUP Categorization	Mean DUP	Outcome(s)/ Outcome Measures	Relationship between DUP & Outcome(s) [Yes/No]
						Onset	Endpoint				
Ichinose et al. (2010)*	Japan	Medical Institutions with Psychiatry Departments (Private psychiatry hospitals & clinics, Prefectural psychiatry hospital, Public General Hospital Psychiatry Departments, and Health Centers)	28 years	31 Patients with First-Episode Schizophrenia	31/107 (29%)	Disease Onset	Start of treatment at a medical institution	Short DUP = ≤ 3 months Long DUP = > 4 months	8.97 months	Global Assessment Schedule (GAS), Disability Assessment Schedule (DAS), and Clinical Global Impression (CGI)	A long DUP was significantly associated with decreased GAS, DAS, and CGI. [Yes]
Shrivastava et al. (2010) *	India	Non-Governmental Psychiatric Hospital	10 years	101 Hospitalized Patients with First-Episode Schizophrenia	101/200 (51%)	Positive symptoms (hallucinations, delusions, odd beliefs, and thought disorder), negative symptoms (depression, dysphoria, apathy, anergia, apathy, and amotivation), and social decline (withdrawn behavior, poor interpersonal relationship, social avoidance, and lack of interest in education or work)	Not Described	Short DUP = < 12 months Long DUP = ≥ 12 months	12.7 months	<u>Clinical</u> : Clinical Global Impression, Psychopathology, Depressive Symptoms, Factors of Compliance, Extrapyramidal Symptoms, Aggression, Hospitalization, & Suicidality <u>Social</u> : Quality of Life, Global Functioning, Independent Living, Family Burden, & Social Burden	DUP was not significantly associated with any of the clinical or social outcomes. [No]

Note: *DUP main focus; DUP; Duration of Untreated Psychosis; n = count; GAS = Global Assessment Schedule; DAS = Disability Assessment Schedule; CGI = Clinical Global Impression; & = and; % = Percentage.

(Continued)

Table 2.1: Summary of Studies ($n = 12$) Examining the Relationship between DUP and Long-Term (≥ 10 -years) Outcome in People with First-Episode Psychosis or First-Episode Schizophrenia.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Rate of Follow-up n /total (%)	Measurement of DUP		DUP Categorization	Mean DUP	Outcome(s)/ Outcome Measures	Relationship between DUP & Outcome(s) [Yes/No]
						Onset	Endpoint				
Evensen et al. (2012)	Norway & Denmark	The Treatment & Intervention in Psychosis Study (TIPS); Specialist Psychiatric Health-Care Services of four Scandinavian Health Care Sectors	10 years	178 First-Episode Psychosis Patients (Inpatients & Outpatients)	178/301 (59%)	First positive psychotic symptoms	Start of the first adequate treatment of psychosis		6 weeks	Apathy	DUP was not significantly associated with self-rated apathy at 10-years follow-up. [No]
Hill et al. (2012)*	Ireland	Cluain Mhuire Family Centre (provides psychiatric service) or the St John of God Hospital	12 years	123 First-Episode Psychosis Patients	123/171 (72%)	Onset of the first psychotic symptom	Start of antipsychotic treatment	≤ 1 month; >1 and ≤ 3 months; >3 months and ≤ 1 year; >1 year	20.3 months	Symptomatic: Positive Symptoms, Negative Symptoms, Disorganized Symptoms, Symptom Severity, & Remission Functional: General/Global Functioning, Quality of Life, Level of Functioning, Social Functioning, & Occupational Functioning	Longer DUP was significantly associated with poorer remission status, more severe positive and negative symptoms, and greater impairment in general functioning, social functioning, as well as quality of life. [Yes]
Tang et al. (2014)*	Hong Kong	Public Hospitals	13 years	96 First-Episode Psychosis Patients	96/153 (63%)	Onset of positive psychotic symptoms	Treatment initiation	Short DUP = ≤ 30 days Medium DUP = 31-180 days Long DUP = > 180 days	180 days	Clinical – Symptomatic Remission	DUP longer than 30 days adversely impacts the long-term outcome. [Yes]

Note: *DUP main focus; DUP = Duration of Untreated Psychosis; n = count; & = and; % = Percentage.

(Continued)

Table 2.1: Summary of Studies ($n = 12$) Examining the Relationship between DUP and Long-Term (≥ 10 -years) Outcome in People with First-Episode Psychosis or First-Episode Schizophrenia.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Rate of Follow-up n /total (%)	Measurement of DUP		DUP Categorization	Mean DUP	Outcome(s)/ Outcome Measures	Relationship between DUP & Outcome(s) [Yes/No]
						Onset	Endpoint				
Austin et al. (2015)	Denmark	OPUS trial; Inpatient & Outpatient Mental Health Services	10 years	304 People with First-Episode Psychosis	304/496 (61%)	At least one psychotic symptom definitely present	Initiation of treatment		52 weeks (full; baseline sample)	Positive and Negative Symptom Trajectories	Longer DUP was associated with poorer positive symptom trajectories (i.e., higher levels of psychotic symptoms). [Yes]
Jaracz et al. (2015)	Poland	Hospital	9 years+	64 Patients Hospitalized for First-Episode Schizophrenia	64/86 (74%)	Appearance of the first psychotic symptoms	First psychiatric hospitalization		10.4 months (baseline sample)	<u>Good Outcome</u> = simultaneously meeting criteria for symptomatic and functional remissions, as well as satisfying quality of life <u>Poor Outcome</u> = Not meeting all of the criteria of a good outcome	Longer DUP was significantly associated with poor outcome. [Yes]
Rund et al. (2015)*	Norway & Denmark	The Treatment & Intervention in Psychosis Study (TIPS); Specialist Psychiatric Health-Care Services of four Scandinavian Health Care Sectors	10 years	261 First-Episode Psychosis Patients (Inpatients & outpatients)	261/301 (87%)	PANSS score of 4 or more on one of the following items: P1, P3, P5, P6, or G9	Antipsychotic medication or admission to the hospital for treatment of acute psychosis		11 weeks	Neurocognition	Absence of a significant association between DUP and the neurocognitive composite score. [No]
Friis et al. (2016)	Norway & Denmark	The Treatment & Intervention in Psychosis Study (TIPS); Specialist Psychiatric Health-Care Services of four Scandinavian Health Care Sectors	10 years	186 Patients with Non-Affective First-Episode Psychosis (Inpatients & outpatients)	186/301 (62%)	Psychosis onset = First appearance of being actively psychotic	Start of the first adequate treatment of psychosis (antipsychotic medication or hospitalization)	< 26 weeks ≥ 26 weeks	47.4 weeks	Time in Psychosis; defined as time with scores ≥ 4 on any of the following PANSS items: P1, P3, P5, P6, and G9	DUP of ≥ 26 weeks was significantly associated with longer time in psychosis during the 10-year follow-up period [Yes]

Note: *DUP main focus; DUP = Duration of Untreated Psychosis; n = count; + = Mean length of follow-up (7-11 years); PANSS = Positive and Negative Syndrome Scale; P = Positive Scale; G = General Scale; & = and; % = Percentage.

In the majority of the studies ($n = 7$), the duration of untreated psychosis was treated as a continuous variable, based on the assumption that the duration of untreated psychosis has a *linear* effect on outcomes (Tang et al., 2014), such that the likelihood of poor outcomes increases as the duration of untreated psychosis increases. In the remaining studies ($n = 5$), the duration of untreated psychosis variable was categorized or dichotomized, based on the assumption that the duration of untreated psychosis has a *threshold* effect on outcomes (Singh, 2007; Tang et al., 2014), such that the duration of untreated psychosis will have no effect on outcomes unless a particular threshold value is reached or exceeded. Once the threshold value of the duration of untreated psychosis is reached or exceeded, the likelihood of a poor outcome increases. Different cut-off values were used to classify the duration of untreated psychosis as “long.” For instance, Tang and colleagues (2014) defined “long” as greater than four-months, whereas Ichinose and colleagues (2010) defined “long” as greater than one-year.

Overall, a majority of studies ($n = 8$) reported a statistically significant relationship between the duration of untreated psychosis and long-term outcomes (Austin et al., 2015; Friis et al., 2016; Hill et al., 2012; Jaracz et al., 2015; Ichinose et al., 2010; Kinoshita et al., 2005; Tang et al., 2014; White et al., 2009). Among the studies that kept the duration of untreated psychosis as a continuous variable ($n = 7$), a few of these studies ($n = 4$) reported that the longer the duration of untreated psychosis the poorer the outcome (Austin et al., 2015; Jaracz et al., 2015; Kinoshita et al., 2005; White et al., 2009). These outcomes included:

- Poorer positive symptom trajectories (Austin et al., 2015)
- Poor outcome (i.e., not meeting criteria for symptomatic and functional remissions, nor satisfying quality of life) (Jaracz et al., 2015)
- Higher outcome symptom burden (White et al., 2009)

Kinoshita and colleagues (2005) reported that a long duration of untreated psychosis was significantly associated with poor outcome at 10-year follow-up, but not at 15-year follow-up.

Among the studies that categorized or dichotomized the duration of untreated psychosis ($n = 5$), a majority of these studies ($n = 4$) reported that a longer duration of untreated psychosis was significantly associated with poorer outcomes (Friis et al., 2016; Hill et al., 2012; Ichinose et al., 2010; Tang et al., 2014). These poorer outcomes included:

- Longer time in psychosis (Friis et al., 2016)
- Poorer remission status, greater severity of positive and negative symptoms, greater impairment in general functioning, social functioning, and quality of life (Hill et al., 2012)
- Decreased scores on the Global Assessment Schedule, Disability Assessment Schedule, and Clinical Global Impression (Ichinose et al., 2010)
- Poor symptomatic remission (Tang et al., 2014)

2.1.3 Long DUP-Poor Outcome Link: Underlying Mechanism

To date, the mechanism underlying the observed association between a long duration of untreated psychosis and poor short-term (< 10 -years) or long-term (≥ 10 -years) outcome in people with first-episode psychosis is not yet known (Chou et al., 2015; Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). The duration of untreated psychosis has been proposed to have a direct and/or indirect impact on outcomes because of its hypothesized neurotoxic and/or socially toxic effects (Norman, 2014; Wyatt, 1991) (Figure 2.2).

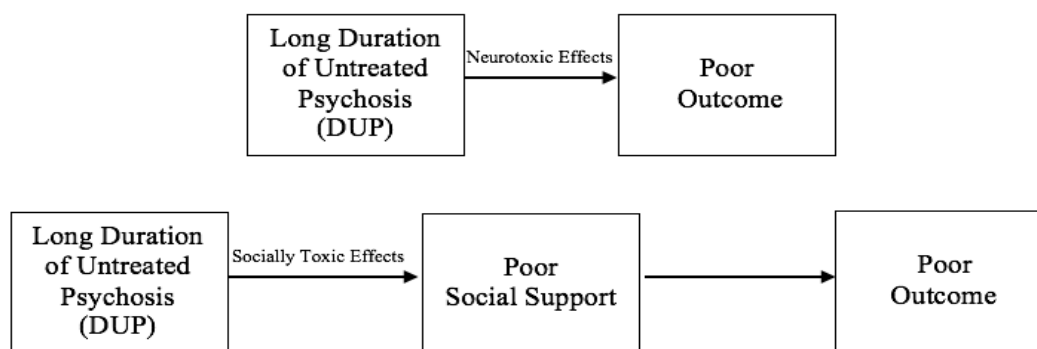


Figure 2.2: A Visual Representation of the Hypothesized Neurotoxic and Socially Toxic Effects that a Long Duration of Untreated Psychosis has on Outcomes in People with First-Episode Psychosis.

Wyatt (1991) proposed that untreated psychosis is somehow neurotoxic because it results in potentially irreversible damage to the brain, with longer durations of untreated psychosis resulting in greater damage to the brain. Hypothesized mechanisms to explain this toxicity include dopaminergic (catecholaminergic) hyperactivity and prolonged hypothalamic-pituitary-adrenal activation (Andersen, Voineskos, Mulsant, Gerorge, & McKenzie, 2014). Evidence for the possible neurotoxic effects of untreated psychosis is inconclusive (Anderson et al., 2015; McGlashan, 2006; Rund, 2014).

Recently, Norman (2014) proposed that a longer duration of untreated psychosis may have socially toxic effects, which mediate its impact on outcomes. He argues that a third variable, specifically a psychosocial factor such as social support, may mediate the relationship between duration of untreated psychosis and outcomes. For instance, a long duration of untreated psychosis could result in poor social support, poor social support in turn, could have an adverse impact on outcomes (Figure 2.2). Therefore, a long duration of untreated psychosis has an impact on outcomes indirectly through a third variable, poor social support. However, evidence for possible socially toxic effects is needed, with examination of the mediating role of different types of social support and other psychosocial factors (Norman, 2014).

2.1.4 Long Term Outcome (≥ 10 -years): Relapse

Based on our literature search of studies examining the association between the duration of untreated psychosis and long-term (≥ 10 -years) outcomes in people with first-episode psychosis or first-episode schizophrenia, no study to date has examined relapse as a long-term outcome (Table 2.1).

2.2 Recovery

2.2.1 Definition of Recovery

The most influential definition of recovery was put forth by Anthony (Wallcraft, 2012):

“Recovery is described as a deeply personal, unique process of changing one’s attitudes, values, feelings, goals, skills, and/or roles. It is a way of living a satisfying, hopeful, and contributing life even with limitations caused by illness. Recovery involves the development of new meaning and purpose in one’s life as one grows beyond the catastrophic effects of mental illness. Recovery from mental illness involves much more than recovery from the illness itself...”
(Anthony, 1993).

While this definition has not been widely accepted in its entirety, elements of this definition have been extracted by others in ongoing efforts to define recovery. Therefore, no standardized definition or set of criteria for recovery exists, which may in part be complicated by the multi-dimensional nature of this construct (Davidson, O’Connell, Tondora, Staehuli, & Evans, 2005; Harvey & Bellack, 2009; Liberman & Kopelowicz, 2005; Silverstein & Bellack, 2008).

2.2.2 Recovery Following a First Episode of Psychosis

2.2.2.1 Variability in Recovery

People can and do recover after a first episode of psychosis; however, considerable variability exists (de Koning et al., 2009; Lam et al., 2010; Marshall & Rathbone, 2011). Rates of recovery following a first episode of psychosis range between 14% (Austin et al., 2013) to 29.4% (Verma, Subramaniam, Abidin, Poon, & Chong, 2012) depending on how recovery was operationalized and the length of follow-up. Moreover, factors perceived to facilitate or hinder recovery and the signs of recovery may potentially contribute to the variability observed across people who have or have not recovered after a first episode of psychosis. Even among those who have recovered, variability exists in their recovery style.

Factors Perceived to Facilitate or Hinder Recovery

From the perspective of people who have experienced a first episode of psychosis, there are a number of factors that either facilitate or hinder one's chance of recovery. Factors perceived to facilitate recovery include social support, medication, having to care for someone, spirituality, lifestyle modification, meaningful activities, individual characteristics such as personal effort and hope, and interpersonal relationships with the professional team and members of a psychoeducation group (de Wet, Swartz, & Chiliza, 2015; Eisenstadt, Monteiro, Diniz, & Chaves, 2012; Windell & Norman, 2012). Factors such as stigma, substance use, and adverse effects of medication are perceived to hinder recovery (de Wet, Swartz, & Chiliza, 2015; Eisenstadt, Monteiro, Diniz, & Chaves, 2012; Lam et al., 2010; Windell & Norman, 2012).

Signs of Recovery

The signs or meaning of recovery varies based on the person that is being asked, such as a clinician, family member, or the person who experienced a first episode of psychosis (Lam et al., 2010). Even among those who experienced a first episode of psychosis, the signs of recovery vary. Table 2.2 summarizes the signs of recovery as indicated by people who experienced a first episode of psychosis. As summarized in Table 2.2, there are a number of signs of recovery, each reflecting different domains of a person's life, which suggests that recovery is multidimensional and that assessment of recovery should take into account a person's functioning in different domains of his or her life.

Table 2.2: Signs of Recovery as Indicated by People who Experienced a First Episode of Psychosis.

Study	Sample	Signs of Recovery (Overall Themes)
Lam et al., (2010)	6 people treated for a first episode of psychosis at an early intervention program	<ul style="list-style-type: none"> • Regaining previous cognitive functions (e.g., being able to concentrate) • Regaining previous social functions (e.g., engage with family and friends) • Being normal • No medication
Eisenstadt et al., (2012)	16 people treated for a first episode of affective or non-affective psychosis at an early intervention program	<ul style="list-style-type: none"> • Improvement in psychotic symptoms (decrease or absence) • Changes in social relationships (e.g., return to social life) • Renewed autonomy & independence (e.g., feel safe again to go out alone) • Restoration of self-reliance & trust in others (i.e., trust themselves and others)
Windell et al., (2012)	30 people who received initial treatment for a first episode of psychosis at an early intervention service 3 to 5-years ago	<ul style="list-style-type: none"> • Alleviation of symptoms, especially positive symptoms • Subjective control over the extent and influence of symptoms, and reduction of distress associated with the symptoms • Regaining a sense of control and a coherent sense of self (e.g., acceptance of illness) • Engagement in meaningful activities (resume or engage in new work and/or school) • Participation in social relationships (e.g., peer or romantic relationships) • Taking medication • Medication discontinuance

Note: Signs of recovery (overall themes) as reported by participants in qualitative interviews.

We also noted that divergent views exist as to whether taking medication is a sign of recovery (Lam et al., 2010; Windell, Norman, & Malla, 2012). We further noted that elimination or reduction of symptoms (Eisenstadt, Monteiro, Diniz, & Chaves, 2012; Windell, Norman, & Malla, 2012) was found to be a common sign of recovery, which is generally the sign of recovery acknowledged by clinicians (Lam et al., 2010). However, for some, elimination or reduction of symptoms was not acknowledged to be a sign of recovery (Lam et al., 2010), which illustrates that the signs of recovery according to the clinician do not always align with those of the client. Therefore, it is important to incorporate the signs or meaning of recovery based on perspectives of both the clinician

and the client allowing them to work towards a shared set of objectives to promote recovery (Ng et al., 2008).

Recovery Style

During the recovery phase of a first episode of psychosis (Figure 1.1), one of two recovery styles is adopted including *integration or integrative* versus *sealing or seal over* (Thompson, McGorry, & Harrigan, 2003). Those with an *integrative* recovery style incorporate their psychotic episode experience as part of their overall life experience and have a more optimistic outlook as he or she was able to learn new information about themselves (Thompson, McGorry, & Harrigan, 2003). In contrast, those with a *sealing over* recovery style tend to dissociate their psychotic episode experience from their overall life experience in an effort to protect themselves from the stigma associated with psychosis and to preserve their mental well-being (Thompson, McGorry, & Harrigan, 2003). Furthermore, those with an integrative recovery style tend to be more compliant with treatment, whereas those with the latter recovery style deny that anything is wrong and resist treatment (McGlashan & Levy, 1997; Thompson, McGorry, & Harrigan, 2003), which may explain why those with the former recovery style have better outcomes post-recovery than those with the latter recovery style (Thompson, McGorry, & Harrigan, 2003).

2.2.2.2 Relapse

Views vary on whether vulnerability to relapse risk can impact recovery. These views include: (i) vulnerability of relapse risk does impede recovery; (ii) recovery is possible and attainable while acknowledging vulnerability to relapse risk; and (iii) recovery is possible and attainable again after experiencing a relapse (Windell, Norman, & Malla, 2012). These varying views demonstrate that for some, recovery is an end-state whereas for others it is an ongoing process in which a person oscillates between recovery and relapse.

Risk Factors for Relapse

The existing literature suggests that a number of factors are associated with an increased risk of relapse after a first episode of psychosis, and consequently a decreased chance of recovery or period of recovery. These include younger age (Hui et al., 2013), younger age at onset (< 24 years) (Stefanescu et al., 2013), single marital status (Stefanescu et al., 2013), poor premorbid adjustment (Alvarez-Jimenez et al., 2012), schizophrenia diagnosis (Hui et al., 2013), schizophrenia load in the family (Stefanescu et al., 2013), comorbid diagnosis of substance abuse (Malla et al., 2008), persistent substance use disorder (Alvarez-Jimenez et al., 2012), cannabis use (Bergé et al., 2015), smoking (Hui et al., 2013), shorter baseline hospitalization (Stefanescu et al., 2013), carer's critical comments (Alvarez-Jimenez et al., 2012), poor insight (Bergé et al., 2015), and medication non-adherence (Alvarez-Jimenez et al., 2012; Hui et al., 2013). Factors identified to be associated with an early relapse after a first episode of psychosis include longer first hospitalization, higher severity of negative symptoms at onset, and a longer duration of untreated psychosis (Stefanescu et al., 2013).

2.2.3 Empirical Study of Recovery: Recovery Models

The definition, conceptualization, and assessment of recovery has generally been based on the traditional medical model of recovery or the more recent consumer model of recovery (Ahmed, Birgenheir, Buckley, & Mabe, 2013; Roe, Mashiach-Eizenberg, & Lysaker, 2011). The former model is based on the definition of recovery in the scientific literature and reflects the perspective of the clinician, researcher, or service provider, while the latter model is based on the definition of recovery in the consumer and rehabilitation literatures and reflects the patient, service user, or client's own perspective. In the traditional model, recovery is conceptualized as an outcome or endpoint and it is defined as the elimination or reduction of psychotic symptoms and return to pre-illness levels of function for a certain period of time (Bellack, 2006; Liberman & Kopelowicz, 2005). In the more recent model, recovery is conceptualized as an ongoing process that is subjective, unique, person-centered (Davidson, O'Connell, Tondora, Staehuli, & Evans, 2005; Silverstein & Bellack, 2008), and it is defined by the person. Therefore, recovery can be conceptualized as either an outcome or as a process.

Both models each represent one of the two broad dimensions of recovery: (i) objective and (ii) subjective (Lysaker, Taylor, Miller, Beattie, Strasburger, & Davis, 2006), with the former dimension represented by the traditional model and the latter dimension represented by the newer model (Roe, Mashiach-Eizenberg, & Lysaker, 2011). The objective and subjective dimensions of recovery are often referred to as objective recovery and subjective recovery, respectively. In this thesis, we used the terms subjective recovery and self-perceived recovery interchangeably. A list of other synonyms for the term subjective recovery is provided in Appendix A.

2.2.4 Assessment of Recovery as an Outcome

The increased interest in the assessment of recovery as an outcome may perhaps be attributed to the potential of improving recovery-oriented services directed to promote and/or sustain recovery following a first episode of psychosis (Drake, Noel, & Deegan, 2015).

2.2.4.1 Objective Recovery

The assessment of objective recovery in the past has generally been based on the reduction or elimination of symptoms (Addington, Young, & Addington, 2003; Resnick, Rosenheck, & Lehman, 2004). More recently, it has been acknowledged that other objective indicators (or measures) of recovery, aside from or in conjunction with symptomatic outcomes, need to be taken into account, such as social, functional, or vocational outcomes (Gee et al., 2016; Kam, Singh, & Upthegrove, 2015; Major et al., 2010). One such indicator that is increasingly being used is engagement in meaningful activities such as work and/or school, which is often referred to as vocational outcomes, vocational activity, or occupational activity (Major et al., 2010; Norman et al., 2007; Norman et al., 2012). We chose to use occupational activity as an indicator of objective recovery, defined as engagement in work and/or school on a full-time or part-time basis in the past year.

2.2.4.2 Subjective Recovery

The assessment of subjective recovery in the past has focused on the process, experience, or meaning of recovery based on first-person accounts of those with first-episode psychosis (e.g., Connell, Schweitzerder, & King, 2015; de Wet, Swartz, & Chiliza, 2015; Windell & Norman, 2012; Windell, Norman, & Malla, 2012). The shift towards the assessment of subjective recovery as an outcome is a relatively new phenomenon, which can be attested to by the relatively few studies that currently exist in the literature (Law, Shryane, Bentall, & Morrison, 2015; Morland, 2007; Morrison et al., 2013; Norman, Windell, Lynch, & Manchanda, 2013) (Table 2.3).

Among the few ($n = 4$), mostly cross-sectional studies ($n = 3$) that did assess subjective recovery as an outcome, albeit with different subjective recovery measures, findings from these studies suggest that people with first-episode psychosis or experience with psychosis are more likely to report higher levels of subjective recovery when experiencing lower levels of the following:

- Anxiety and depression (Morland, 2007)
- Negative emotion (Morrison et al., 2013; Law, Shryane, Bentall, & Morrison, 2015)
- Hopelessness (Law, Shryane, Bentall, & Morrison, 2015)
- Positive and negative symptoms (Norman, Windell, Lynch, & Manchanda, 2013)

also when experiencing higher levels of the following:

- Internal locus of control (Morrison et al., 2013)
- Perceived relational evaluation (Norman, Windell, Lynch, & Manchanda, 2013)
- Positive self-esteem (Law, Shryane, Bentall, & Morrison, 2015) (Table 2.3)

Table 2.3: Studies ($n = 4$) Assessing Subjective Recovery as an Outcome in People with First-Episode Psychosis or Experience with Psychosis.

Study	Study Design	Sample Source (n)	Sample Size	Variables of Interest (Measure)	Subjective Recovery Outcome Measure	Findings
Morland (2007)	Cross-Sectional	Stand-alone' Early Intervention Service team ($n = 54$) or 'Augmented' Community Mental Health Team ($n = 6$)	60 people with first-episode psychosis	i) General psychopathology symptoms of anxiety & depression ii) Positive symptoms (hallucinations & delusions) iii) Negative symptoms iv) Engagement in paid employment or education v) Gender vi) Age (years) at the time of interview vii) Length of time (months) in service	Mental Health Recovery Scale (MHRS)	-Significant negative association between anxiety and subjective recovery. -Significant negative association between depression and subjective recovery. -No significant association between subjective recovery and the other factors of interest.
Morrison et al. (2013)	Cross-Sectional	Early intervention services ($n = 40$), other community-based mental health teams ($n = 81$), & an inpatient unit ($n = 1$).	122 people with experience of psychosis	<u>Psychosocial:</u> Self-esteem, locus of control, & emotion <u>Neuropsychiatric:</u> Psychotic symptoms, neurocognition, & insight	Questionnaire Process of Recovery (QPR) & Recovery Analogue Scale (RecA)	-Findings from structural equation modeling indicated that self-rated recovery from psychosis was directly influenced by negative emotion (i.e., anxiety, depression, and negative self-esteem) and internal locus of control.

Note: n = count; & = and; PEPP = Prevention and Early Intervention Program for Psychosis; MHRS = Mental Health Recovery Scale; RAS = Recovery Assessment Scale; MES= Modified Engulfment Scale; QPR = Questionnaire Process of Recovery; RecA = Recovery Analogue Scale.

(Continued)

Table 2.3: Studies ($n = 4$) Assessing Subjective Recovery as an Outcome in People with First-Episode Psychosis or Experience with Psychosis.

Study	Study Design	Sample Source (n)	Sample Size	Variables of Interest (Measure)	Subjective Recovery Outcome Measure	Findings
Norrman et al. (2013)	Cross-Sectional	Early Intervention Program (PEPP)	84 people receiving treatment for a first-episode of psychosis	i) Positive Symptoms (SAPS) ii) Negative Symptoms (SANS) iii) Social Support (ISEL & PRES)	Recovery Assessment Scale (RAS) & Modified Engulfment Scale (MES)	-Significant negative association between <u>positive</u> symptoms and two or more of the five subscales of the Recovery Assessment Scale. - Significant negative association between <u>negative</u> symptoms and two or more of the five subscales of the Recovery Assessment Scale. - Significant positive association between PRES with the MES, and with each of the subscales of the RAS and MES.
Law et al. (2015)	Longitudinal (6-months)	Early intervention services ($n = 27$), community-based mental health teams ($n = 45$), in-patient service ($n = 1$). Unknown referral type ($n = 37$)	110 people with experience of psychosis	Negative emotion, Psychiatric symptoms, Hopelessness, Positive self-esteem, and Functioning	Questionnaire Process of Recovery (QPR)	-Finding from path analysis indicated that subjective recovery at 6-months follow-up was negatively associated with both negative emotion (baseline) and hopelessness (baseline), and positively associated with positive self-esteem (baseline). -Subjective recovery at 6-months follow-up was negatively associated with psychiatric symptoms (baseline) and positively associated with functioning (baseline); however, these associations with subjective recovery were not as strong as the associations between the other factors of interest.

Note: n = count; & = and; QPR = Questionnaire Process of Recovery; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; ISEL = Interpersonal Support Evaluation List; PRES = Perceived Relational Evaluation Scale.

Comparability of findings of these and future studies assessing subjective recovery as an outcome is precluded by the lack of a universal gold standard measure. A recent review of existing subjective recovery measures identified a total of 13 such measures (Shank et al., 2013). The Maryland Assessment of Recovery in People with Serious Mental Illness Scale (MARS) (Bellack & Drapalski, 2012) was among the 13 measures identified in the review, which is the measure used in the current study to assess subjective recovery. The MARS is unique as a recovery measure because it is the only measure to assess recovery using the Substance Abuse Mental Health Services Administration (SAMHSA) operational definition of recovery (Ahmed, Birgenheir, Buckley, & Mabe, 2013) that states:

“Mental health recovery is a journey of healing and transformation enabling a person with a mental disability to live a meaningful life in the community of his or her choice while striving to achieve full human potential or personhood.” (SAMHSA, p.1).

2.2.5 Comprehensive Assessment of Recovery

The relationship between objective and subjective recovery from a first episode of psychosis or from a psychotic disorder (e.g., schizophrenia) has been examined by several empirical studies (Jørgensen et al., 2015; Kukla, Lysaker, & Roe, 2014; Lloyd, King, & Moore, 2010; Morland, 2007; Norman, Windell, Lynch & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004; Roe, Mashiach-Eizenberg & Lysaker, 2011). However, findings from these studies have been inconclusive. Given that there is some evidence suggesting an absence of an association (Jørgensen et al., 2015; Lloyd, King, & Moore, 2010; Morland, 2007; Norman, Windell, Lynch, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004), assessment of a person’s recovery would not be comprehensive and potentially inaccurate if both objective and subjective recovery are not taken into account. We therefore decided to include both objective and subjective recovery as outcomes in this thesis.

2.3 DUP & Recovery: Existing Literature

The duration of untreated psychosis is one of the few most widely studied modifiable risk factors of poor outcome in people with first-episode psychosis (e.g., Compton et al., 2007; Tang et al., 2014). With growing research and clinical interest in recovery as an outcome, the impact of the duration of untreated psychosis on recovery following a first episode psychosis has increasingly come into focus in recent years.

Our existing knowledge of the association between the duration of untreated psychosis and recovery has mainly been based on studies with follow-up periods of less than 10-years, and those conducted in countries other than Canada (Table 2.4). The duration of untreated psychosis has been reported to be negatively associated with objective recovery (Chang 2012b; Verma, Subramaniam, Abdin, Poon, & Chong, 2012), and with specific types of objective recovery including clinical recovery (Chang et al., 2012a; Faber et al., 2011; Winderink, Sytema, Nienhuis, & Wiersma, 2009), vocational recovery (Major et al., 2010) and psychiatric recovery (Gumley et al., 2014) (Table 2.4). Interestingly, across different studies, both a shorter and longer (≥ 3 -months) duration of untreated psychosis has been reported to be negatively associated with objective recovery, specifically clinical recovery (Chang et al., 2012a; Chang et al., 2012b) at 3-year follow-up (Table 2.4).

Table 2.4: Summary of Studies (n = 9) Investigating the Association between DUP and Recovery.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Follow-up Rate n/total (%)	Measurement of DUP		Mean DUP	Recovery Dimension [Objective/ Subjective]	Operational Criteria for Recovery	Recovery Rate n/total; %	Presence of an Association between DUP & Recovery [Yes/No]
						Onset	Endpoint					
Wunderink et al. (2009)**	Netherlands	MESIFOS (Medication Strategies In First Onset Schizophrenia) study; Seven Mental Health Services	Last 9-months of 2-year period	125 Patients with First-Episode Psychosis	125/257 (49%)	First manifestation of any positive psychotic symptom	Start of antipsychotic treatment	Recovered = 31.8 days Non-recovered = 320.9 days	Clinical [Objective]	Symptomatic & Functional Remission <u>Symptomatic Remission:</u> Exacerbation of symptoms for at least 1 week with at least one relevant PANSS item score above 3 (mild):P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing), and G9 (unusual thought content). <u>Functional Remission:</u> A patient should function adequately in all 7 social roles with none or only a minimal disability in any of them (not allowing a score of 2 or 3 on any GSDS role).	24/125; 19.2% (End of 2-year follow-up period)	Presence of a statistically significant association between DUP and clinical recovery. [Yes]
Major et al. (2010)	London	Early Intervention Service	1 year	114 Service Users with First-Episode Psychosis	114/129 (88%)	Emergence of the first positive psychotic symptom	Initiation of treatment	86 days (median)	Vocational [Objective]	Gaining or returning to competitive employment (competitively accessed work, paid at the market rate) or an educational activity which clearly led to a nationally recognized vocational qualification or degree, entered into at any point in the follow-up period and for any duration.	Not Specified	Absence of a statistically significant association between DUP and vocational recovery during 1-year follow-up. [No]

Note: ** Recovery was assessed before the end of the follow-up period; DUP = Duration of Untreated Psychosis; n = count; GSDS = Groningen Social Disabilities Schedule; PANSS = Positive and Negative Syndrome Scale;

P = Positive Scale; N = Negative Scale; G = General Psychopathology Scale; & = and; % = Percentage.

(Continued)

Table 2.4: Summary of Studies ($n = 9$) Investigating the Association between DUP and Recovery.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Follow-up Rate n/total (%)	Measurement of DUP		Mean DUP	Recovery Dimension [Objective/ Subjective]	Operational Criteria for Recovery	Recovery Rate n/total; %	Presence of an Association between DUP & Recovery [Yes/No]
						Onset	Endpoint					
Albert et al. (2011)	Denmark	OPUS trial; Inpatient & Outpatient Mental Health Services	5 years	255 Patients with First-Episode Non-Affective Psychosis	255/468 (54%)	Not Specified	Onset of adequate treatment	Recovered = 92 weeks Non-Recovered = 121 weeks	Not Specified [Objective]	Recovery was defined as working or studying, having a GAF-function score of 60 or above, having remission of negative and psychotic symptoms, and not living in a supported housing facility or being hospitalized during the last 2 years.	40/255; 15.7%	Absence of a statistically significant association between DUP and recovery at 5-year follow-up. [No]
Faber et al. (2011)	Netherlands	Add onto MESIFOS (Medication Strategies In First Onset Schizophrenia) study; Seven Mental Health Services for Psychosis	2 years	45 Patients with Non-Affective First-Episode Psychosis	45/125 (36%)	First manifestation of any positive psychotic symptom	Start of antipsychotic treatment	Recovered = 34 days Non-recovered = 294 days	Clinical [Objective]	Symptomatic & Functional Remission <u>Symptomatic Remission:</u> An exacerbation of symptoms for at least 1 week with at least one relevant PANSS item score above 3 (mild):P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity), G5 (mannerisms/posturing), and G9 (unusual thought content). <u>Functional Remission:</u> Function adequately in all social roles (Self-care, Housekeeping, Family relationships, Partner relationships, Community integration, Relationship with peers, Vocational role & Parental role) with none or only a minimal disability in any of them (not allowing a score of 2 or 3 on any GSDS role).	9/45; 20%	Presence of a statistically significant association between DUP and clinical recovery. [Yes]

Note: DUP = Duration of Untreated Psychosis; n = count; GSDS = Groningen Social Disabilities Schedule; GAF-F = Global Assessment of Functioning-Functioning Scale; PANSS = Positive and Negative Syndrome Scale; P = Positive Scale; N = Negative Scale; G = General Psychopathology Scale; & = and; % = Percentage.

(Continued)

Table 2.4: Summary of Studies (n = 9) Investigating the Association between DUP and Recovery.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Follow-up Rate n/total (%)	Measurement of DUP		Mean DUP	Recovery Dimension [Objective/ Subjective]	Operational Criteria for Recovery	Recovery Rate n/total; %	Presence of an Association between DUP & Recovery [Yes/No]
						Onset	Endpoint					
Chang et al. (2012a)	Hong Kong	EASY programme (Early Assessment Service for Young People with Psychosis); Early Intervention Program	3 years	539 Chinese people with First-Episode Psychosis	539/700 (77%)	Onset of positive psychotic symptoms	First contact with the psychiatric service (EASY programme)	226.3 days	Clinical [Objective]	Symptomatic & Functional Remission <u>Recovery</u> : Simultaneous fulfillment of the following criteria in the last 12 months of study period: (i) CGI-S scores < 3 for both positive and negative symptoms; (ii) no psychiatric admission; (iii) achieving functional remission. Functional remission was defined as attaining both sustained employment (full-time or part-time work/study) and SOFAS score > 60 in the last 12 months of the follow-up period.	94/539; 17.4%	Presence of a statistically significant association between shorter DUP (< 3 months) and recovery. [Yes]
Chang et al. (2012b)	Hong Kong	EASY programme; Early Intervention Program	3 years	700 Chinese people with First-Episode Psychosis	700/839 (83%)	Onset of positive psychotic symptoms	First contact to psychiatric service	DUP < 3 months = 30.1 days (n = 346) DUP > 3 months = 444.8 days (n = 354)	Not Specified [Objective]	Symptom Remission & Full-Time Employment Status <u>Recovery</u> : Maintaining CGI-S scores < 3 for both positive and negative symptoms and full-time employment status for at least 12 consecutive months after treatment initiation.	Not Specified	Presence of a statistically significant association between long DUP (≥ 3 months) and recovery. [Yes]
Verma et al., (2012)	Singapore	Early Psychosis Intervention Programme	2 years	1175 Patients with First-Episode Psychosis	1175/1718 (68%)	Onset of psychotic symptoms (delusions, hallucinations, disorganized behavior)	Definitive diagnosis and treatment established	16.2 months	Not Specified [Objective]	Symptomatic & Functional Remission <u>Recovery</u> : Meeting criteria for both symptomatic & functional remission; Criteria for symptomatic remission as proposed by the Schizophrenia Working Group, that is, achieving.....(continued)	345/1175; 29.4%	Presence of a statistically significant association between shorter DUP and recovery at 2-year follow-up. [Yes]

Note: DUP = Duration of Untreated Psychosis; n = count; CGI-S = Clinical Global Impression-Severity of Illness Scale; SOFAS = Social Occupational Functioning Assessment Scale; EASY = Early Assessment Service for Young People with Psychosis; & = and; % = Percentage.

(Continued)

Table 2.4: Summary of Studies (n = 9) Investigating the Association between DUP and Recovery.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Follow-up Rate n/total (%)	Measurement of DUP		Mean DUP	Recovery Dimension [Objective/ Subjective]	Operational Criteria for Recovery	Recovery Rate n/total; %	Presence of an Association between DUP & Recovery [Yes/No]
						Onset	Endpoint					
(Continued)	--	--	--	--	--	--	--	--	--	and maintaining a PANSS rating of three or less for a duration of at least 6-months on the following items: Delusions (P1), unusual thought contents (G9), hallucinatory behaviour (P3), conceptual disorganization (P2), mannerisms (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6) (7). Functional remission was defined as having a GAF disability score of ≥ 61 with engagement in age-appropriate vocation (gainfully employed or studying) at 2 years.	--	--
Austin et al. (2013)*	Denmark	OPUS trial; Inpatient & Outpatient Mental Health Services	10 years	304 People with First-Episode Psychosis	304/496 (61%)	Not Specified	Not Specified	Recovered = 30.79 weeks (median) Non-recovered = 50.43 weeks (median)	Not Specified [Objective]	<u>Full Recovery</u> = Stable remission of both negative and positive symptoms, no psychiatric admissions to hospital or living in supported accommodation for the past two years, currently engaged in work or study and a GAF-F score of over 60 (Lieberman & Kopelowicz, 2005). <u>Functional Recovery</u> = Currently engaged in work/study, a GAF-F score over 60, and no psychiatric hospitalizations or living in supported accommodation for the past two years (Albert et al., 2011)	14% fully recovered 60/304; 20% functionally recovered	Absence of a statistically significant association between DUP and recovery. [No]

Note: * Length of follow-up was 10 years or more. DUP = Duration of Untreated Psychosis; n = count; GAF = Global Assessment of Functioning Scale; GAF-F = Global Assessment of Functioning-Functioning Scale; PANSS = Positive and Negative Syndrome Scale; P = Positive Scale; N = Negative Scale; G = General Psychopathology Scale; & = and; % = Percentage.

(Continued)

Table 2.4: Summary of Studies ($n = 9$) Investigating the Association between DUP and Recovery.

Study Authors (Year)	Country	Sample Source	Length of Follow-up	Sample Size at Follow-up	Follow-up Rate n/total (%)	Measurement of DUP		Mean DUP	Recovery Dimension [Objective/ Subjective]	Operational Criteria for Recovery	Recovery Rate n/total; %	Presence of an Association between DUP & Recovery [Yes/No]
						Onset	Endpoint					
Gumley et al. (2014)	United Kingdom	National Health Service (NHS) Mental Health Services	1 year	68 People with First-Episode Psychosis	68/79 (86%)	Onset of psychotic symptomatology	Onset of treatment	44.37 weeks	Psychiatric [Objective]	Positive & Negative Symptoms	Not Specified	Presence of a statistically significant association between DUP and psychiatric recovery at 1-year follow-up. [Yes]

Note: DUP = Duration of Untreated Psychosis; n = count; & = and; % = Percentage.

Our understanding of the relationship between the duration of untreated psychosis and the other dimension of recovery, subjective recovery, is limited because no study to date has examined the association between these two variables among people with a first episode of psychosis (Tables 2.3 & 2.4).

2.4 Knowledge Gaps in Existing Literature

The duration of untreated psychosis appears to be a widely studied modifiable risk factor of poor outcome in people with first-episode psychosis. It has been a target of early intervention programs because of evidence that shortening the duration of untreated psychosis consequently results in better outcomes. However, whether these beneficial gains are sustained over the long-term is not well known because of the limited number of prospective studies with follow-up periods of ten years or more.

With recovery emerging as an outcome of interest, the association between the duration of untreated psychosis and recovery, specifically objective recovery, has increasingly been examined. However, no study to date has examined the association between the duration of untreated psychosis and subjective recovery.

Furthermore, all studies to date that have examined the association between duration of untreated psychosis and long-term outcomes (≥ 10 -years) including recovery have been conducted in countries outside of Canada.

2.5 Conceptual Framework

We constructed a conceptual framework (Figure 2.3) to help visualize the relationships among the variables and to help identify which variables to treat as potential confounding variables in our pre-planned multivariable regression analyses. The inter-relationships between each of the variables in the context of people with first-episode psychosis are described below and are depicted within the conceptual framework.

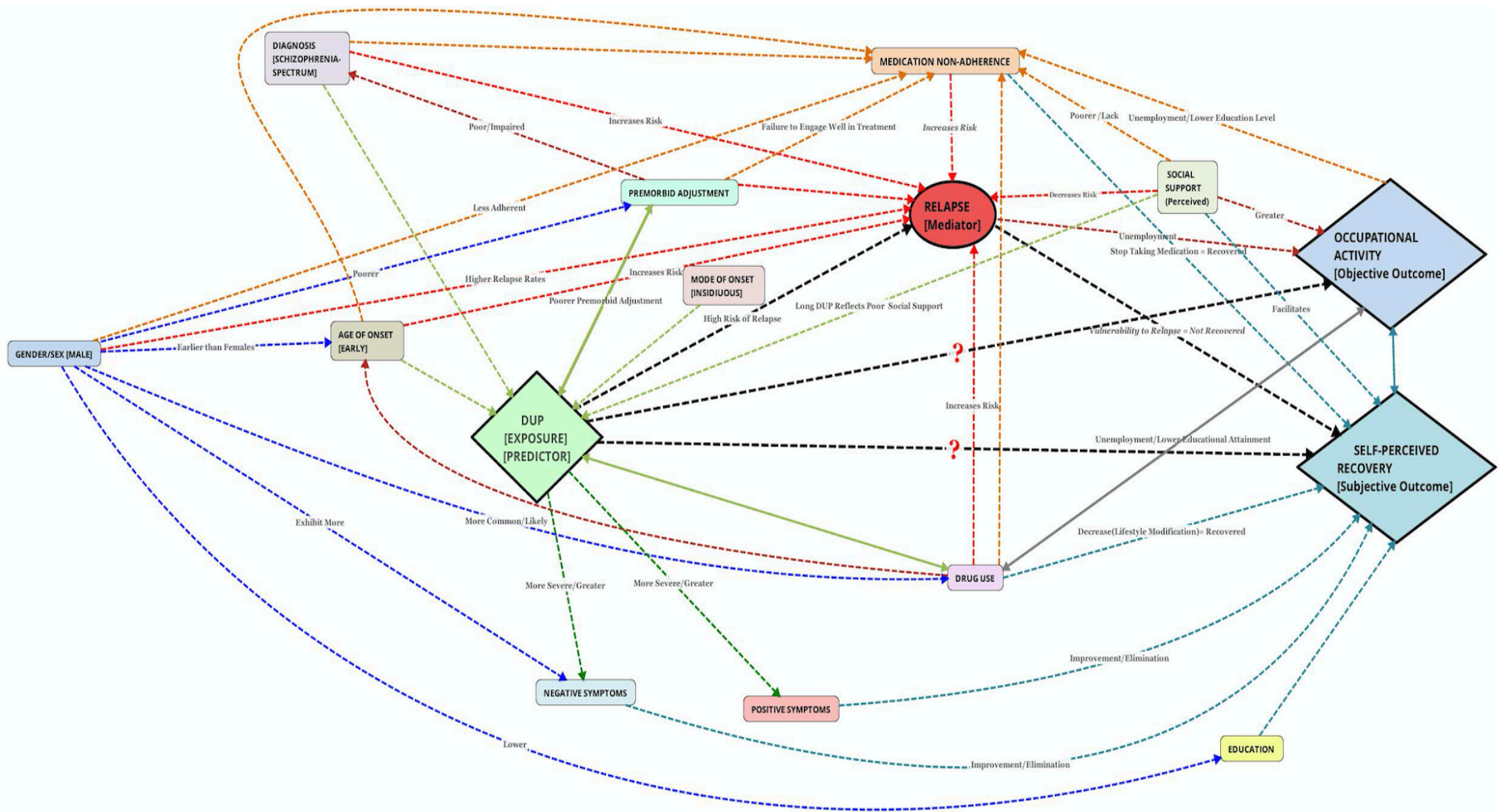


Figure 2.3: Conceptual Framework. Visual Depiction of the Relationships between the Exposure, Outcomes, and Potential Confounding Variables. Note: Self-Perceived Recovery = Self-Perceived Recovery Score.

Exposure

Duration of Untreated Psychosis

A long duration of untreated psychosis has been reported to be associated with an increased risk for relapse (Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), an earlier age of onset (Ehmann et al., 2014), an insidious mode of onset (Compton, Chien, Leiner, Gouldstring, & Weiss, 2008; Morgan et al., 2006), poor premorbid adjustment (Bechard-Evans, Schmitz, Abadi, Joobar, King, & Malla, 2007; Schimmelmann, Huber, Lambert, Cotton, McGorry, & Conus, 2008), schizophrenia-spectrum diagnosis (Bechard-Evans, Schmitz, Abadi, Joobar, King, & Malla, 2007), poor social support (Compton & Broussard, 2011), and greater positive and negative symptom severity (Hill et al., 2012). Furthermore, a long duration of untreated psychosis may result from the misattribution of positive symptoms of psychosis to the experience of ‘being high.’

Outcomes

Occupational Activity

Employment had been found to be a protective factor for relapse (Sariah, Outwater, & Malima, 2014). In addition, engagement in paid employment or education, both activities that hold social status can contribute to a greater sense of one’s self-perceived recovery (Windell & Norman, 2012). Furthermore, increased engagement in occupational activity has been reported to be associated with social support (Norman et al., 2007).

Unemployment and/or lower educational level has been reported to be associated with drug use (Mishra, Ojha, Chapagain, & Tulachan, 2014), increased risk for relapse (Chabungbam, Avasthi, & Sharan, 2007), and medication non-adherence (Leclerc, Noto, Bressan, & Brietzke, 2015).

Potential Mediator

Relapse

A higher risk for relapse has been found to be associated with a long duration of untreated psychosis (Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), medication non-adherence (Alvarez-Jimenez et al., 2012), poorer premorbid adjustment (Alvarez-Jimenez et al., 2012), schizophrenia-spectrum diagnosis (Hui et al., 2013), unemployment (Chabungbam, Avasthi, & Sharan, 2007), drug use (Bergé et al., 2015; Hui et al., 2013; Wade, Harrigan, Edwards, Burgess, Whelan, & McGorry, 2006), early age of onset (Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), single marital status (Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), and lower self-perceived recovery (Windell, Norman, & Malla, 2012). A decreased risk of relapse has been found to be associated with social support (Norman et al., 2005). In addition, males have been reported to have higher relapse rates than females (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012).

Potential Confounding Variables

Gender

As compared to females, males tend to have an earlier age of onset (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012), greater drug use (Arranz et al., 2015), exhibit more negative symptoms (Køster, Lajer, Lindhardt, & Rosenbaum, 2008; Thorup et al., 2014), are less likely to be engaged in education (Thorup et al., 2014), are less compliant with medication (Køster, Lajer, Lindhardt, & Rosenbaum, 2008; Thorup et al., 2014), have higher relapse rates (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012), and poorer premorbid adjustment (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012).

Age of Onset

An earlier age of onset has been shown to be associated with being male (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012), medication non-adherence (Coldham, Addington, & Addington, 2002), a long duration of untreated psychosis (Ehmann et al., 2014),

increased risk for relapse (Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), and drug use. (Tosato et al., 2013)

Mode of Onset

An insidious mode of onset has been reported to be associated with a long duration of untreated psychosis (Compton, Chien, Leiner, Gouldstring, & Weiss, 2008; Morgan et al., 2006).

Premorbid Adjustment

Poor premorbid adjustment has been reported to be associated with a long duration of untreated psychosis (Bechard-Evans, Schmitz, Abadi, Joobar, King, & Malla, 2007; Schimmelmann, Huber, Lambert, Cotton, McGorry, & Conus, 2008), being male (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012), medication non-adherence (Coldham, Addington, & Addington, 2002), and increased risk for relapse (Alvarez-Jimenez et al., 2012). In addition, poor premorbid adjustment has been identified as an early sign of schizophrenia (Gureje, Aderibigbe, Olley, & Bamidele, 1994; Schmael et al., 2007).

Diagnosis of Schizophrenia-Spectrum

A diagnosis of schizophrenia-spectrum has been reported to be associated with a long duration of untreated psychosis (Bechard-Evans, Schmitz, Abadi, Joobar, King, & Malla, 2007), an increased risk for relapse (Hui et al., 2013), greater likelihood of discontinued use of antipsychotic medication compared to people diagnosed with another type of first-episode psychotic disorder (Hui et al., 2013). An early sign of schizophrenia is poor premorbid adjustment (Gureje, Aderibigbe, Olley, & Bamidele, 1994; Schmael et al., 2007).

Positive Symptoms

Greater positive symptom severity has been shown to be associated with a long duration of untreated psychosis (Hill et al., 2012). It has also been reported that alleviation or elimination of symptoms contribute to a greater sense of self-perceived recovery (Windell & Norman, 2012; Windell, Norman, & Malla, 2012).

Negative Symptoms

Greater negative symptom severity has been shown to be associated with a long duration of untreated psychosis (Hill et al., 2012). Furthermore, males tend to exhibit more negative symptoms than females (Køster, Lajer, Lindhardt, & Rosenbaum, 2008; Thorup et al., 2014). It has also been reported that alleviation or elimination of symptoms contribute to a greater sense of self-perceived recovery (Windell & Norman, 2012; Windell, Norman, & Malla, 2012).

Socioeconomic Status

The education variable in the conceptual framework refers to highest level of education, which was used as a proxy measure for socioeconomic status. Males are less likely than females to be engaged in education (Thorup et al., 2014), which in turn can diminish their ability to attain a well-paying job, generally speaking. A lower socioeconomic status may also diminish one's sense of self-perceived recovery because of the difficulty in engaging in meaningful activities or achieving goals due to limited funds.

Medication Non-Adherence

Medication non-adherence has been reported to be associated with drug use (Miller, Ream, McCormack, Gunduz-Bruce, Sevy, & Robinson, 2009), increased risk for relapse (Alvarez-Jimenez et al., 2012; Hui et al., 2013), being male (Køster, Lajer, Lindhardt, & Rosenbaum, 2008; Thorup et al., 2014), an earlier age of onset (Coldham, Addington, & Addington, 2002), schizophrenia-spectrum diagnosis (Hui et al., 2013), poorer premorbid adjustment (Coldham, Addington, & Addington, 2002), poor social support (Rabinovitch, Bechard-Evans, Schmitz, Jooper, & Malla, 2009), and unemployment or lower education level (i.e., poor occupational activity) (Leclerc, Noto, Bressan, & Brietzke, 2015). In addition, medication non-adherence has been reported to be essential for one's sense of self-perceived recovery (Windell, Norman & Malla, 2012).

Social Support (Perceived)

Social support has been reported to be associated with a decreased risk of relapse and increased engagement in occupational activity (Norman et al., 2005). In addition, social support has also been cited as an important factor to facilitate recovery from a first episode of psychosis (Windell & Norman, 2012). Poor social support has been reported to be associated with a long duration of untreated psychosis (Compton & Broussard, 2011) and medication non-adherence (Rabinovitch, Bechara-Evans, Schmitz, Joobar, & Malla, 2009).

2.6 Detailed Thesis Objectives & Hypotheses

All four objectives of this thesis are visually summarized in the conceptual framework (Figure 2.3) presented in the previous section. In this section, each of the four objectives and hypotheses will be described. In addition, the corresponding section of the conceptual framework depicting each objective will be highlighted using a simplified version of the conceptual framework. The simplified version includes the exposure, potential mediator, and outcome variables (Figure 2.4).

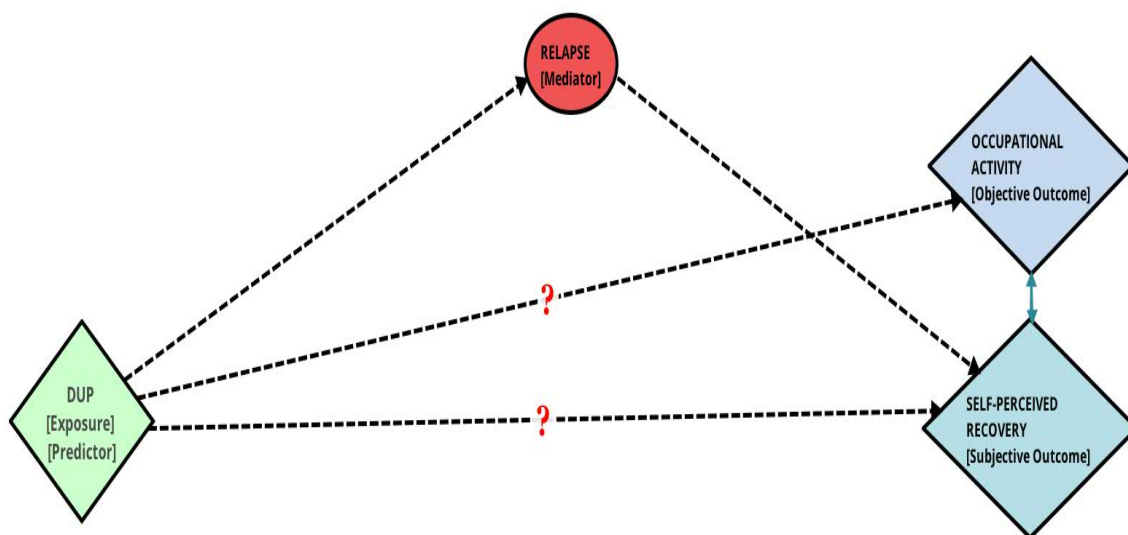


Figure 2.4: Simplified Conceptual Framework. Note: DUP = Duration of Untreated Psychosis; SELF-PERCEIVED RECOVERY = Self-Perceived Recovery Score.

2.6.1 Objective 1

Findings from empirical studies that have investigated the relationship between objective and subjective recovery from psychotic disorders (e.g. schizophrenia) or other serious mental illness have been equivocal, with evidence for and against the presence of an association (Jørgensen et al., 2015; Kukla, Lysaker, & Roe, 2014; Lloyd, King, & Moore, 2010; Morland, 2007; Norman, Windell, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004; Roe, Mashiach-Eizenberg & Lysaker, 2011). Given these inconsistent findings, we sought to examine the association at 10-year follow-up between occupational activity (less than 52 weeks of the past year vs. 52 weeks of past year), an objective measure of recovery, and self-perceived recovery score, a subjective measure of recovery, among people 16 to 50 years of age who experienced a first episode of psychosis (Figure 2.5).

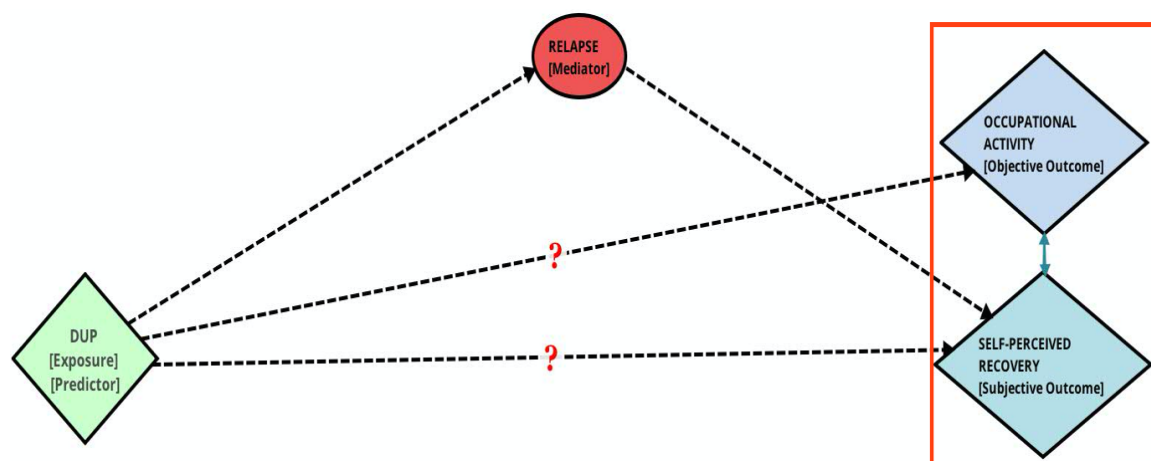


Figure 2.5: Objective 1 depicted within the Simplified Conceptual Framework. Note: DUP = Duration of Untreated Psychosis; SELF-PERCEIVED RECOVERY = Self-Perceived Recovery Score.

Hypothesis 1

We hypothesized that there would be a statistically significant positive association between occupational activity (i.e., objective recovery) and self-perceived recovery score (subjective recovery) at 10-year follow-up, such that people who engaged in occupational activity for 52 weeks of the past year would have higher self-perceived recovery scores.

2.6.2 Objective 2

The study conducted by Austin and colleagues (2013) is the only study to date that has investigated whether the duration of untreated psychosis is associated with objective recovery among people with first-episode psychosis over a long follow-up period (≥ 10 -years). To add to this essentially non-existent body of literature, we sought to investigate whether duration of untreated psychosis is associated with occupational activity (i.e., objective recovery) among people 16 to 50 years of age, 10-years after being treated for a first episode of psychosis, adjusting for gender, age of onset, and other confounding variables (Figure 2.6).

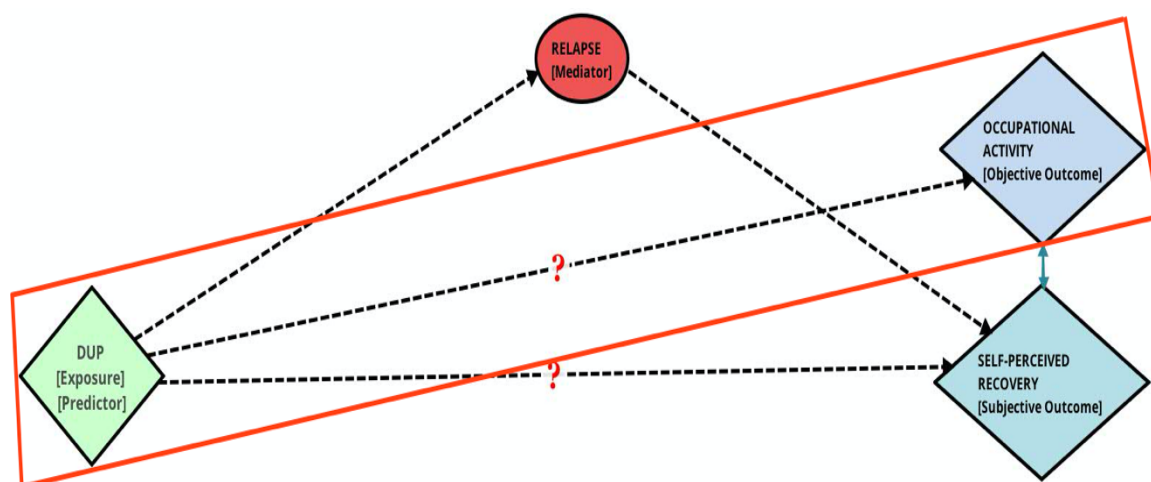


Figure 2.6: Objective 2 depicted within the Simplified Conceptual Framework. Note: DUP = Duration of Untreated Psychosis; SELF-PERCEIVED RECOVERY = Self-Perceived Recovery Score.

Hypothesis 2

We hypothesized that a longer duration of untreated psychosis would decrease the odds of engagement in occupational activity, adjusting for gender, age of onset, and other confounding variables.

2.6.3 Objective 3

To our knowledge, no study to date has examined the association between the duration of untreated psychosis and subjective recovery among people with first-episode psychosis.

To address this current gap in the literature, we investigated whether the duration of untreated psychosis is associated with self-perceived recovery score (i.e., subjective recovery) among people 16 to 50 years of age, 10-years after being treated for a first episode of psychosis, adjusting for gender, age of onset, and other confounding variables (Figure 2.7).

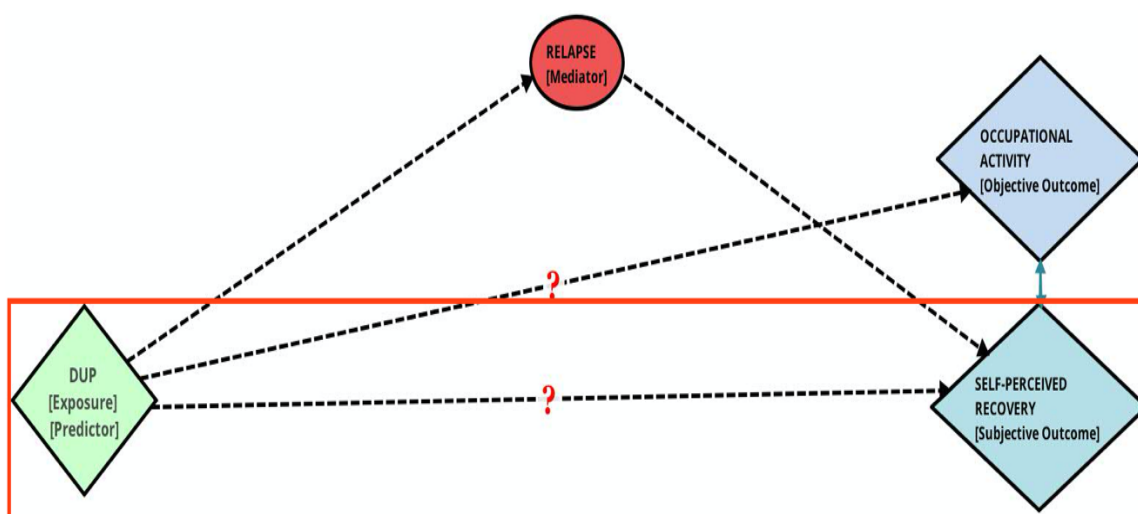


Figure 2.7: Objective 3 depicted within the Simplified Conceptual Framework. Note: DUP = Duration of Untreated Psychosis; SELF-PERCEIVED RECOVERY = Self-Perceived Recovery Score.

Hypothesis 3

We hypothesized that there will be a statistically significant negative association between the duration of untreated psychosis and self-perceived recovery score (i.e., subjective recovery), such that longer duration of untreated psychosis would be associated with lower self-perceived recovery scores, after adjusting for gender, age of onset, and other confounding variables.

2.6.4 Objective 4

Vulnerability to relapse has been found to be associated with a long duration of untreated psychosis (Saravanan et al., 2010; Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013), and it has also been perceived, by some, to be a barrier to one's recovery from a first-episode of psychosis (Maddigan, 2011; Windell, Norman, & Malla, 2012). We thus sought to investigate whether relapse mediates the relationship between the duration of untreated psychosis and self-perceived recovery score among people 16 to 50 years of age who experienced a first episode of psychosis, adjusting for gender, age of onset, and other confounding variables (Figure 2.8).

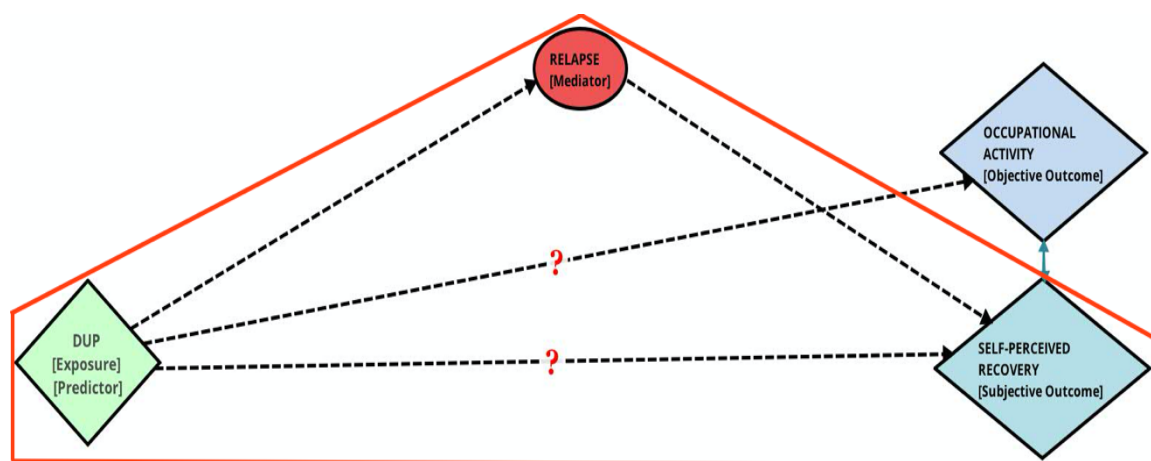


Figure 2.8: Objective 4 depicted within the Simplified Conceptual Framework. Note: DUP = Duration of Untreated Psychosis; SELF-PERCEIVED RECOVERY = Self-Perceived Recovery Score.

Hypothesis 4

We hypothesized that relapse will mediate the relationship between the duration of untreated psychosis and self-perceived recovery score (i.e., subjective recovery), such that a longer duration of untreated psychosis would be associated with greater relapse, which in turn would result in lower self-perceived recovery scores, after adjusting for gender, age of onset, and other confounding variables.

Chapter 3

3 Methods

In this chapter, the data source is described in Section 3.1, followed by the study procedure for the follow-up assessments conducted at 10-years (i.e., 10-year follow-up study) in Section 3.2. In Section 3.3, the process to obtain access to the data of the source study will be discussed. Thereafter in Section 3.4, a description of the observations and variables used in the statistical analyses will be provided. Next in Section 3.5, missing data and the method to handle missing data will be described. Lastly, the statistical analysis plan will be described in Section 3.6.

3.1 Data Source

As mentioned in Chapter 1, this thesis used data from a prospective cohort study that assessed outcomes of clients 10-years following initial treatment for a first episode of psychosis, received from an early intervention program (PEPP; London, Canada). This study titled, “*Assessment of 10 Year Outcomes for Clients of the Prevention and Early Intervention Program for Psychoses (PEPP)*” received ethics approval from Western University’s Ethics Board for Health Sciences Research. No further ethics approval for this thesis was required since our objectives fell within the scope of the objectives of the prospective cohort study.

PEPP is a comprehensive early psychosis intervention program that has been in operation since 1997 (Malla, Norman, McLean, Scholten, & Townsend, 2003; Norman & Manchanda, 2016), located in Zone A, on the 2nd floor of Victoria Hospital, London Health Sciences Centre (LHSC). This program is designed to treat non-affective first-episode psychotic disorders, and has an open referral policy, which allows family members, individuals, and concerned persons (e.g., teacher) to make a referral. A physician referral is not required (Norman & Manchanda, 2016; www.PEPP.ca).

Admission to PEPP is restricted to people who: 1) Are between the ages of 16 and 50 years; 2) Are experiencing symptoms of a first-episode non-affective psychotic disorder; 3) Have never been treated for psychosis or have taken antipsychotic medication for no

more than one month; 4) Do not suffer from organic brain damage, pervasive developmental disorder, epilepsy, or other brain disorders or injuries; 5) Have no current outstanding legal matters, such that contact with forensic psychiatric services is needed; and 6) Who live within the predominantly urban catchment area of Middlesex County and the city of London (www.PEPP.ca). People who meet these admission criteria are rapidly admitted to PEPP since this program does not have a waiting list (Norman & Manchanda, 2016).

Following admission to PEPP, an individualized treatment plan is created in collaboration with the client, family (if applicable), and with other professionals involved in the client's care including, but not limited to, a case manager, psychiatrist, or psychologist (Norman & Manchanda, 2016; www.PEPP.ca). The treatment plan includes medical management, psychosocial management, and case management (Malla, Norman, McLean, Scholten, & Townsend, 2003; Norman & Manchanda, 2016). Medical management refers to treatment by low-dose antipsychotic medication (primarily second-generation), prescribed by a psychiatrist to the client on a regular basis (Manchanda, Norman, Malla, Harricharan, & Northcott, 2008). Psychosocial management refers to treatment with psychosocial interventions such as individual supportive psychotherapy (i.e., cognitive behavioural therapy) (Malla, Norman, McLean, Scholten, & Townsend, 2003; Norman & Manchanda, 2016). Lastly, case management refers to treatment in the form of support and advocacy by one's case manager. The case manager coordinates care, develops goals, and ensures the needs of the client are being met, among many other functions (Malla, Norman, McLean, Scholten, & Townsend, 2003; www.PEPP.ca).

The treatment plan is structured around a modified case management model in which intensity of treatment is determined by the stage of a client's illness, the client's needs, and the needs of the client's family (Malla, Norman, McLean, Scholten, & Townsend, 2003). Each client will receive intense treatment for a minimum of two-years and up to a period of five-years (Malla, Norman, McLean, Scholten, & Townsend, 2003; Norman & Manchanda, 2016). Intense treatment involves the client receiving all forms of treatment offered by PEPP. At the end of the two-year treatment period, the clinical status of the client is assessed to determine whether to provide him or her with extended treatment in

the form of both medication management and case management (one- to three-years) or to provide less intense treatment in the form of medication management only (Malla, Norman, McLean, Scholten, & Townsend, 2003; Norman, Manchanda, Malla, Windell, Harricharan, & Northcott, 2011). Throughout the two to five-year period, the clinical status of the client is assessed every three to six months to determine whether to provide the client with greater or lesser treatment (Norman, Manchanda, Malla, Windell, Harricharan, & Northcott, 2011).

3.2 Study Procedure

The prospective cohort study (i.e., source study) collected data from clients at baseline, 5-year follow-up, and again at 10-year follow-up. We will focus our discussion of study procedures pertaining mainly to the follow-up assessment conducted 10-years following initial treatment for first-episode psychosis at PEPP.

3.2.1 Participant Recruitment

Between March 1997 and February 2002, a total of 132 people were admitted to PEPP. Each person provided informed consent to which he or she agreed to be followed-up for outcome assessments even if he or she was no longer receiving treatment at PEPP, as described in the letter of information (Malla et al., 2002; Norman, Manchanda, Malla, Windell, Harricharan & Northcott, 2011).

The eligibility criteria to take part in the source study were the same as the admission criteria for PEPP (Section 2.1). Additional eligibility criteria for participation in the study included: 1) Ability to speak or understand English; 2) Competent and willing to provide written informed consent; 3) Diagnosed with a non-affective psychotic disorder that meets Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria; and 4) Current Outpatient Status.

3.2.2 Follow-up Assessments

Between February 2014 and June 2015, the research coordinator at PEPP re-contacted some of the 132 clients admitted to PEPP between March 1997 and February 2002, with a request to participate in the 10-year follow-up assessment. Clients were re-contacted if

at least 10-years had elapsed since receiving initial treatment for a first episode of psychosis at PEPP. If the client agreed to participate, an assessment interview was scheduled at a time convenient for the client.

3.2.3 Assessment Interviews

Participation in the 10-year follow-up assessment involved the completion of an outcome assessment that included a battery of clinical and non-clinical outcome measures, some of which were also administered at 5-year follow-up. Completion of the outcome assessment was split between two assessment interviews that were scheduled a week or two apart. A random number system was used to determine the order in which outcome measures were to be administered to the participant in either the first and/or second assessment interview. The random number system is described in Figure 3.1.

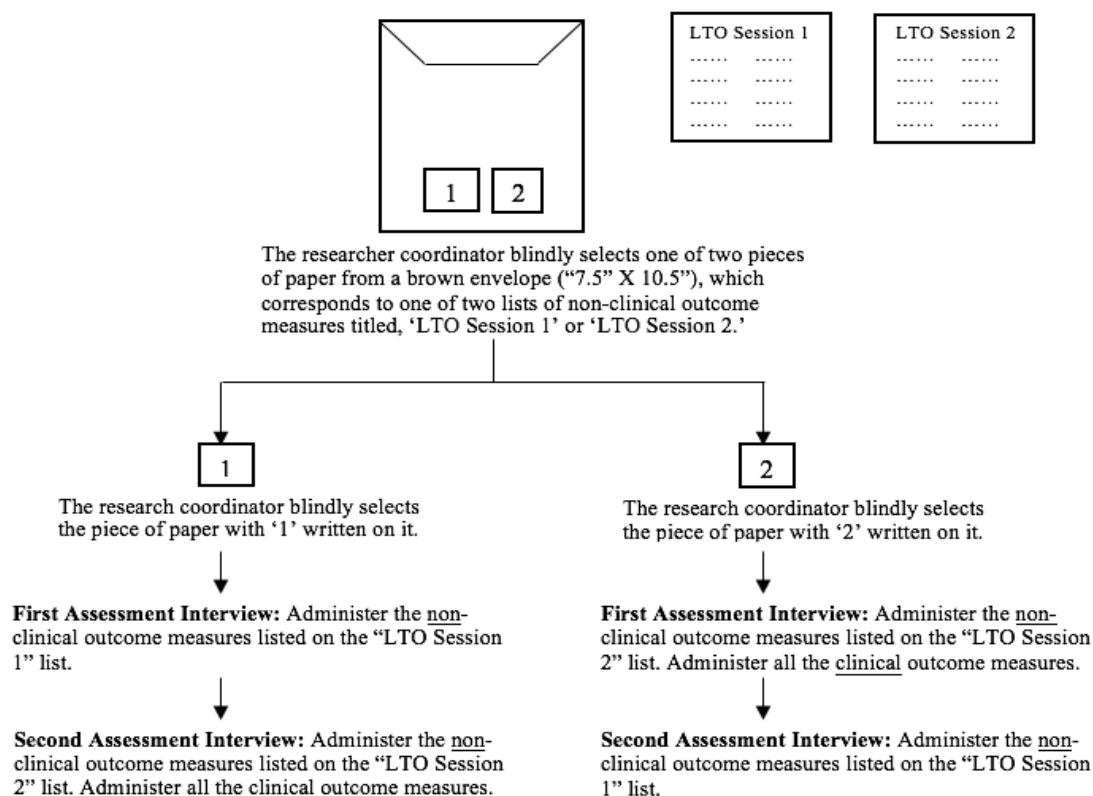


Figure 3.1: Random Number System. Note: Determined the order in which non-clinical and clinical outcome measures were to be administered during the first and/or second assessment interview; LTO = Long Term Outcome.

When the participant arrived for his or her first assessment interview, written informed consent was obtained. Demographic information was then obtained from the participant by use of a demographics questionnaire, and outcome measures were administered in a semi-structured interview format. *Non-clinical* outcome measures were administered to the participant by the research coordinator, who was trained and supervised by a licensed clinical psychologist. A licensed clinical psychologist or psychiatrist with PEPP administered all *clinical* outcome measures to the participant, ensuring a standardized presentation of study measures. Inter-rater reliability between these two clinicians with PEPP was good (Interclass correlation coefficient = 0.80). Outcome measures were administered verbally to participants with literacy or comprehension problems.

As the participant was completing the outcome measures, the interviewer took note of the participant's tolerance level, energy level, and level of cognitive functioning. Based on these factors, the participant may have been encouraged to take a break or to complete the rest of the interview another day. If a participant did not complete the 10-year assessment during the first interview, a second assessment interview was scheduled a week or two later.

Most participants completed the 10-year follow-up assessment over two interviews. Each assessment interview took between 1 to 1.5 hours to complete. All assessment interviews were conducted in research offices at PEPP. For each of the assessment interviews, participants were reimbursed for their time in the amount of \$30.00, as well as their travel expenses in the form of a parking pass or bus tickets. Participants were also provided with snacks and water at each of the assessment interviews.

3.3 Data Set

3.3.1 Data Access Process

Obtaining access to data from the prospective cohort study consisted of five steps. The first step involved having a meeting with the primary investigator of the source study. The purpose of this meeting was two-fold. First, to determine which studies were currently being conducted using the same data set, and second, to discuss possible research questions based on research currently being conducted in the field. The second

step involved formulating objectives and a statistical plan based on available data. The third step involved submitting a request for access to a subset of variables, which was submitted to the primary investigator. The fourth step involved the primary investigator extracting the requested variables from the main PEPP database containing demographic and longitudinal outcome data, and creating a data set. The final step of this process involved the primary investigator transferring the de-identified data set.

3.3.2 Data Cleaning

Upon receiving the data set, we used Stat/Transfer to convert the data from SPSS format to Stata format (sav to .dta). We then used Stata, version 14 (StataCorp, 2015) to ‘clean’ the data. This included dropping variables that were not required for pre-specified analyses, and checking for temporal consistency of data, distributions of all variables, and for potential outliers. Additional data cleaning included relabeling variables, recoding of variables, and transforming variables with a skewed distribution.

3.4 Variables & Measures

3.4.1 Exposure Variable

Duration of Untreated Psychosis

Duration of untreated psychosis was defined as the length of time in weeks between the date of onset of positive psychotic symptoms (e.g., hallucination) to the date of initiation of adequate treatment for 1-month. Adequate treatment referred to treatment with antipsychotic medication for 1-month (or until symptoms have resolved) or psychosocial treatment (i.e., assertive case management) for 1-month. These dates were extracted from select items from the CORS as part of the baseline assessment (Norman & Malla, 2002). The CORS is a semi-structured questionnaire administered at baseline by trained research assistants. This questionnaire is divided into five main sections: 1) Identifying Information; 2) Demographic Information; 3) Family Structure and Health; 4) Pathways to Care; and 5) Topography of Psychotic Episode (TOPE). In completing the CORS, information was obtained from the client, family, and referring source.

The CORS has been used in previous first-episode psychosis studies (e.g., Flanagan & Compton, 2012; Franz et al., 2010; Monte, Golding, & Compton, 2008), and has demonstrated excellent interrater reliability with ICC's ranging from 0.86 to 0.90 for the duration of untreated psychosis and for the duration of untreated illness (Iyer et al., 2008).

We assessed the distribution of the duration of untreated psychosis, which was observed to be positively skewed. For comparability of results, we normalized the duration of untreated psychosis distribution by taking the logarithm to base10 (\log_{10}), a routine approach used by other researchers in the field (e.g., Austin et al., 2013; Gumley et al., 2014; Norman et al., 2012). For all analyses conducted in this thesis, we used the duration of untreated psychosis (i.e., transformed version) as a continuous variable.

3.4.2 Outcome Variables

Self-Perceived Recovery

Self-perceived recovery was assessed at 10-year follow-up using the MARS (Bellack & Drapalski, 2012), a self-report measure of one's perceived status of recovery from serious mental illness. The MARS consists of 25-items, each scored on a 5-point Likert scale ranging from 1-*Strongly Disagree* to 5-*Strongly Agree*. The MARS covers six components of recovery based on those identified by SAMHSA, including **self-direction** (e.g., "I usually know what is best for me."), **empowerment** (e.g., "I have abilities that can help me reach my goals."), **holistic** (e.g., "I feel accepted as who I am."), **non-linear** (e.g., "When I have a relapse, I am sure that I can get back on track."), **strengths-based** (e.g., "My strengths are more important than my weaknesses."), **responsibility** (e.g., "I am responsible for making changes in my life."), and **hope** (e.g., "I am hopeful about the future."). All six components are considered to be essential to recovery and each domain exclusively focuses on measureable aspects of the person (Drapalski et al., 2012).

The MARS has demonstrated strong internal consistency for the entire measure ($\alpha = 0.95$), as well as strong test-retest reliability ($\alpha = 0.898$) when used with a sample of 166 people with severe mental illness including schizophrenia, schizoaffective disorder,

bipolar I disorder, or major depression with psychotic features (Drapalski et al., 2012). This empirical measure can be used for both research and clinical purposes (Bellack & Drapalski, 2012).

For the purpose of this thesis, we used the total MARS score as an overall assessment of self-perceived recovery. Total scores on this uni-dimensional measure range from 25 to 125. Higher scores are indicative of greater self-perceived recovery from severe mental illness. Self-perceived recovery score was used as a subjective measure of recovery. We used self-perceived recovery score at 10-year follow-up as a continuous variable in all analyses.

Occupational Activity

Occupational activity included engagement in work and/or school on a full-time or part-time basis in the past year. This was assessed at 10-year follow-up using items from the Life Chart Schedule (LCS) (WHO, 1992), which was designed to assess the long-term outcomes and course of schizophrenia in four domains: Symptoms, treatment, residence, and work (Sartorius, Gulbinat, Harrison, Laska, & Siegel, 1996). Specifically, we used items 2, 3, 10, and 11 of the 16-item modified “Work & Disability” subscale. Items 2 (“*Weeks in full-time jobs.*”) and 3 (“*Weeks in part-time jobs.*”) were used to assess the number of weeks during the past year the participant was employed full-time or part-time. Items 10 (“*Weeks as full-time student.*”) and 11 (“*Weeks as part-time student.*”) were used to assess the number of weeks during the past year the participant attended school on a full-time or part-time basis.

We generated the occupational activity variable by summing together responses for Items 2 (“*Weeks in full-time jobs.*”), 3 (“*Weeks in part-time jobs.*”), 10 (“*Weeks as full-time student.*”), and 11 (“*Weeks as part-time student.*”) of the 16-item modified “Work and Disability” subscale of the LCS. We followed the approach that Norman and colleagues (2007; 2012) have used to compute and assess occupational activity among people with first-episode psychosis. However, we additionally included engagement in work and/or school on a part-time basis. Psychometric information for the use of this approach was not available.

We assessed the distribution of weeks of occupational activity, which was observed to be bimodal. We therefore decided to dichotomize weeks of occupational activity by using the median as the cut-point. Thus, participants were engaged in occupational activity for either 52 weeks of the past year or for less than 52 weeks of the past year. Occupational activity was used as an objective measure of recovery. We used occupational activity at 10-year follow-up as a dichotomous variable in all analyses.

3.4.3 Mediator Variable

Relapse

We used number of hospitalizations for a mental health reason, as derived from medical charts, as a proxy indicator for relapse. Number of hospitalizations were extracted from baseline to 5-year follow-up (time 1) and from 5-year follow-up to 10-year follow-up (time 2). The number of hospitalizations at time 2 were used in the mediation analysis.

A more accurate measure of relapse is the recurrence of the positive symptoms of psychosis, however, these data were not collected between the 5- and 10-year follow-up periods. Nonetheless, hospitalization data are a sensitive (87%), yet, non-specific (47%) indicator of relapse among people with first-episode psychosis (Addington, Patten, McKenzie, & Addington, 2013).

3.4.4 Potential Confounding Variables

For all analyses, we adjusted for 11 of the 13 variables we identified as potential confounders in our conceptual framework (Chapter 2). A description of the inter-relationships among the exposure variable, the two outcome variables, the mediator variable, and the potential confounding variables is provided in Chapter 2. A rationale for why we did not adjust for two of the potential confounding variables in all analyses is provided in this section.

Gender

Gender was assessed at baseline using the demographics questionnaire, with response options of either *Male* or *Female*.

Age of Onset

Age of onset refers to one's chronological age at the time of the first onset of psychotic symptoms (e.g., hallucinations) (Norman et al., 2007). To calculate age of onset, date of *birth* and date of *first change* were obtained from the TOPE section of the CORS (Norman & Malla, 2002). At baseline, information for the CORS was obtained from patient reports and combined with any information provided by the family and referral source. We used age of onset as a continuous variable in all analyses.

Mode of Onset

Mode of onset refers to how quickly psychotic symptoms develop over the course of a first episode of psychosis (Compton, 2010). Mode of onset was calculated by subtracting date of *onset of psychosis* (day/month/year) from date of *first change* (day/month/year), which were obtained from the CORS (Norman & Malla, 2002). At baseline, information was obtained from patient reports and combined with any information provided by the family and referral source.

Mode of onset was used as a dichotomous variable in all analyses, with participants labelled with *insidious* or *acute* mode of onset. An *insidious* mode of onset was defined as equal or greater to 1-month, and an *acute* mode of onset defined as less than 1-month.

Diagnosis of a Psychotic Disorder

A primary diagnosis of a non-affective psychotic disorder was made at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1995). The SCID-CV is a semi-structured interview that was administered by trained research assistants and cross-checked with the treating clinician. In completing the SCID-CV, information was obtained from various sources including client report, information provided by family, and any available medical records.

The SCID-CV is comprised of three main sections: 1) Overview; 2) Modules A to F; and 3) Diagnostic Summary. The modules section of the SCID-CV is used for the purposes of

making a diagnosis. This section is comprised of six modules corresponding to six diagnostic categories: A) Mood Episodes (69-items); B) Psychotic and Associated Symptoms (15-items); C) Differential Diagnosis of Psychotic Disorders (39-items); D) Mood Disorders (19-items); E) Alcohol and Other Substance Use Disorders (32-items); and F) Anxiety and Other Disorders (91-items). Modules C and D were used to make a diagnosis of a psychotic disorder.

Items within each module correspond to specific criteria or symptoms of a specific disorder. Items are rated according to one of the two response ratings: 1) Inadequate information (?), Absent/Subthreshold (-), Present (+); or 2) Yes/No. Some items are skipped depending on how that item was rated. For each disorder, a certain number of criteria/symptoms or certain criteria/symptoms must be present (rated as either + or Yes) in order to be diagnosed with a particular disorder.

We dichotomized diagnosis into *schizophrenia-spectrum* or *other psychotic disorder*. We categorized the following diagnoses as *schizophrenia-spectrum*: Schizophrenia-Disorganized; Schizophrenia-Paranoid; Schizophreniform; Schizoaffective; and Schizophrenia-Undifferentiated. We then categorized the remaining diagnoses as *other psychotic disorder*: Substance-Induced Psychosis; Bipolar I with Psychotic Features; Major Depression with Psychotic Features; Brief Psychotic Disorder; and Psychosis Not Otherwise Specified.

Premorbid Adjustment

Premorbid adjustment refers to the person's psychosocial functioning before the onset of psychotic illness or symptoms (Cannon-Spoor, Potkin, & Wyatt, 1982), and was assessed at baseline using the Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982). The PAS is a rating scale that assesses premorbid adjustment from a developmental perspective. This scale consists of a general section and four sections pertaining to distinct developmental age periods including childhood (up to 11 years), early adolescence (12 to 15 years), late adolescence (16 to 18 years), and adulthood (19 years and above). Within each of the four developmental age periods, all or some of the following five domains of psychosocial functioning are assessed: 1) Sociability and

withdrawal; 2) Peer relationships; 3) Scholastic performance; 4) Adaptation to school; and 5) Ability to form social-sexual relationships. Ability to form social-sexual relationships is not included nor assessed in the childhood period, while scholastic performance and adaptation to school are not included nor assessed in the adulthood period. The general section contains items assessing energy level, interest in life, independence, education, social-personal adjustment, highest level of global functioning achieved, work (employed for pay, change in work, and frequency of job change), or school (attendance, functioning, and performance). This section was not completed by participants in the baseline assessment.

To minimize confounding of onset of illness and premorbid adjustment, ratings from the late adolescence and adulthood periods were excluded from the analysis because onset of psychotic or early symptoms generally occurs in late adolescence or early adulthood (Norman, Malla, & Manchanda, 2007). Thus, ratings of items from the childhood and early adolescence periods were used to assess premorbid adjustment, specifically items pertaining to the sociability and scholastic performance domains. Each item was rated on a Likert-type scale ranging from 0 to 6. For each psychosocial domain assessed in these age periods, ratings were summed and divided by the total possible rating, resulting in an index varying between 0 and 6, with higher scores indicating worse adjustment. All ratings were made with reference to the premorbid period, which ends 6-months before the onset of positive psychotic symptoms (Cannon-Spoor, Potkin, & Wyatt, 1982). Ratings were based on information obtained from patient reports and combined with any information provided by the family and referral source.

With respect to psychometric properties, Brill and colleagues (2008) results support the predictive and concurrent validity of the PAS when used with 91 males with schizophrenia or schizoaffective disorder, based on the Pearson correlations between the PAS (school achievements and school adjustment items) and the Draft Board's (functioning in structured environments scale) concurrent ratings ($r = 0.71$ and $r = 0.72$) and ratings obtained again at the age of 17 years (re-administered; $r = 0.43$ and $r = 0.47$). The PAS also demonstrated good scale reliability: Childhood ($\alpha = 0.72$; four items);

Early adolescence ($\alpha = 0.79$; five items); and Late adolescence ($\alpha = 0.79$; five items) (Brill, Reichenberg, Weiser, & Rabinowitz, 2008).

We used the overall premorbid adjustment scale rating for childhood and adolescence (i.e., premorbid adjustment score) as a continuous variable in our descriptive analysis. We were unable to use this variable in our simple and multivariable regression analyses because of the lack of variability in the distribution of scores.

Positive Symptoms

The presence and severity of the positive symptoms of psychosis were assessed at baseline, 5-year follow-up, and 10-year follow-up using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). The SAPS consists of 34-items, each rated on a 6-point Likert-type scale ranging from 0-*Absent* to 5-*Severe*. The SAPS yields cumulative ratings and subscale ratings (i.e., global ratings) pertaining to four positive symptoms: 1) ***Hallucinations*** (7 items; e.g., Visual Hallucinations, “*The patient sees shapes or people that are not actually present.*”); 2) ***Delusions*** (13 items; e.g., Thought Insertion, “*The patient believes that thoughts that are not his or her own have been inserted into his or her head.*”); 3) ***Bizarre Behaviour*** (5 items; e.g., Repetitive or Stereotyped Behaviour, “*The patient develops a set of repetitive actions or rituals that he or she must perform over and over.*”); and 4) ***Positive Formal Thought Disorder*** (9 items; e.g., “Tangentiality, “*Replying to a question in an oblique or irrelevant manner.*”).

All ratings were completed with reference to the past month. Cumulative ratings range from 0 to 170, with higher ratings reflective of a greater severity of positive symptoms. Global ratings for each positive symptom range from 0 to 20, with higher ratings reflective of a greater severity of a particular positive symptom.

The SAPS has been used in previous first-episode psychosis studies (e.g., Austin et al., 2015; Malla et al., 2008; Norman, Malla, & Manchanda, 2007), but specific psychometric information was not provided.

To obtain a single continuous measure of severity of positive symptoms, we computed a composite score using the global ratings of each of the four positive symptoms (Norman et

al., 2012). We used the positive symptoms scores at baseline and 10-year follow-up as continuous variables in all analyses.

Negative Symptoms

The presence and severity of the negative symptoms of psychosis were assessed at baseline, 5-year follow-up, and 10-year follow-up using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). The SANS consists of 25-items, each rated on a 6-point Likert-type scale ranging from 0-*Absent* to 5-*Severe*. The SANS yields cumulative ratings and subscale ratings (i.e., global ratings) pertaining to five negative symptoms: 1) ***Affective Flattening or Blunting*** (8 items; e.g., Affective Nonresponsivity, “*The patient fails to laugh or smile when prompted.*”); 2) ***Alogia*** (5 items; e.g., Poverty of Speech, “*The patient’s replies to questions are restricted in amount, tend to be brief, concrete, unelaborated.*”); 3) ***Avolition-Apathy*** (4 items; e.g., Physical Anergia, “*The patient tends to be physically inert. He or she may sit for hours and not initiate spontaneous activity.*”); 4) ***Anhedonia-Asociality*** (5 items; e.g., Ability to Feel Intimacy and Closeness, “*The patient may display an inability to form close or intimate relationships, especially with opposite sex and family.*”); and 5) ***Attention*** (3 items; Social Inattentiveness, “*The patient appears uninvolved or unengaged. He or she may seem spacey.*”).

All ratings were completed with reference to the past month. Cumulative ratings range from 0 to 125, with higher ratings reflective of a greater severity of negative symptoms. Global ratings for each negative symptom range from 0 to 25, with higher ratings reflective of a greater severity of a particular negative symptom.

The SANS was initially developed for those with a diagnosis of schizophrenia. However, a recent study reported that the SANS structure was similar among a sample of people with first-episode schizophrenia spectrum ($n = 191$) or non-schizophrenia spectrum ($n = 246$) diagnoses, thus supporting the use of the SANS among people with first-episode psychosis (Lyne et al., 2013). The SANS has been used in previous first-episode psychosis studies (e.g., Austin et al., 2015; Lyne et al., 2013; Malla et al., 2008; Norman,

Malla, & Manchanda, 2007), and has been reported to have good psychometric properties (Lyne et al., 2013); however, specific psychometric information was not provided.

To obtain a single continuous measure of severity of negative symptoms, we computed a composite score using the global ratings of each of the five negative symptoms (Norman et al., 2012). We used the negative symptoms scores at baseline and 10-year follow-up as continuous variables in all analyses.

Highest Level of Education

Highest level of education attained was assessed at 10-year follow-up using the demographics questionnaire. The response options for highest level of education included: “*No formal schooling completed*,” “*Elementary School (8th grade)*,” “*Some High School (no diploma)*,” “*High School graduate or the equivalent (GED)*,” “*Some college or university (no degree/diploma)*,” “*Trade/technical/vocational training*,” “*College*,” “*University*,” and “*Graduate School*.” Information collected on participants’ highest level of education was used as a proxy indicator of socioeconomic status. Based on the lack of variability in response options, we recoded this variable to allow participants to be grouped into one of two levels of education: 1) Less than or completed high school; 2) Some post-secondary or higher.

Social Support (Perceived)

Social support was assessed at 10-year follow-up using the Interpersonal Support Evaluation List (ISEL; Cohen, Mermelstein, Kamarck, & Hoberman, 1985), a 40-item, dichotomously scored (*Probably True /Probably False*) self-report measure of perceived social support. The ISEL yields total scores and subscale scores assessing four domains of social support including ***appraisal*** (10 items; e.g., “*There is at least one person I know whose advice I really trust.*”), ***tangible*** (10 items; e.g., “*If I needed a quick emergency loan of \$100, there is someone I could get it from.*”), ***self-esteem*** (10 items; e.g., “*Most of my friends are more interesting than I am.*”), and ***belonging*** (10 items; e.g., “*When I feel lonely, there are several people I could call and talk to.*”). The ***appraisal*** subscale measures a person’s perception of having someone to talk to about his or her problems.

The *tangible* subscale measures a person's perception of having someone to provide material aid. The *self-esteem* subscale measures a person's perception of having someone that will provide positive comparison when comparing him or herself to others. The *belonging* subscale measures a person's perception of having people with whom he or she can do things with.

The ISEL has demonstrated strong internal consistency ($\alpha = 0.93$) and high 4-month test-retest reliability ($r = 0.83$) among a sample of 59 people with a diagnosis of bipolar I disorder (Johnson, Winett, Meyer, Greenhouse, & Miller, 1999). Total scores on this measure range from 0 to 40. Higher scores are indicative of greater perceived social support.

To obtain a single continuous measure of perceived social support, we computed a composite score using the subscale ratings of each of the four domains of social support, and the perceived social support score was used as a continuous variable in all analyses.

Drug Use

Drug use was assessed at baseline, 5-year follow-up, and 10-year follow-up using the 20-item Drug Abuse Screening Test (DAST-20; Skinner, 1982), a self-report measure of one's involvement and abuse of drugs in the last 3-months (e.g., "*In the last 3 months, have you used drugs other than those required for medical reasons?*"). For the purposes of the DAST-20, drug use is operationalized as any non-medical use of drugs (i.e., street drugs). Non-medical use of drugs does not include alcohol.

All 20-items on this uni-dimensional measure are dichotomously scored (*Yes/No*). A score of "1" is given for each *Yes* response, except for items 4 ("*Did you get through the week without using drugs (other than those required for medical reasons)?*") and 5 ("*Were you always able to stop using drugs when you want to?*"), for which a *No* response is given a score of "1." If the response to item 1 ("*Have you used drugs other than those required for medical reasons?*") and item 2 ("*Have you abused prescription drugs?*") are both "No," the remaining 18-items are not to be completed. Total scores on

this measure range from 0 to 20, with higher scores indicating a greater severity of drug use.

The use of a cut-off score of 3 or above (sensitivity, 85%; specificity, 73%) on the DAST-20 has been recommended for optimal detection of problem drug use in a sample of people with first-episode psychosis sampled from an early intervention service, as compared to the conventional score of 6 or above (sensitivity, 55%; specificity, 86%) (Cassidy, Schmitz, & Malla, 2008).

The DAST-20 has demonstrated strong internal consistency when used with a sample of 128 people with first-episode psychosis ($\alpha = 0.998$) (Cassidy, Schmitz, & Malla, 2008), and has demonstrated good test/retest reliability (ICC = 0.78) when used with a sample of 97 outpatients with an Axis I disorder, other than substance abuse or dependence (e.g., schizophrenia) (Cocco & Carey, 1998).

We did not use either of the cut-off score recommendations (i.e., 3 or 6) because a majority of the participants had a score of zero (i.e., no drug use) at 10-year follow-up. We therefore dichotomized drug use at 10-year follow-up into *Yes*, indicative of any drug use (DAST-20 score is greater than zero) or *No*, indicative of no drug use (DAST-20 score is zero).

Medication Adherence

Adherence to first- or second-generation antipsychotic medication was assessed at 5-year follow-up and at 10-year follow-up using a single-item question pertaining to the past month and year: “*Based on all available information, approximately what percentage of time has the patient been taking medication as prescribed.*” This question was formulated based on findings from a comparison study of multiple measures of adherence to antipsychotic medication in first-episode psychosis by Cassidy and colleagues (2010).

Responses reflected the interviewer’s estimate of medication adherence based on information from four different subjective sources including the client, the case manager, the family, and the treating clinician. The estimate was rated on a four-point scale: 1 (0-25%), 2 (26-50%), 3 (51-75%), and 4 (76-100%). In the event that the sources disagreed,

the case was discussed and a consensus was reached based upon all available information; however, the treating clinician's estimation carried the most weight.

The reliability of using a consensus rating of medication adherence based on different sources has been examined in a study involving a sample of 81 clients with first-episode psychosis, treated at a specialized early intervention service in Montreal, Quebec (Cassidy, Rabinovitch, Schmitz, Jooper, & Malla, 2010). The researchers reported that there was good agreement between measures of adherence obtained from three different sources including pill count, clinician report, and patient report (ICC = 0.84) (Cassidy, Rabinovitch, Schmitz, Jooper, & Malla, 2010).

Due to the lack of variability in ratings, we recoded medication adherence at 10-year from a categorical variable to a dichotomous variable. Participants were grouped into either less than or equal to 75% medication adherence (ratings 1 or 3) or greater than 75% medication adherence (rating 4). Medication adherence at 10-year follow-up was reported as a dichotomous variable in our descriptive analysis, but we were unable to use this variable in our multivariable analyses due to a lack of variability in its distribution.

3.5 Missing Data

3.5.1 Missing Data Approaches

We examined the amount of missing data using the following approaches:

- 1) Determining the total number of observations (i.e., participants) with missing data (i.e., missing data for one or more variables);
- 2) Determining the total number of variables with an observation (i.e., participant) missing data;
- 3) Calculating the amount of missing data for the exposure, outcomes, potential mediator, and potential confounding variables;
- and 4) Examining the pattern and mechanism of missing data. Findings for the first three missing data approaches are presented in Table 3.1.

Table 3.1: Missing Data Approaches.

Missing Data Approach	<i>n</i> (Percent Missing)
1. Total number of observations with missing data	28 (41.2%)
2. Total number of variables with missing data (i.e., observation)	26 (60.5%)
3. Total missing data for exposure, outcomes, potential mediator, and potential confounding variables	
Exposure	
Duration of Untreated Psychosis (weeks)	1 (1.5%)
Outcomes	
Occupational Activity (Less than 52 weeks of past year vs. 52 weeks of past year)	1 (1.5%)
Self-Perceived Recovery Score	2 (2.9%)
Mediator (Assessment Point)	
Number of Hospital Admissions (<i>Baseline to 5-year follow-up; time 1</i>)**	12 (17.7%)
Number of Hospital Admissions (<i>5-year to 10-year follow-up; time 2</i>)	1 (1.5%)
Potential Confounding Variables (Assessment Point)	
Gender (<i>Baseline</i>)	0 (0.0%)
Diagnosis of a Psychotic Disorder (<i>Baseline</i>)	0 (0.0%)
Positive Symptoms (<i>10-year follow-up</i>)	0 (0.0%)
Negative Symptoms (<i>10-year follow-up</i>)	0 (0.0%)
Highest Level of Education (<i>10-year follow-up</i>)	0 (0.0%)
Drug Use (<i>10-year follow-up</i>)	0 (0.0%)
Mode of Onset (<i>Baseline</i>)	1 (1.5%)
Perceived Social Support Score (<i>10-year follow-up</i>)	1 (1.5%)
Age of Onset (<i>Baseline</i>)	2 (2.9%)
Positive Symptoms (<i>Baseline</i>)	3 (4.4%)
Negative Symptoms (<i>Baseline</i>)	3 (4.4%)
Medication Adherence (<i>10-year follow-up</i>) +	4 (5.9%)
Premorbid Adjustment Score (<i>Baseline</i>) +	9 (13.2%)
Positive Symptoms (<i>5-year follow-up</i>) **	12 (17.7%)
Negative Symptoms (<i>5-year follow-up</i>)**	13 (19.1%)
Medication Adherence (<i>5-year follow-up</i>) **	14 (20.6%)
Drug Use (<i>5-year follow-up</i>) **	20 (29.4%)
Drug Use (<i>Baseline</i>) **	40 (58.8%)

Note: **Variables missing a large percentage of data and were excluded for all analyses; +Variables not included in all analyses; *n* = Count; Observation = Participant; Total number of observations = 68; Total number of variables = 43.

For the final missing data approach, we examined the pattern and mechanism of missing data. We had to distinguish between two patterns of missing data: 1) Monotone; and 2) Arbitrary (Bouhlila & Sellaouti, 2013). A missing monotone pattern exists if one can observe a clear pattern among the missing values. If no clear pattern is observed, then the pattern of missing data is referred to as missing arbitrarily, also referred to as general or non-monotone (Munguía & Armando, 2014).

In addition to determining the pattern of missing data, we further determined the mechanism of missing data for which three such mechanisms exist: 1) Missing completely at random (MCAR); 2) Missing at random (MAR); and 3) Missing not at random (MNAR) (Little & Rubin, 2002; Rubin, 1976). MCAR describes the case where the probability a data value missing for a particular variable is *unrelated* to other measured (or observed) variables in the data set and is unrelated to the variable with missing values itself. MAR refers to the case where the probability a data value is missing for a variable is *related* to other measured (or observed) variables in the data set, but unrelated to the variable with missing data itself. Lastly, MNAR, sometimes called not missing at random (NMAR), describes the case where the probability a data value is missing for a particular variable depends on the *unobserved* (i.e., missing) value for the variable itself (Nakai & Ke, 2011; Vittinghoff, Glidden, Schiboski, & McCulloch, 2011).

We assumed the pattern of missing data to be missing arbitrarily and we assumed the mechanism of missing to be MAR for all data, except for all data collected at 5-year follow-up. For number of hospitalizations (time 1) and for data collected at 5-year follow-up including medication adherence, drug use, positive and negative symptoms, we assumed the pattern of missing data to be monotone and the mechanism of missing data to be MNAR because these data were missing for those who refused to participate in the 5-year follow-up assessment. We therefore excluded all data collected at 5-year follow-up from all analyses.

3.5.2 Method to Handle Missing Data

The pattern and mechanism of missing data, along with our intention to retain our entire sample ($n = 68$) guided our approach to use multiple imputation (MI) to handle missing

data in our data set (Vittinghoff, Glidden, Schiboski, & McCulloch, 2011). Compared to single imputation methods such as mean imputation where the missing value is imputed with the sample mean (Figure 3.2), in MI, a missing value is imputed multiple times (m times) by a set of plausible values sampled from an imputation model (Karahalios, Baglietto, Carline, English, & Simpson, 2012; Vittinghoff, Glidden, Schiboski, & McCulloch, 2011; White, Royston, & Wood, 2011).

Prior to executing MI, we had to decide whether we wanted to construct our imputation model using the multivariate normal or the chained equations approach (Bouhlila & Sellaouti, 2013; Karahalios, Baglietto, Carline, English, & Simpson, 2012; Vittinghoff, Glidden, Schiboski, & McCulloch, 2011), and we had to decide on the number of imputations (m). We decided to use the chained equations approach, sometimes referred to as imputation using chain equations (ICE) or multiple imputation by chained equations (MICE) (Bouhlila & Sellaouti, 2013). We selected MICE because of its unique ability to handle different types of variables such as continuous, binary, and categorical, by modelling each variable using a model tailored to its distribution. For instance, linear regression for a continuous variable and logistic regression for a binary variable. (Bouhlila & Sellaouti, 2013; Vittinghoff, Glidden, Schiboski, & McCulloch, 2011). We also selected 50 imputations ($m = 50$) based on the following rule of thumb, “The number of imputations should be similar to the percentage of cases that are incomplete” (Bodner, 2008; Von Hippel, 2009). We did not impute data for our outcomes of interest, and participants missing these data were excluded ($n = 3$).

The execution of MI involves three steps (Figure 3.2); 1) **Impute** -The missing values are imputed m times to generate m complete data sets by sampling from a specified imputation model; 2) **Analyze**- The m completed data sets are analyzed to obtain m sets of parameter estimates and corresponding standard errors; and 3) **Pool**- The parameter estimates and corresponding standard errors and confidence intervals for each of the m complete data sets are averaged to yield one overall MI estimate (Biering, Hjollund, & Frydenburg, 2015; Nakai & Ke, 2011; White, Royston, & Wood, 2011). To obtain valid statistical inferences, the mechanism of missing data is assumed to be MAR (Bouhlila & Sellaouti, 2013; Little & Rubin, 2002). In order to obtain valid statistical inferences with

MI, we decided to exclude variables (i.e., all 5-year follow-up data) with missing data assumed to be MNAR from the imputation model and from the regression models. We also incorporated a seed number in the first step of MI in order to ensure replicability of results.

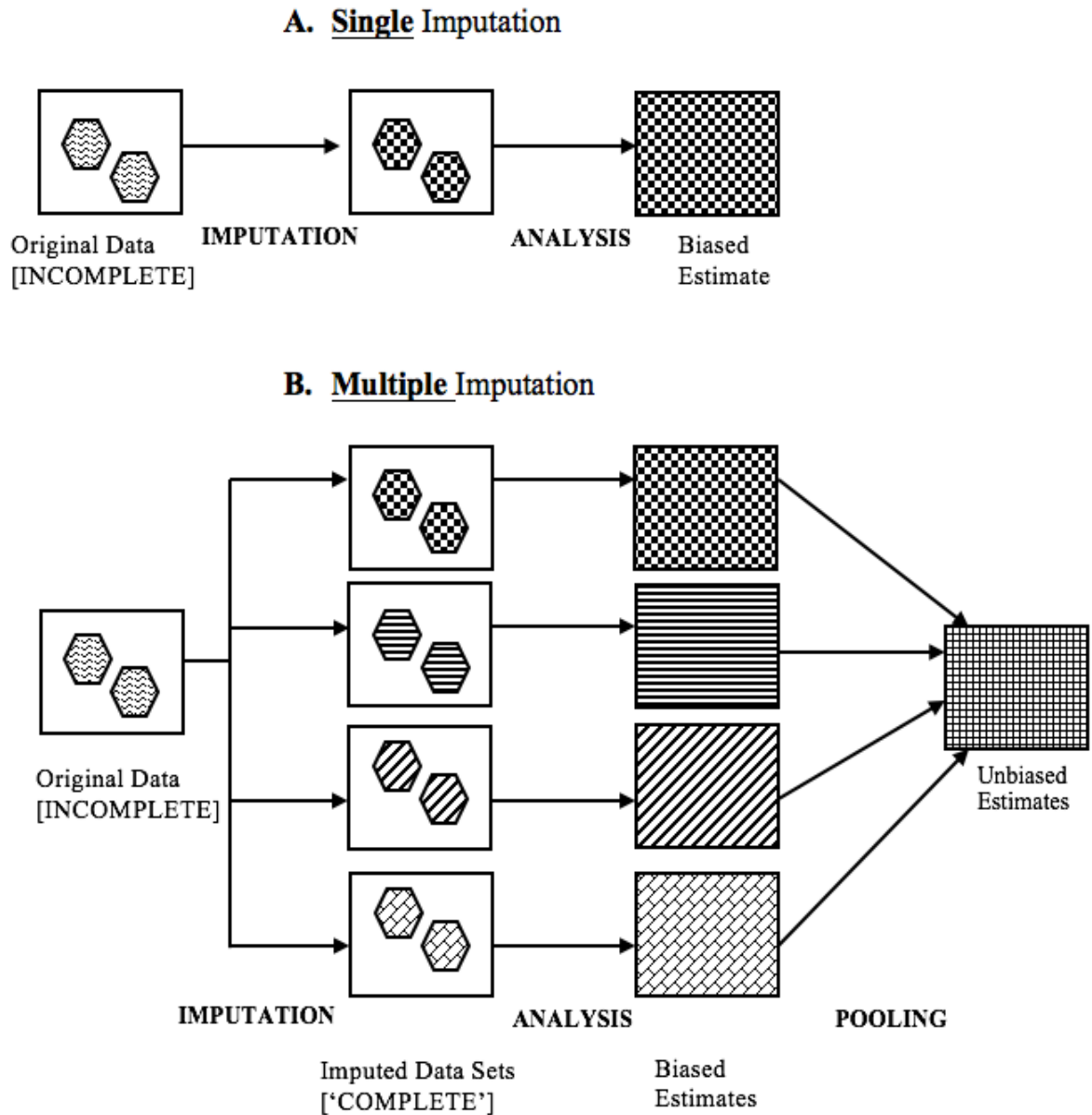


Figure 3.2: Conceptual Depiction of the Single Imputation Process and the Multiple Imputation Process ($m = 4$). Note: Modified from Nakagawa & Freckleton (2008).

Panel (A) Visually illustrates the process of single imputation. Panel (B) Visually illustrates the process of multiple imputation.

To ensure that our execution of MI worked, we conducted a few diagnostic checks to compare means and frequencies of observed and computed data, as well as looking at the variance information such as relative increase in variance, fraction of missing information, degrees of freedom, relative efficiency, and between and within variance estimates (UCLA, 2016).

3.6 Statistical Analyses

We conducted all statistical analyses using Stata, version 14 (StataCorp, 2015), and we conducted all hypothesis tests using a Type I error rate set at $\alpha = 0.05$, two-tailed.

3.6.1 Attrition Analysis

We conducted an attrition analysis, comparing baseline sociodemographic and clinical characteristics between those who participated in the 10-year follow-up assessment and those who did not. For comparison of continuous baseline characteristics, we conducted a two independent samples t-test, and for comparison of categorical baseline characteristics, we conducted a chi-square test or Fisher's exact test.

3.6.2 Descriptive Statistics

For all included participants, we computed descriptive statistics for categorical variables using counts, percentages, and frequencies. We summarized continuous variables using means and standard deviations.

3.6.3 Multicollinearity

For objectives 2, 3, and 4 of this thesis, we conducted multiple linear or logistic regression analyses. Prior to conducting our planned regression analyses, we assessed for degree of multicollinearity. Multicollinearity occurs when two or more of the independent variables (X_1, X_2, X_3), that are highly correlated with one another are included in the same regression model and then analyzed together to predict the outcome (Y) (Lauridesn & Mur, 2006; Mansfield & Helms, 1982). Multicollinearity can have negative effects on estimation and on inference (Mansfield & Helms, 1982). We used Variance Inflation Factors (VIF) to assess for the presence of problematic

multicollinearity ($VIF \geq 4$). The exposure and potential confounding variables were below the selected VIF cut-off value ($VIF < 4$), indicating that we did not have problematic multicollinearity in our regression models. We should note that no standard VIF cut-off value exists, and various cut-off values ranging from four to ten have been suggested and/or used in prior studies (e.g., Craney & Surles, 2002; O'Brien, 2007; Pan & Jackson, 2008).

3.6.4 Analysis: Objective 1

For objective 1, we conducted a point biserial correlation to examine the correlation at 10-year follow-up between our two recovery outcomes, occupational activity (less than 52 weeks of the past year vs. 52 weeks of the past year), an objective measure of recovery, and self-perceived recovery score, a subjective measure of recovery. We hypothesized that there would be a statistically significant positive association between occupational activity and self-perceived recovery score at 10-year follow-up.

3.6.5 Analysis: Objective 2

For objective 2, we conducted a simple logistic regression analysis with the duration of untreated psychosis as the exposure variable and occupational activity as the outcome variable. Additionally, we conducted a series of simple logistic regression analyses with each potentially confounding variable of interest as the exposure variable and occupational activity as the outcome variable. We then constructed two multiple logistic regression models that included the duration of untreated psychosis as the exposure variable, occupational activity as the outcome variable, and blocks of potentially confounding variables identified from our conceptual framework. All baseline confounding variables were entered as a block (Baseline-adjusted model), and all 10-year confounding variables were entered as a block in a separate model (10-year adjusted model). Both models additionally adjusted for gender and age of onset. We hypothesized that a longer duration of untreated psychosis would decrease the odds of engagement in occupational activity, adjusting for gender, age of onset, and other confounding variables.

3.6.6 Analysis: Objective 3

For objective 3, we conducted a simple linear regression analysis with the duration of untreated psychosis as the exposure variable and self-perceived recovery score as the outcome variable. Additionally, we conducted a series of simple linear regression analyses with each potentially confounding variable of interest as the exposure variable and self-perceived recovery score as the outcome. We then constructed two multiple linear regression models that included the duration of untreated psychosis as the exposure variable, self-perceived recovery score as the outcome variable, and adjusted for blocks of confounding variables identified from our conceptual framework. All baseline confounding variables were entered as a block (Baseline-adjusted model) and then gender, age of onset, and all 10-year confounding variables were entered as a block (10-year adjusted model) in a separate model. We hypothesized that there will be a statistically significant positive association between the duration of untreated psychosis and self-perceived recovery score, adjusting for gender, age of onset, and other confounding variables.

3.6.7 Analysis: Objective 4

For objective 4, we used the causal steps method of mediation proposed by Baron and Kenny (1986), in conjunction with the bootstrapping method of mediation, to determine whether relapse is a potential mediator in the causal pathway between the duration of untreated psychosis and self-perceived recovery score. We performed a series of four regression analyses according to the method outlined by Baron and Kenny (1986):

- (1) Regressing self-perceived recovery score (outcome) on the duration of untreated psychosis (exposure);
- (2) Regressing relapse (mediator) on the duration of untreated psychosis (exposure);
- (3) Regressing self-perceived recovery score (outcome) on relapse (mediator), adjusting for the duration of untreated psychosis (exposure);
- (4) Regressing self-perceived recovery score (outcome) on both the duration of untreated psychosis (exposure) and relapse (mediator).

If relapse is in fact a mediator, the following conditions must be met: (A) The duration of untreated psychosis (exposure) is significantly correlated with relapse (mediator); (B) Relapse (mediator) is significantly correlated with self-perceived recovery score (outcome); and (C) When the effect of relapse (mediator) is controlled, the significant relationship between the duration of untreated psychosis (exposure) and self-perceived recovery score (outcome) either becomes not statistically significant (i.e., full mediation) or greatly attenuated (i.e., partial mediation) (Baron & Kenny, 1986). We adjusted for all potential confounding variables in the mediation analysis.

We decided to conduct the causal steps method of mediation regardless of the result (i.e., statistically significant or not statistically significant) of step 1. Researchers (e.g. Shrout and Bolger, 2002; Zhao, Lynch, & Chen, 2010), including Kenny himself (Kenny et al., 1998) have stated that the first step can often be overlooked in many cases because the absence of a relationship between the exposure (X) and the outcome (Y) in the context of mediation can occur for several reasons (as cited in Pardo & Roman, 2013). For instance, Shrout and Bolger (2002) argue that the further apart the exposure (X) and outcome (Y) are from one another in the causal chain, the less likely the relationship (if any) between the two variables will be statistically significant. This may perhaps be attributed to unidentified suppressing or moderating variables, which are altering the relationship between the exposure (X) and the outcome (Y) (Mackinnon, Krull, & Lockwood, 2000; Shrout and Bolger, 2002).

To assess for indirect effects, we used the bootstrap method of mediation developed by Preacher and Hayes (2008). As compared to traditional tests such as the Sobel test, the bootstrap method does not require the assumption of a normal distribution of the indirect effects to be met (Preacher & Hayes, 2008). Furthermore, it has been suggested to use bootstrap methods to assess mediation in experimental and non-experimental studies that have small to moderate sample sizes (Shrout & Bolger, 2002). In order to calculate the bias-corrected 95% confidence interval (BC 95% CI), we used 5000 bootstrap resamples. The indirect effect is deemed statistically significant, when the BC 95% CI does not contain the value of zero.

3.6.8 Sensitivity Analyses

We performed sensitivity analyses to assess the robustness of findings by conducting the analyses for objectives two, three, and four again, using complete data ($n = 40$). We also repeated these sensitivity analyses using the imputed data ($n = 65$), with the duration of untreated illness substituted for the duration of untreated psychosis, as the exposure variable in the regression models. Prior to conducting the latter sensitivity analyses, we assessed the distribution of the duration of untreated illness, which was positively skewed. For comparability of results, we normalized the duration of untreated illness distribution by using a square root transformation, an approach used by other researchers in the field (e.g., Norman et al., 2012). We used the transformed duration of untreated illness variable as a continuous variable in all sensitivity analyses.

Chapter 4

4 Results

In this chapter, the sample is described in Section 4.1, including presentation of descriptive statistics for sociodemographic and clinical characteristics of the sample. In Section 4.2, findings from the attrition analysis are presented, comparing baseline sociodemographic and clinical characteristics between those who did and did not participate at 10-year follow-up. In Section 4.3, results of a bivariate analysis conducted for objective 1 are reported. Thereafter in Section 4.4, the results of a series of simple and multiple logistic regression analyses conducted for objective 2 are presented. Subsequently, in Section 4.5, the results of a series of simple and multiple linear regression analyses conducted for objective 3 are presented. Next in Section 4.6, findings from the mediation analysis are described. Lastly, findings from our sensitivity analyses are reported in Section 4.7.

4.1 Sample

Of the cohort of 132 clients admitted to PEPP (March 1997 to February 2002) for treatment of a first episode of psychosis, 56 clients were followed up at 5-years and 68 clients were followed up at 10-years. An overview of participation at each of the three assessment points is presented in Figure 4.1. Although 68 clients participated at 10-year follow-up, we excluded three participants from analyses because they were missing data for one of the two outcome variables, specifically self-perceived recovery score ($n = 2$) or occupational activity ($n = 1$). Thus, our final sample included 65 clients (Figure 4.1).

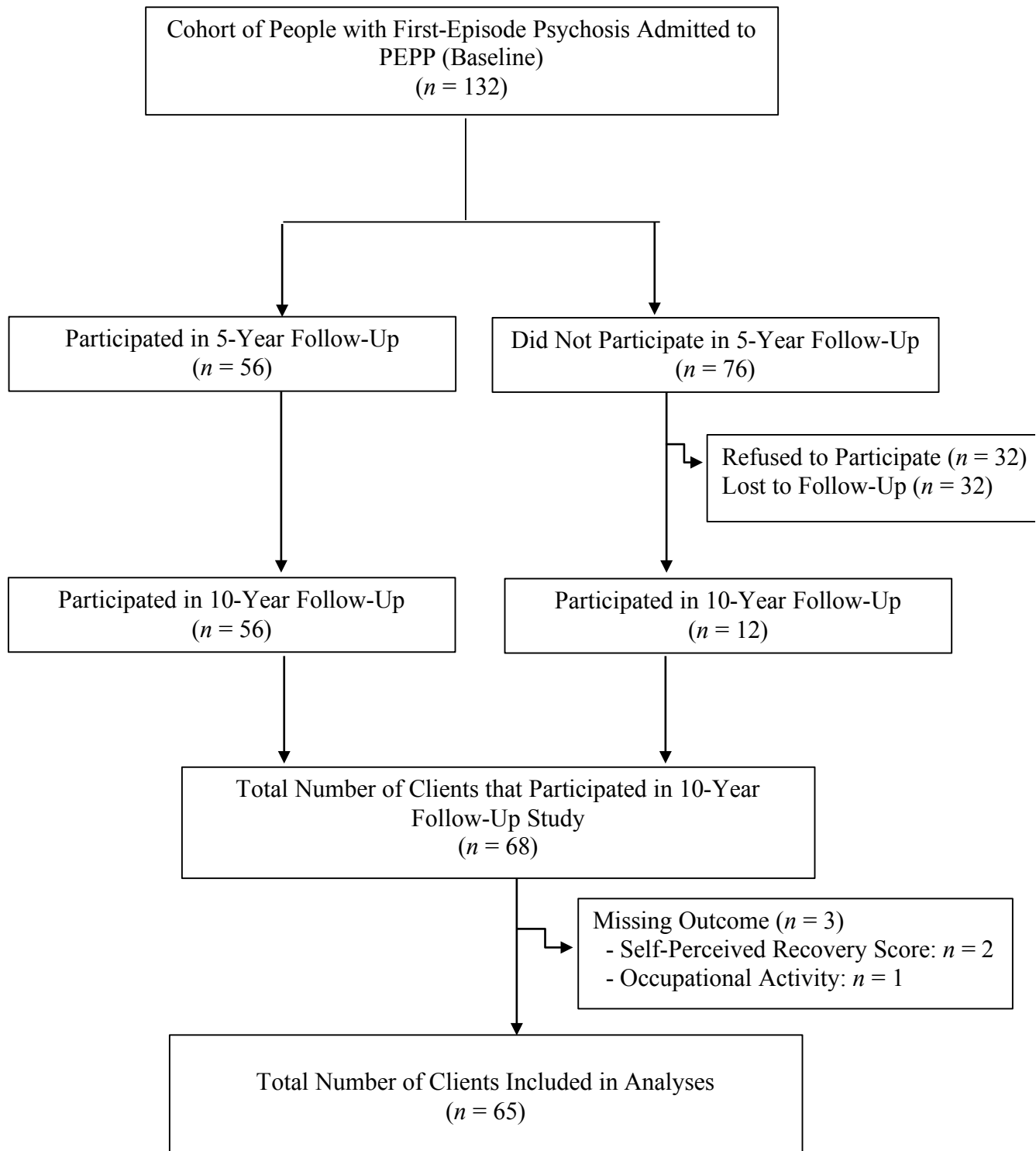


Figure 4.1: Flow-Chart Outlining Participation and Non-Participation in a Prospective Cohort Study at Baseline, 5-Year Follow-Up, and 10-Year Follow-Up.

4.1.1 Descriptive Statistics of the Sample

The sociodemographic and clinical characteristics of the sample at baseline and 10-year follow-up are summarized in Tables 4.1 and 4.2, respectively. The sample was comprised of a higher proportion of males (75%) than females (25%). Mean age was 38.8 years ($SD = 8.6$) with a range between 26 to 60 years, and the mean duration of untreated psychosis was 67.4 weeks ($SD = 139.3$) with a range between 0.1 to 917.7 weeks. A majority of the participants were Caucasian (88%), were single (63%), diagnosed with a schizophrenia-spectrum disorder (85%), lived with others (63%), generated an annual income of less than \$10,000 to \$29,999 (80%), and reported no drug use (74%). Over half of the participants completed at least some post-secondary education (52%). Additionally, over half of the participants were employed (54%), while the remainder (46%) were unemployed. None of the participants identified student, homemaker, or retired as their employment status.

4.2 Attrition Analysis

An overall follow-up rate of 52% (68/132) was attained at the 10-year assessment point. Comparison between participants ($n = 56$) and non-participants ($n = 76$) revealed no statistically significant differences on any of the baseline sociodemographic or clinical characteristics (Table 4.3).

Table 4.1: Sociodemographic and Clinical Characteristics of the Sample ($n = 65$) at Baseline.

Characteristic	n (%)		
Baseline			
Gender*			
Male	49 (75.4)		
Female	16 (24.6)		
Mode of Onset*			
Acute	13 (20.3)		
Insidious	51 (79.7)		
Diagnosis of a Psychotic Disorder*			
Schizophrenia-Spectrum			
Schizophrenia- Disorganized	3 (4.6)		
Schizophrenia-Paranoid	17 (26.2)		
Schizophreniform	1 (1.5)		
Schizoaffective	10 (15.4)		
Schizophrenia-Undifferentiated	24 (36.9)		
Other Psychotic Disorder			
Substance-Induced Psychosis	1 (1.5)		
Bipolar I with Psychotic Features	3 (4.6)		
Major Depression with Psychotic Features	1 (1.5)		
Brief Psychotic Disorder	2 (3.1)		
Psychosis Not Otherwise Specified	3 (4.6)		
Characteristic	Mean (SD)	Median	Range
Age of Onset (years)*	23.9 (8.0)	21.8	10.0 to 46.5
Premorbid Adjustment (score)	0.3 (0.2)	0.3	0.0 to 0.8
Positive Symptoms (total global items score)*	10.4 (3.3)	10	2 to 17
Negative Symptoms (total global items score)*	11.6 (5.2)	12	2 to 23
DUP (weeks)*	67.4 (139.3)	23.6	0.1 to 017.7
DUI (weeks)*	284.9 (298.6)	198.4	0.0 to 1206.7

Note: * Included in simple and multivariable regression analyses; n = count (frequency);

SD = Standard Deviation; DUP = Duration of Untreated Psychosis (weeks);

DUI = Duration of Untreated Illness (weeks); % = Percentage.

Table 4.2: Sociodemographic and Clinical Characteristics of the Sample ($n = 65$) at 10-Year Follow-Up.

Characteristic	<i>n</i> (%)		
10-year Follow-up			
Ethnicity			
Caucasian	57 (87.7)		
Black/African American	2 (3.1)		
Native American/American Indian	3 (4.6)		
Asian/Pacific Islander	2 (3.1)		
Other	1 (1.5)		
Marital Status			
Single (Never Married)	41 (63.1)		
Married/Common Law	18 (27.7)		
Divorced/Separated	5 (7.7)		
Widowed	1 (1.5)		
Highest Level of Education Attained*			
Less than or completed high school	31 (47.7)		
Some post-secondary	34 (52.3)		
Living Arrangement			
Lives Alone	24 (37.0)		
Lives with Other(s)	41 (63.0)		
Employment Status			
Employed	35 (53.8)		
Unemployed	30 (46.2)		
Annual Income			
Less than \$10, 000 to \$29, 999	52 (80.0)		
\$30, 000 to \$49, 999	13 (20.0)		
Drug Use*			
No	48 (73.9)		
Yes	17 (26.1)		
Medication Adherence			
Less than or equal to 75%	5 (8.20)		
Greater than 75%	56 (91.80)		
Characteristic	Mean (<i>SD</i>)	Median	Range
Age (years)	38.8 (8.6)	36	26 to 60
Total Years of Formal Education	13.1 (2.1)	13	8 to 17
Perceived Social Support (score)*	31.5 (6.5)	33	14 to 40
Positive Symptoms (total global items score)*	3.8 (3.4)	3	0 to 14
Negative Symptoms (total global items score)*	6.0 (5.5)	4	0 to 18

Note: * Included in simple and multivariable regression analyses; n = count (frequency); SD = Standard Deviation; % = Percentage.

Table 4.3: Comparison of Baseline Sociodemographic and Clinical Characteristics between Participants ($n = 56$) and Non-Participants ($n = 76$) at 10-Year Follow-Up.

Characteristic	Participants ($n = 56$)	Non-Participants ($n = 76$)	P-value
Sociodemographic			
Gender n (%)			0.91
Male	43 (77)	59 (78)	
Female	13 (23)	17 (22)	
Highest Level of Education n (%)			0.36
Special education	1 (1.8)	5 (6.6)	
Less than high school diploma	24 (42.9)	34 (44.7)	
High school diploma	11(19.6)	20 (26.3)	
Some post-secondary	20 (35.7)	17 (22.4)	
Marital Status n (%)			0.80
Single	46 (82.1)	63 (82.9)	
Married/Common Law/Stable Relationship	7 (12.5)	11 (14.5)	
Separated	3 (5.4)	2 (2.6)	
Clinical			
Age of Onset (years) Mean (SD)	24.2(8.2)	23.5 (8.2)	0.64
Premorbid Adjustment (score) Mean (SD)	0.3(0.2)	0.3 (0.1)	0.45
DUP (weeks) Mean (SD)	53.5 (92.0)	88.6 (125.3)	0.45
DUI (weeks) Mean (SD)	271.6 (289.1)	287.1 (251.5)	0.06
Positive Symptoms (total global items) Mean (SD)	10.5 (3.2)	10.1 (3.5)	0.52
Negative Symptoms (total global items) Mean (SD)	11.8 (5.1)	11.9 (4.9)	0.91
Diagnosis of a Psychotic Disorder n (%)			0.54
Schizophrenia-Spectrum			
Schizophrenia-Disorganized	4 (7.1)	5 (6.6)	
Schizophrenia-Paranoid	16 (28.6)	26 (34.2)	
Schizophreniform	2 (3.6)	2 (2.6)	
Schizoaffective	9 (16.1)	12 (15.8)	
Schizophrenia-Undifferentiated	17 (30.3)	15 (19.7)	
Other Psychotic Disorder			
Substance-Induced Psychosis	1 (1.8)	7 (9.2)	
Bipolar I with Psychotic Features	2 (3.6)	5 (6.6)	
Major Depression with Psychotic Features	1 (1.8)	0 (0.0)	
Brief Psychotic Disorder	1 (1.8)	0 (0.0)	
Psychosis Not Otherwise Specified	3 (5.3)	3 (3.9)	

Note: DUP = Duration of Untreated Psychosis (weeks); DUI = Duration of Untreated Illness (weeks); n = count; SD = Standard Deviation; % = Percentage.

4.3 Objective 1

At 10-year follow-up, participants were engaged in occupational activity for either less than 52 weeks of the past year ($n = 33$) or for 52 weeks of the past year ($n = 32$).

At 10-year follow-up, the mean total self-perceived recovery score obtained by participants on the MARS was 106.9 ($SD = 13.2$). The total MARS scores ranged from 70 to 125. The distribution of the total MARS scores within the sample ($n = 65$) is presented in Figure 4.2.

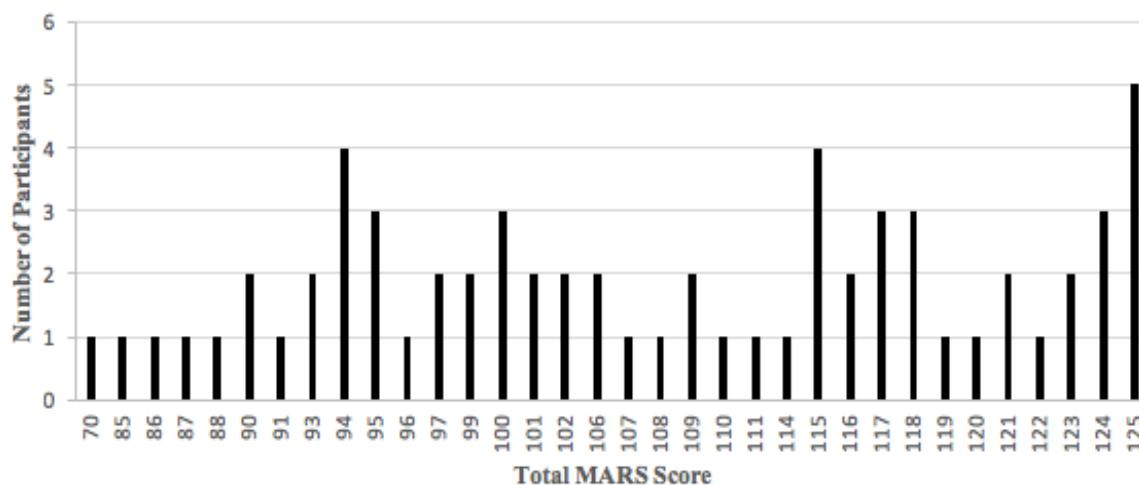


Figure 4.2: Total MARS Scores for Sample ($n = 65$).

The point biserial (pbi) correlation coefficient revealed a positive association between self-perceived recovery score, a subjective measure of recovery, and occupational activity (less than 52 weeks of the year vs. 52 weeks of the year), an objective measure of recovery, at 10-year follow-up; however, this association was not statistically significant ($r_{\text{pbi}} = 0.14$, $P = 0.28$).

4.4 Objective 2

4.4.1 Variables Associated with Objective Recovery

Table 4.4 contains the results of the unadjusted, baseline adjusted, and 10-year adjusted regressions models, with the duration of untreated psychosis as the exposure variable, and occupational activity as the outcome variable.

Duration of Untreated Psychosis

Across all regression models, results revealed no statistically significant association between the duration of untreated psychosis and occupational activity at 10-year follow-up (Table 4.4). In the unadjusted and the baseline adjusted regression models, the magnitude of the odds ratio is less than one, but in the 10-year adjusted regression model, the magnitude of the odds ratio is greater than one.

Highest Level of Education

Findings from the unadjusted regression model revealed a statistically significant association between some post-secondary education and occupational activity at 10-year follow-up (OR = 3.32, 95% CI: 1.21 to 9.21). However, this result was no longer statistically significant in the 10-year adjusted regression model.

Negative Symptoms Score

In both the unadjusted and 10-year adjusted regression models, results revealed a statistically significant association between negative symptoms score at 10-year follow-up and occupational activity at 10-year follow-up (OR = 0.73, 95% CI: 0.63 to 0.85; OR = 0.69, 95% CI: 0.57 to 0.84). In both regression models, the magnitude of the odds ratio was less than 1, suggesting that the odds of engagement in occupational activity in the past year decreases, as number of negative symptoms increases. Findings further indicated that the magnitude of the odds ratio slightly attenuated with the addition of confounding variables (Table 4.4).

Table 4.4: Unadjusted and Adjusted Logistic Regression Models with DUP as the Exposure Variable and Occupational Activity (Less than 52 weeks in past year vs. 52 weeks of the past year) as the Outcome Variable ($n = 65$).

Potential Confounding Variables	Value	Unadjusted OR (95% CI)	Baseline Adjusted OR (95% CI)	10-Year Adjusted OR (95% CI)
DUP* (weeks)	N/A	0.91 (0.77 to 1.20)	0.91 (0.67 to 1.26)	1.26 (0.81 to 1.95)
Baseline				
Gender	Male	Ref.	Ref.	Ref.
	Female	1.34 (0.43 to 4.18)	1.05 (0.30 to 3.74)	1.90 (0.31 to 11.59)
Age of Onset (years)	N/A	1.03 (0.97 to 1.09)	1.03 (0.95 to 1.12)	0.97 (0.87 to 1.07)
Mode of Onset	Acute	Ref.	Ref.	-
	Insidious	0.33 (0.09 to 1.21)	0.31 (0.08 to 1.26)	-
Diagnosis of a Psychotic Disorder	Other Psychotic Disorder	Ref.	Ref.	-
	Schizophrenia-Spectrum	0.38 (0.09 to 1.65)	0.48 (0.10 to 2.29)	-
Positive Symptoms (score)	N/A	0.92 (0.79 to 1.08)	0.93 (0.79 to 1.12)	-
Negative Symptoms (score)	N/A	0.99 (0.90 to 1.08)	1.04 (0.92 to 1.17)	-
10-year Follow-up				
Highest Level of Education	Less than or Completed High School	Ref.	-	Ref.
	Some Post-Secondary	3.32 (1.21 to 9.21)**	-	2.89 (0.67 to 12.30)
Perceived Social Support (score)	N/A	1.13 (1.02 to 1.23)**	-	1.13 (1.00 to 1.28)
Drug Use	No	Ref.	-	Ref.
	Yes	0.82 (0.27 to 2.48)	-	0.29 (0.05 to 1.72)
Positive Symptoms (score)	N/A	0.86 (0.73 to 1.01)	-	0.86 (0.69 to 1.07)
Negative Symptoms (score)	N/A	0.73 (0.63 to 0.85)**	-	0.69 (0.57 to 0.84)**

Note: * Exposure; ** Indicates statistically significant findings; OR = Odds Ratio; CI = Confidence Interval; DUP = Duration of Untreated Psychosis (weeks); Ref. = Reference Group; N/A = Not Applicable; A statistically significant association between occupational activity and DUP or confounding variables exists when the 95% CI does not contain the value of one.

Perceived Social Support Score

Findings from the unadjusted regression model (OR = 1.13, 95% CI: 1.02 to 1.23) indicated a statistically significant association between perceived social support score at 10-year follow-up and occupational activity at 10-year follow-up, but the association was no longer statistically significant association in the 10-year adjusted regression model.

4.5 Objective 3

4.5.1 Variables Associated with Subjective Recovery

Table 4.5 summarizes the results of the unadjusted, baseline adjusted, and 10-year adjusted regression models, with the duration of untreated psychosis as the exposure variable, and self-perceived recovery score as the outcome variable.

Duration of Untreated Psychosis

Results revealed no statistically significant association between the duration of untreated psychosis and self-perceived recovery score at 10-year follow-up across all regression models (Table 4.5). In general, findings indicated that the magnitude of the effect is attenuated with the addition of confounding variables.

Negative Symptom Score

Findings indicated a statistically significant association between negative symptom score at 10-year follow-up and self-perceived recovery score at 10-year follow-up in the unadjusted regression model ($\beta = -0.71$, 95% CI: -1.29 to -0.13), but not in the 10-year adjusted regression model (Table 4.5).

Table 4.5: Unadjusted and Adjusted Linear Regression Models with DUP as the Exposure Variable and Self-Perceived Recovery Score as the Outcome Variable ($n = 65$).

Potential Confounding Variables	Value	Unadjusted β (95% CI)	Baseline Adjusted β (95% CI)	10-Year Adjusted β (95% CI)
DUP* (weeks)	N/A	-1.24 (-3.04 to 0.56)	-1.57 (-3.50 to 0.36)	-0.73 (-2.42 to 0.97)
Baseline				
Gender	Male	Ref.	Ref.	Ref.
	Female	-2.49 (-10.14 to 5.16)	-3.61 (-11.83 to 4.60)	-5.07 (-12.45 to 2.31)
Age of Onset (years)	N/A	0.00 (-0.42 to 0.43)	0.08 (-0.41 to 0.57)	0.10 (-0.32 to 0.53)
Mode of Onset	Acute	Ref.	Ref.	-
	Insidious	-5.75 (-13.69 to 2.20)	-7.31 (-15.65 to 1.03)	-
Diagnosis of a Psychotic Disorder	Other Psychotic Disorder	Ref.	Ref.	-
	Schizophrenia-Spectrum	-0.78 (-9.95 to 8.38)	1.25 (-8.56 to 11.05)	-
Positive Symptoms (score)	N/A	0.39 (-0.63 to 1.41)	0.44 (-0.67 to 1.55)	-
Negative Symptoms (score)	N/A	0.09 (-0.55 to 0.73)	0.11 (-0.65 to 0.87)	-
10-year Follow-up				
Highest Level of Education	Less than or Completed High School	Ref.	-	Ref.
	Some Post-Secondary	5.00 (-1.50 to 11.50)	-	2.99 (-3.21 to 9.19)
Perceived Social Support (score)	N/A	1.01 (0.55 to 1.27)**	-	0.94 (0.45 to 1.42)**
Drug Use	No	Ref.	-	Ref.
	Yes	3.43 (-4.05 to 10.90)	-	2.51 (-4.32 to 9.35)
Positive Symptoms (score)	N/A	-0.40 (-1.37 to 0.57)	-	0.14 (-0.79 to 1.07)
Negative Symptoms (score)	N/A	-0.71 (-1.29 to -0.13)**	-	-0.36 (-0.95 to 0.24)

Note: * Exposure; ** Indicates statistically significant findings; β = Beta Coefficient; CI = Confidence Interval; DUP = Duration of Untreated Psychosis (weeks); Ref. = Reference Group; N/A = Not Applicable; A statistically significant association between self-perceived recovery score and DUP or confounding variables exists when the 95% CI does not contain the value of zero.

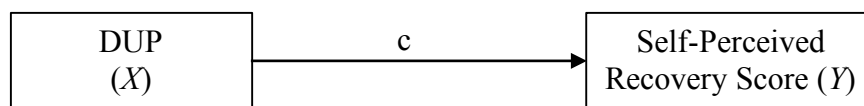
Perceived Social Support Score

In both the unadjusted and 10-year adjusted regression models, results revealed a statistically significant association between perceived social support score at 10-year follow-up and self-perceived recovery score at 10-year follow-up ($\beta = 1.01$, 95% CI: 0.55 to 1.27; $\beta = 0.94$, 95% CI: 0.45 to 1.42). In both regression models, the direction of the effect was positive, which suggests that as social support increases, self-perceived recovery increases. Results further revealed that the magnitude of the effect slightly attenuated with the addition of confounding variables (Table 4.5).

4.6 Objective 4

Figure 4.3 visually illustrates our mediation analysis.

A. Unmediated Model



B. Mediated Model

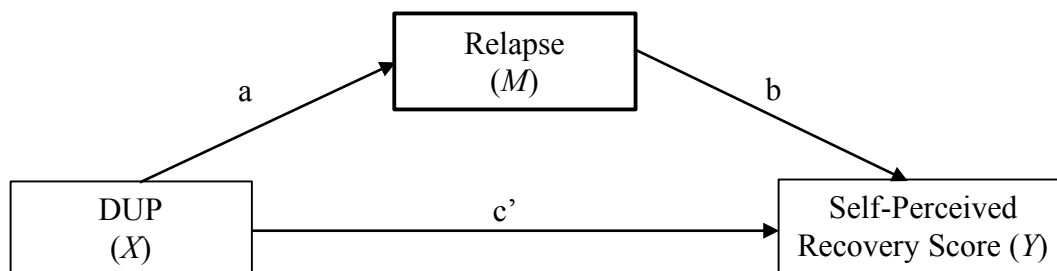


Figure 4.3: Hypothesized Mediation Model with Relapse as the Mediator in the Relationship between DUP and Self-Perceived Recovery Score. Note: DUP = Duration of Untreated Psychosis; X = Exposure; Y = Outcome; M = Mediator. A. Unmediated model: *Path c* illustrates the total effect of DUP on self-perceived recovery score (no mediator). B. Mediated model: *Path a* illustrates the direct effect of DUP on relapse. *Path b* illustrates the direct effect of relapse on self-perceived recovery score after controlling for DUP. *Path c'* depicts the direct effect of DUP on self-perceived recovery score after controlling for relapse.

The results of each of the four regression analyses corresponding to the four steps of the causal steps method of mediation (Baron & Kenny, 1986) are presented in Table 4.6. Regression analyses for all four steps were not statistically significant, suggesting no evidence of a mediating effect of relapse on the association between the duration of untreated psychosis and self-perceived recovery score.

Table 4.6: Testing for Mediation Using the Causal Steps Methods of Mediation ($n = 65$).

Step (Regression Analysis)	Variable (Exposure)	β [95% CI] (Exposure)	Pathway (Figure 4.3)
1. Conduct a regression analysis with X and Y .	DUP	-1.12 (-2.88 to 0.64)	c
2. Conduct a regression analysis with X and M .	DUP	-0.16 (-0.39 to 0.07)	a
3. Conduct a regression analysis with M and Y , adjusting for X .	Relapse	0.04 (-2.26 to 2.34)	b
4. Conduct a regression analysis with X and Y , adjusting for M .	DUP	-1.17 (-3.00 to 0.65)	c'

Note: DUP = Duration of Untreated Psychosis; X = Exposure = DUP (weeks); Y = Outcome = Self-Perceived Recovery Score; M = Mediator = Relapse; β = Beta Coefficient. The direct effects are statistically significant at the 95% confidence interval (CI), when the 95% CI does not include 0.

Findings from the bootstrap method of mediation (Preacher & Hayes, 2008) indicated that the indirect effect of the duration of untreated psychosis on self-perceived recovery score via relapse is not statistically significant ($\beta = -0.00$, BC 95% CI: -0.34 to 0.23).

4.7 Sensitivity Analyses

4.7.1 Sensitivity Analyses for Complete Data

4.7.1.1 Objective 2

In contrast to the main analyses, results from the sensitivity analyses with participants who had complete data ($n = 40$) revealed that the magnitude of the odds ratio for the duration of untreated psychosis across all three regression models were slightly larger, and the corresponding 95 % CI's were slightly wider, but remained non-significant.

All other findings were consistent with the findings from the main analyses.

4.7.1.2 Objective 3

In contrast to the main analyses, results from the sensitivity analyses with participants who had complete data ($n = 40$) revealed that in the unadjusted ($\beta = -1.29$, 95% CI: -3.86 to 1.28) and baseline adjusted ($\beta = 2.12$, 95% CI: -5.04 to 0.80) regression models, the magnitude of the effect of the duration of untreated psychosis was larger and the corresponding 95% CI's were wider but remained non-significant. In the 10-year adjusted regression model ($\beta = -0.38$, 95% CI: -2.68 to 1.92), the magnitude of the effect of the duration of untreated psychosis was smaller and the corresponding 95% CI was narrower.

In contrast to the findings of the main analyses, findings from the 10-year adjusted regression model revealed a statistically significant association between negative symptoms score at 10-year follow-up and self-perceived recovery score at 10-year follow-up ($\beta = -1.04$, 95% CI: -1.75 to -0.32). In the unadjusted ($\beta = -1.28$, 95% CI: -1.94 to -0.63) and 10-year adjusted ($\beta = -1.04$, 95% CI: -1.75 to -0.32) regression models, the magnitude of the effect was larger and the corresponding 95% CI's were wider than those in the main analyses.

All other findings were consistent with the findings of the main analyses.

4.7.1.3 Objective 4

Findings from the sensitivity analyses using participants with complete data ($n = 40$) to assess the hypothesized mediation model are consistent with the main findings using imputed data.

4.7.2 Sensitivity Analyses for Measure of Untreated Illness

4.7.2.1 Objective 2

In contrast to the findings from the main analyses with the duration of untreated psychosis as the exposure variable, findings from the sensitivity analyses with the duration of untreated illness as the exposure variable revealed a statistically significant

association between the duration of untreated illness and occupational activity at 10-year follow-up in the unadjusted (OR = 0.93, 95% CI: 0.88 to 0.99) and baseline adjusted (OR = 0.92, 95% CI: 0.86 to 0.99) regression models. In the 10-year adjusted regression model, the magnitude of the odds ratio for the duration of untreated psychosis was less than one, which suggests that the odds of engagement in occupational activity in the previous year decreases as the duration of untreated illness increases.

All other findings were consistent with the findings of the main analyses.

4.7.2.2 Objective 3

In contrast to the findings from the main analyses with the duration of untreated psychosis as the exposure variable, findings from the sensitivity analyses with the duration of untreated illness as the exposure variable revealed a statistically significant association between the duration of untreated illness and self-perceived recovery score at 10-year follow-up in the unadjusted ($\beta = -0.66$, 95% CI: -1.00 to -0.33), baseline adjusted ($\beta = -0.65$, 95% CI: -1.03 to -0.28), and 10-year adjusted ($\beta = -0.52$, 95% CI: -0.87 to -0.16) regression models. These findings suggest that as the duration of untreated illness increase, self-perceived recovery decreases. Across all models, the magnitude of the effect was smaller and the corresponding 95% CI's were narrower.

4.7.2.3 Objective 4

In contrast to the main analyses, findings from the sensitivity analyses that included the duration of untreated illness as the exposure variable in the hypothesized mediation model revealed that steps 1 and 4 of the causal steps method of mediation were statistically significant.

All other findings were consistent with the main analyses.

Chapter 5

5 Discussion & Conclusion

In this final chapter, key findings from the analyses conducted for each of the four objectives of this thesis are discussed in the context of existing literature. Section 5.1 begins with a discussion of the findings from the bivariate analysis examining the association between the two recovery outcomes at 10-year follow-up (Objective 1). Next, the findings from multiple logistic and linear regression analyses investigating whether the duration of untreated psychosis is associated with occupational activity (objective recovery) and/or self-perceived recovery score (subjective recovery) at 10-year follow-up, adjusting for confounding variables (Objectives 2 & 3) are discussed. Subsequently, findings from the mediation analysis investigating whether relapse mediates the relationship between the duration of untreated psychosis and self-perceived recovery score at 10-year follow-up (Objective 4) are discussed. Next in Section 5.2, evidence from previous studies reporting a differential relationship of the duration of untreated psychosis and the duration of untreated illness to particular outcome measures is provided. Thereafter in Section 5.3, the strengths of this thesis are discussed, followed by a discussion of the limitations in Section 5.4. Finally, clinical implications are discussed in Section 5.5, and an overall conclusion is provided in Section 5.6.

5.1 Summary of Key Findings by Study Objective

5.1.1 Objective 1

Several empirical studies have investigated the relationship between objective and subjective recovery from psychotic disorders (e.g., schizophrenia) or other serious mental illness (Jørgensen et al., 2015; Kukla, Lysaker, & Roe, 2014; Lloyd, King, & Moore, 2010; Morland, 2007; Norman, Windell, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004; Roe, Mashiach-Eizenberg & Lysaker, 2011). However, findings from these studies have been equivocal, with evidence for and against the presence of an association between these two dimensions of recovery. Given these inconsistent findings, we sought to examine the association between our two 10-year outcomes of interest, specifically objective and subjective recovery from a first episode of psychosis. We

hypothesized that there would be a statistically significant positive association between occupational activity and self-perceived recovery score at 10-year follow-up, such that people who attained objective recovery would have higher self-perceived recovery scores. Results revealed a positive association between occupational activity, our objective measure of recovery, and self-perceived recovery score, our subjective measure of recovery; however, contrary to our hypothesis, the positive association was not statistically significant. This finding is consistent with results of previous studies (Kukla, Lysaker, & Roe, 2014; Roe, Mashiach-Eizenberg & Lysaker, 2011), suggesting that self-assessment of recovery from first-episode psychosis and other psychotic disorders is independent of occupational activity, symptom severity (Roe, Mashiach-Eizenberg & Lysaker, 2011), level of functioning (Roe, Mashiach-Eizenberg & Lysaker, 2011), and the presence of positive and negative symptoms (Kukla, Lysaker, & Roe, 2014), which are all objective measures of recovery. In other words, one's perception of recovery is not determined by some persisting, overt, and measureable characteristics that have been compromised by or associated with the diagnosis itself.

Inconclusive evidence regarding the presence or absence and direction of an association between objective and subjective recovery may perhaps be attributed to the following differences: 1) How objective and subjective recovery are operationalized and measured; and 2) Number of assessment points.

1. Operationalization and Measurement of Subjective and Objective Recovery.

Variability in the operationalization and measurement of subjective and objective recovery across studies precludes comparability because the same construct is not being assessed. In some studies, operationalization of subjective and objective recovery may refer to total scores (Kukla, Lysaker, & Roe, 2014; Morland, 2007; Roe, Mashiach-Eizenberg & Lysaker, 2011), individual domains/subscales (Norman, Windell, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004), or a combination of total scores and individual domains/subscales (Jørgensen et al., 2015; Llyod, King, & Moore, 2010) of the measures used to assess subjective and objective recovery. Subjective recovery (i.e., self-reported recovery) has been assessed with different measures - in this thesis we used the MARS (total score), whereas others have used the Recovery

Assessment Scale (Jørgensen et al., 2015; Kukla, Lysaker, & Roe, 2014; Lloyd, King, & Moore, 2010; Norman, Windell, & Manchanda, 2013; Roe, Mashiach-Eizenberg & Lysaker, 2011) or the Mental Health Recovery Scale (Morland, 2007). Furthermore, objective recovery in this thesis was defined by occupational activity (less than 52 weeks of past year vs. 52 weeks of past year), in other studies, objective recovery refers to the assessment or severity of symptoms. (Kukla, Lysaker, & Roe, 2014; Morland, 2007; Norman, Windell, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004; Roe, Mashiach-Eizenberg & Lysaker, 2011). The measures used to assess objective recovery defined by symptoms or the severity of symptoms also varies across studies. For instance, Kukla and colleagues (2014) and Morland (2007) used the Positive and Negative Symptoms Scale, whereas Norman and colleagues (2013) used the SAPS and SANS, while Resnick and colleagues (2004) used the shortened version of the Symptom Checklist, and Roe and colleagues (2011) used the Brief Psychiatric Rating Scale Expanded. Future studies should therefore adhere to the same operationalization of objective and subjective recovery, as well use consistent recovery measures to allow comparison of findings across studies.

2. Number of Assessment Points. Assessment of objective and subjective recovery at a single time-point does not capture the fluctuating nature of recovery over time. A majority of studies, including this thesis, assessed the relationship between objective and subjective recovery at a single time-point (Kukla, Lysaker, & Roe, 2014; Lloyd, King, & Moore, 2010; Morland, 2007; Norman, Windell, & Manchanda, 2013; Resnick, Rosenheck, & Lehman, 2004; Roe, Mashiach-Eizenberg & Lysaker, 2011), whereas the study conducted by Jørgensen and colleagues (2015) assessed the relationship across multiple time-points, which allowed them to assess change over time. In the latter study, fluctuation in the presence or absence of a relationship between domains of self-reported recovery (subjective recovery) and domains of symptoms (objective recovery) was found across the four time points. Future studies should therefore assess recovery at multiple time-points to capture its changing state.

5.1.2 Objective 2

Austin and colleagues (2013) conducted the only study to date that investigated whether the duration of untreated psychosis is associated with objective recovery among people with first-episode psychosis over a long follow-up period (≥ 10 -years). To add to this essentially non-existent body of literature, we sought to investigate whether duration of untreated psychosis is associated with occupational activity (objective recovery), 10-years after a first episode of psychosis. We hypothesized that a longer duration of untreated psychosis would decrease the odds of engagement in occupational activity, adjusting for gender, age of onset, and other confounding variables. Contrary to our hypothesis, results revealed a statistically non-significant association between duration of untreated psychosis and occupational activity (objective recovery) with or without controlling for confounding variables, suggesting that duration of untreated psychosis is not associated with objective recovery at 10-year follow-up among people with first-episode psychosis. Our finding is consistent with the findings reported by Austin and colleagues (2013); however, objective recovery was operationalized differently in each study. In this thesis, we operationalized objective recovery (i.e., occupational activity) as engagement in work and/or school on a full-time or part-time basis for less than 52 weeks of the past year or for 52 weeks of the past year. In the study conducted by Austin and colleagues (2013) with 304 people with first-episode psychosis, objective recovery was differentiated into full and functional recovery. Functional recovery was defined as currently engaged in work/study, a Global Assessment of Functioning-Functioning Scale score over 60, and no psychiatric hospitalizations or living in supported housing for the past two years (Albert et al., 2011). Full recovery was defined as stable remission of both negative and positive symptoms and functional recovery (Lieberman & Kopelowicz, 2005).

Comparison of our finding to other studies that used occupational activity as an outcome measure suggest that perhaps there is a relationship between the duration of untreated psychosis and objective recovery for shorter follow-up periods. Major and colleagues (2010), in a 1-year follow-up of 114 people with first-episode psychosis, found that longer duration of untreated psychosis decreased the likelihood of gaining or returning to

competitive employment or an educational activity that has led to a nationally recognized vocational qualification or degree (i.e., vocational recovery). Similarly, Norman and colleagues (2007) reported that a shorter duration of untreated psychosis was significantly associated with more occupational activity at 3-year follow-up among 163 people with first-episode psychosis, after adjusting for other confounding variables. However, in a 5-year prospective study with the same cohort of participants ($n = 132$) used in this thesis, the association between the duration of untreated psychosis and occupational activity was not assessed in subsequent regression analyses because the negative bivariate association was not statistically significant (Norman et al., 2012). Aside from differences in length of follow-up, other possible explanations for discrepancies in findings include the criteria used to define occupational activity, and the stratification of duration of untreated psychosis as long or short.

Interestingly, results demonstrated that after adjusting for all confounding variables, the only statistically significant factor associated with occupational activity (objective recovery) at 10-year follow-up was negative symptoms score, with lower negative symptom scores at 10-year follow-up associated with increased likelihood of engagement in occupational activity (objective recovery) for 52 weeks of the past year at 10-year follow-up. Our finding extends previous findings of a 5-year prospective study that revealed a statistically significant, negative association between weeks of occupational activity and two dimensions of negative symptoms (i.e., reduced motivation and expressiveness) among the same cohort of participants ($n = 132$) used in this thesis. (Norman, Manchanda, Harricharan, & Northcott, 2015). Taken together, these findings suggest that the less negative symptoms a person with first-episode psychosis experiences, the more engaged (number of weeks) he or she will be in work and/or school on a full-time or part-time basis.

5.1.3 Objective 3

To our knowledge, no study to date has examined the association between the duration of untreated psychosis and subjective recovery. We hypothesized that there will be a statistically significant negative association between the duration of untreated psychosis and self-perceived recovery score at 10-year follow-up, such that longer duration of

untreated psychosis would be associated with lower self-perceived recovery scores, after adjusting for gender, age of onset, and other confounding variables. Results revealed a negative association between duration of untreated psychosis and self-perceived recovery score (subjective recovery) at 10-year follow-up, controlling for confounding variables. However, we acknowledge that we conducted a secondary analysis of data, and our study was not designed or powered to look at the association between DUP and self-perceived recovery score. Therefore, we cannot determine if there was a negative association or lack of power to detect one.

5.1.4 Objective 4

Vulnerability to relapse has been perceived, by some, to impede one's recovery from a first episode of psychosis (Maddigan, 2011; Windell, Norman, & Malla, 2012), and it has also been found to be a consequence of a long duration of untreated psychosis (Saravanan et al., 2010; Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013). We thus sought to investigate whether relapse mediates the relationship between the duration of untreated psychosis (exposure) and self-perceived recovery score (subjective recovery; outcome), and found no evidence of mediation. Specifically, we noted an absence of a statistically significant relationship between our exposure and our outcome, which perhaps is attributed to latency since we assessed our exposure at baseline and our outcome at 10-year follow-up. We also noted there was no statistically significant relationship between duration of untreated psychosis and relapse, which is inconsistent with previous findings (Saravanan et al., 2010; Stefanescu, Macrea, Popescu, Ilies, & Miclutia, 2013). A possible explanation for the discrepancy is that the duration of untreated psychosis may be more strongly associated with relapse during the first 5-years (i.e., baseline to 5-year follow-up), for which we did not have data available on hospitalizations during this period of time.

We additionally noted that there was no statistically significant relationship between relapse and self-perceived recovery score at 10-year follow-up (subjective recovery). It is possible that factors such as medication discontinuation may further mediate the relationship between relapse and self-perceived recovery (Windell, Norman, & Malla, 2012).

The lack of evidence for mediation may perhaps be attributed to our use of a less accurate, non-inclusive measure of relapse. We used hospitalization data as a proxy measure of relapse, and the use of these data as an indicator of relapse among people with first-episode psychosis using a specialization early intervention service has only 47% specificity (Addington, Patten, McKenzie, & Addington, 2013).

We also did not have complete data available on hospitalizations occurring between baseline and 5-year follow-up, and therefore did not include this information in our analyses. We thus may have underestimated relapse because 80% of people who experience a first episode of psychosis will experience a relapse during the 5-year period after the first-episode (Gitlin, 2001; Robinson et al., 1999; Wiersma, Nienhuis, Slooff, & Giel, 1998).

5.2 DUI vs. DUP: Relationship to Outcomes

The duration of untreated psychosis was not found to be statistically associated with either of the two recovery outcomes in our main analyses, whereas, the duration of untreated illness was found to be statically associated with both of the recovery outcomes in our sensitivity analyses. This finding is consistent with previous studies that have found the duration of untreated illness, rather than the duration of untreated psychosis, to be more consistently associated with certain outcomes (Crumlish et al., 2009; Harris et al., 2005; Keshavan et al., 2003; Norman et al., 2012). For instance, the duration of untreated illness has been reported to be more consistently associated with negative symptoms, levels of functioning, use of a disability pension, and social and occupational functioning at 2-, 5-, and/or 8-year follow-up (Crumlish et al., 2009; Harris et al., 2005; Keshavan et al., 2003; Norman et al., 2012). Thus, the duration of untreated illness has a differential relationship with particular outcome measures, including recovery at 10-year follow-up.

5.3 Strengths

Our study has several strengths. It uses a prospective study design, which allowed us to not only assess multiple recovery outcomes simultaneously, but also assess the temporal

relationship between the exposure (i.e., duration of untreated psychosis) and the outcomes (i.e., objective and subjective recovery). Our prospective study was unique because to our knowledge, no prospective study with a 10-year follow-up period has been conducted in Canada, and no study to date has examined the association between the duration of untreated psychosis and subjective recovery. In contrast to other prospective or retrospective studies that assess one type of recovery outcome among people with first-episode psychosis (e.g. Faber et al., 2011; Gumley et al., 2014; Major et al., 2010), we assessed both types of recovery outcomes, that is, objective and subjective recovery. We also used a standardized definition of recovery (i.e., SAMHSA definition), as well as a standardized and validated measure of self-perceived recovery that is specific to people with serious mental illness (i.e., MARS). We adhered to the recommendations made by Compton and colleagues (2007) with respect to the measurement of the duration of untreated psychosis, which involves the use of a standardized, structured interview assessment (i.e., CORS), and the integration of information from multiple informants (i.e., consensus-based estimate). We used multivariable regression analyses, which allowed us to assess the independent effect of our exposure of interest (duration of untreated psychosis), controlling for known confounding variables. Our choice of variables to be included as confounding variables in our regression analyses was guided by our conceptual framework we created based on findings from previous studies in the literature. Lastly, we conducted two sets of sensitivity analyses to assess the robustness of findings.

5.4 Limitations

Several methodological limitations in this study merit consideration in conjunction with suggestions for future studies. Follow-up data was not available for 52% (68/132) of participants, as they either refused to participate or were lost to follow-up. However, this attrition rate of 52% is comparable to other prospective studies with long follow-up periods (≥ 10 -years), including those conducted by Wunderink and colleagues (2009), and Albert and colleagues (2011), who reported attrition rates of 49% and 54%, respectively.

Given the 52% attrition rate, we acknowledge that the sample for this thesis was small in size. The sample consisted of 68 participants, but we excluded three participants because they were missing one of the two recovery outcome variables, for a final sample of 65 participants. The use of a small sample size in all analyses reduced the statistical power of the study. Findings need to be replicated with a larger sample.

The combination of a small sample size, and the higher proportion of males than females comprising the sample, precluded us from conducting subgroup analyses by gender. Gender differences exist with respect to sociodemographic and clinical presentations (ElTayebani, ElGamal, Roshdy, & Al-Khadary, 2014; Thorup et al., 2014), as well as recovery (Thorup et al., 2014). Given that that males with first-episode psychosis have significantly higher levels of negative symptoms at all times of follow-up (Thorup et al., 2014), and that females are more likely to reach a state of recovery (Thorup et al., 2014), it would be interesting to investigate whether females report more objective recovery, based on our finding of an inverse relationship between negative symptoms at 10-year follow-up and objective recovery at 10-year follow-up. Future research should investigate gender differences with respect to recovery using a larger sample that is comprised of roughly equal proportions of males and females.

We acknowledge that the sample, recruited from an early intervention service (outpatient service) was not only predominantly male, but also predominantly Caucasian. Thus, these sample characteristics may limit the generalizability of our results. Specifically, our findings may not generalize to people receiving care from other health and social service providers, females, people with affective psychotic disorders, or to different ethnic groups who may have different definitions or concepts of subjective recovery. Thus, replication of findings with a sample that addresses these sample characteristics is needed.

Another limitation of this study is that we did not use all of the data that we had for the 65 participants. We had to exclude variables collected at 5-year follow-up including positive and negative symptoms, medication adherence, drug use, and number of hospital admissions. We also excluded drug use collected at baseline. These variables were

excluded from all analyses because the mechanism of missing data was assumed to be *Missing Not At Random* since they are all from the 5-year follow-up assessment. We were thus unable to impute these variables because the mechanism of missing data assumption required for multiple imputation (i.e., *Missing At Random*) was violated. The exclusion of these variables from all analyses may have altered the associations observed.

We also removed premorbid adjustment score at baseline and medication adherence at 10-year follow-up from all analyses post-hoc because of the lack of variability in scores and ratings, attributed in part to how these variables were measured. The exclusion of these variables from our analyses may have altered the associations observed.

The combination of a large number of potential confounding variables and the small sample size, precluded us from conducting fully-adjusted multivariable regression models. We were therefore unable to assess the true association between duration of untreated psychosis and the recovery outcomes because we did not control for all known confounding variables. It is possible that after controlling for all known confounding variables, a statistically significant association between the duration of untreated psychosis and the recovery outcomes may have been observed.

We acknowledge that the duration of untreated psychosis was assessed retrospectively, which means there is a high probability of recall bias from the participant and other sources of information (e.g., family), especially for a participant with a longer duration of untreated psychosis, and those who were experiencing a higher level of psychotic symptoms at the time of assessment (Compton et al., 2007).

In contrast to other studies (e.g., Primavera et al., 2012; Tang et al., 2014), we included the duration of untreated psychosis as a continuous variable in all analyses, therefore assuming a linear relationship between the duration of untreated psychosis and outcome. However, other researchers dichotomize the duration of untreated psychosis (e.g., Primavera et al., 2012; Tang et al., 2014), assuming that the likelihood that the duration of untreated psychosis will have a negative impact on outcome increases when the duration of untreated psychosis crosses a particular threshold (Singh, 2007). Various threshold values have been proposed and used to dichotomize the duration of untreated

psychosis as “short” or “long” including less than or greater than 31 days, 3-, 6-, or 12-months (Primavera et al., 2012). Perhaps if we had used the duration of untreated psychosis as a dichotomous variable in all analyses, the findings may have been different. We thus recommend future studies to follow Primavera and colleagues (2012) approach of including the duration of untreated psychosis as a continuous and dichotomous variable in all regression analyses to examine the impact on findings.

Another limitation was that data for our two recovery outcomes was only available for 10-year follow-up since both recovery outcomes were not assessed at baseline or at 5-year follow-up. Given that recovery is a fairly changeable state (Albert et al., 2011), it is possible that our findings may have been different if we examined the relationship with our recovery outcomes at multiple time-points across the 10-year follow-up period. Future studies should thus assess recovery outcomes at multiple time points over the follow-up period in order to capture the changing state of recovery. Furthermore, we were unable to use a validated instrument to measure occupational activity, our objective measure of recovery, since no such measure exists.

We acknowledge that we dichotomized our continuous objective recovery outcome and as a consequence we have lost statistical power and that results may potentially be biased by our use of a data-derived cut-point value (Naggara et al., 2011).

Another limitation was that perceived social support was only assessed at 10-year follow-up. We had to assume that perceived social support remains constant throughout the 10-year follow-up period, even though it likely fluctuates, particularly in relation to illness trajectories.

We also note that we used a less accurate measure of relapse, specifically hospitalization data (Section 3.1.4). Future research would benefit from using a more accurate measure of relapse such as the recurrence of the positive symptoms of psychosis. It would then be possible to examine the influence of time to relapse and the number of relapses (recurrent relapses) on the associations of interest.

We further note that objective recovery may have been misclassified for older adults in our sample who were nearing retirement age. However, we had very few people who were over the age of 50 ($n = 3$), therefore this is unlikely to have impacted our findings.

5.5 Clinical Implications

A clinical implication from this thesis is that there is value in concurrently assessing different dimensions of recovery to attain a more comprehensive overview of a person's recovery after a first episode of psychosis. Furthermore, the finding that negative symptoms are statistically associated with objective recovery at 10-year follow-up can directly inform clinical practice by way of targeting the reduction and/or elimination of negative symptoms to enhance one's functional status (Austin et al., 2013; Emsley, Chiliza, & Schoeman, 2008). Similarly, the finding that perceived social support is a statistically associated with subjective recovery at 10-year follow-up can also directly inform clinical practice by way of fostering social support to enhance one's subjective recovery (Austin et al., 2013; Emsley, Chiliza, & Schoeman, 2008).

5.6 Conclusion

To our knowledge, this thesis was not only the first prospective study with a long follow-up period of 10-years to be conducted in Canada, but also the first study to examine whether the duration of untreated psychosis is statistically associated with subjective recovery among people with a first episode of psychosis, making it a unique contribution to the existing literature. Our findings suggest that factors other than the duration of untreated psychosis have an impact on objective and subjective recovery outcomes at 10-year follow-up. Specifically, negative symptoms have an impact on objective recovery, while perceived social support has an impact on subjective recovery at 10-year follow-up. Further research examining factors associated with self-perceived recovery after a first episode of psychosis is warranted.

References

- Addington, J., Young, J., & Addington, D. (2003). Social Outcome in Early Psychosis. *Psychological Medicine, 33*(6), 1119-1124. doi: 10.1017/S0033291703007815
- Addington, D. E., Patten, S. B., McKenzie, E., & Addington, J. (2013). Relationship between Relapse and Hospitalization in First-Episode Psychosis. *Psychiatric Services, 64*(8), 796-799. doi: 10.1176/appi.ps.201200440
- Ahmed, A. O., Birgenheir, D., Buckley, P. F., & Mabe, P. A. (2013). A Psychometric Study of Recovery among Certified Peer Specialists. *Psychiatry Research, 209*(3), 721-731. doi: 10.1016/j.psychres.2013.01.011
- Albert, N., Bertelsen, M., Thorup, A., Petersen, L., Jeppesen, P., Le Quack, P., ... & Nordentoft, M. (2011). Predictors of Recovery from Psychosis: Analyses of Clinical and Social Factors Associated with Recovery among Patients with First-Episode Psychosis After 5 Years. *Schizophrenia Research, 125*(2), 257-266. doi: 10.1016/j.schres.2010.10.013
- Alvarez-Jimenez, M., Priede, A., Hetrick, S. E., Bendall, S., Killackey, E., Parker, A. G., ... & Gleeson, J. F. (2012). Risk Factors for Relapse Following Treatment for First Episode Psychosis: A Systematic Review and Meta-Analysis of Longitudinal Studies. *Schizophrenia Research, 139*, 116-128. doi:10.1016/j.schres.2012.05.007
- American Psychiatric Association DSM-5 Task Force (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)*. Washington, DC: American Psychiatric Association.
- Anderson, K. K., Fuhrer, R., Abrahamowicz, M., & Malla, A. K. (2012). The Incidence of First-Episode Schizophrenia-Spectrum Psychosis in Adolescents and Young Adults in Montreal: An Estimate from an Administrative Claims Database. *Canadian Journal of Psychiatry, 57*(10), 626-633. doi:10.1177/070674371205701007

- Anderson, K. K., Rodrigues, M., Mann, K., Voineskos, A., Mulsant, B. H., George, T. P., & McKenzie, K. J. (2015). Minimal Evidence that Untreated Psychosis Damages Brain Structures: A Systematic Review. *Schizophrenia Research, 162*, 222-233. doi: 10.1016/j.schres.2015.01.021
- Anderson, K. K., Voineskos, A., Mulsant, B. H., George, T. P., & McKenzie, K. J. (2014). The Role of Untreated Psychosis in Neurodegeneration: A Review of Hypothesized Mechanisms of Neurotoxicity in First-Episode Psychosis. *Canadian Journal of Psychiatry, 59*(10), 513-517.
- Andreasen, N.C., 1983. Scale for the Assessment of Negative Symptoms. University of Iowa, Iowa City, IA.
- Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms. University of Iowa, Iowa City, IA.
- Anthony, W. (1993). Recovery from Mental Illness: The Guiding Vision of the Mental Health Service System in the 1990s. *Psychosocial Rehabilitation Journal, 16*(4), 11-23. doi:10.1037/h0095655
- Arranz B., Corripio I., Safont G., Ramirez N., Dueñas R. M., Perez, V., ... & San L. (2012). Substance Use in First-Episode Psychosis: Does Gender Matter? *Schizophrenia Research, 2*(2), 1-6.
- Austin, S. F., Mors, O., Secher, R. G., Hjorthøj, C. R., Albert, N., Bertelsen, M., ... & Thorup, A. (2013). Predictors of Recovery in First Episode Psychosis: The OPUS Cohort at 10 Year Follow-up. *Schizophrenia Research, 150*, 163-168. doi: 10.1016/j.schres.2013.07.031
- Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., ... & Nordentoft, M. (2015). Long-Term Trajectories of Positive and Negative Symptoms in First Episode Psychosis: A 10 Year Follow-Up Study in the OPUS Cohort. *Schizophrenia Research, 168*, 84-91. doi: 10.1016/j.schres.2015.07.021

- Baron, R. M., & Kenny, D. A. (1986). The Moderator–Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. *Journal of Personality & Social Psychology*, *51*(6), 1173-1182.
- Becharad-Evans L., Schmitz N., Abadi S., Joobor R., King S., Malla A. (2007). Determinants of Help-Seeking and System Related Components of Delay in the Treatment of First-Episode Psychosis. *Schizophrenia Research*, *96*, 206–214. doi: 10.1016/j.schres.2007.07.017
- Bellack, A. S. (2006). Scientific and Consumer Models of Recovery in Schizophrenia: Concordance, Contrasts, and Implications. *Schizophrenia Bulletin*, *32*(3), 432-442. doi:10.1093/schbul/sbj044
- Bellack, A. S., & Drapalski, A. (2012). Issues and Developments on the Consumer Recovery Construct. *World Psychiatry*, *11*(3), 156-160. doi: 10.1002/j.2051-5545.2012.tb00117.x
- Bergé, D., Mané, A., Salgado, P., Cortizo, R., Garnier, C., Gomez, L., ... & Pérez, V. (2015). Predictors of Relapse and Functioning in First-Episode Psychosis: A Two-Year Follow-Up Study. *Psychiatric Services*, *67*(2), 227-233. doi: 10.1176/appi.ps.201400316
- Biering, K., Hjollund, N. H., & Frydenberg, M. (2015). Using Multiple Imputation to Deal with Missing Data and Attrition in Longitudinal Studies with Repeated Measures of Patient-Reported Outcomes. *Clinical Epidemiology*, *7*, 91-106. doi: 10.2147/CLEP.S72247
- Birchwood, M., Todd, P., & Jackson, C. (1998). Early Intervention in Psychosis: The Critical-Period Hypothesis. *International Clinical Psychopharmacology*, *13*, S31-S40. doi: 10.1192/bjp.bp.109.075804
- Bodner, T. E. (2008). What Improves with Increased Missing Data Imputations? *Structural Equation Modeling: A Multidisciplinary Journal*, *15*, 651-675. doi:10.1080/10705510802339072

- Boonstra, N., Sterk, B., Wunderink, L., Sytema, S., De Haan, L., & Wiersma, D. (2012). Association of Treatment Delay, Migration and Urbanicity in Psychosis. *European Psychiatry*, 27(7), 500-505. doi: 10.1016/j.eurpsy.2011.05.001
- Bouhlila, D. S., & Sellaouti, F. (2013). Multiple Imputation Using Chained Equations for Missing Data in TIMSS: A Case Study. *Large-Scale Assessments in Education*, 1, 1-33. doi: 10.1186/2196-0739-1-4
- Breitborde, N. J., Srihari, V. H., & Woods, S. W. (2009). Review of the Operational Definition for First-Episode Psychosis. *Early Intervention in Psychiatry*, 3(4), 259-265. doi: 10.1111/j.1751-7893.2009.00148.x
- Brill, N., Reichenberg, A., Weiser, M., & Rabinowitz, J. (2008). Validity of the Premorbid Adjustment Scale. *Schizophrenia Bulletin*, 34(5), 981-983. doi: 10.1093/schbul/sbm128
- Brunet, K., Birchwood, M., Lester, H., & Thornhill, K. (2007). Delays in Mental Health Services and Duration of Untreated Psychosis. *Psychiatric Bulletin*, 31(11), 408-410. doi: 10.1192/pb.bp.106.01399
- Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of Premorbid Adjustment in Chronic Schizophrenia. *Schizophrenia Bulletin*, 8(3), 470-484.
- Cassidy, C. M., Rabinovitch, M., Schmitz, N., Jooper, R., & Malla, A. K. (2010). A Comparison Study of Multiple Measures of Adherence to Antipsychotic Medication in First-Episode Psychosis. *Journal of Clinical Psychopharmacology*, 30, 64-67. doi:10.1097/JCP.0b0-13e3181ca03df
- Cassidy, C. M., Schmitz, N., & Malla, A. K. (2008). Validation of the Alcohol Use Disorders Identification Test and the Drug Abuse Screening Test in First Episode Psychosis. *Canadian Journal of Psychiatry*, 53, 26-33. doi: 10.1177/0706743-70805300105

- Chabungbam, G., Avasthi, A., & Sharan, P. (2007). Sociodemographic and Clinical Factors Associated with Relapse in Schizophrenia. *Psychiatry & Clinical Neurosciences*, *61*(6), 587-593. doi: 10.1111/j.1440-1819.2007.01722.x
- Chang, W. C., Tang, J. Y., Hui, C. L., Lam, M. M., Chan, S. K., Wong, G. H., ... & Chen, E. Y. (2012a). Prediction of Remission and Recovery in Young People Presenting with First-Episode Psychosis in Hong Kong: A 3-Year Follow-Up Study. *Australian & New Zealand Journal of Psychiatry*, *46*(2), 100-108. doi: 10.1177/0004867411428015
- Chang, W. C., Tang, J. Y. M., Hui, C. L. M., Lam, M. M. L., Wong, G. H. Y., Chan, S. K. W., ... & Chan, K. (2012b). Duration of Untreated Psychosis: Relationship with Baseline Characteristics and Three-Year Outcome in First-Episode Psychosis. *Psychiatry Research*, *198*(3), 360-365. doi: 10.1016/j.psychres.2011.09.006
- Chou, P. H., Lin, W. H., Lin, C. C., Hou, P. H., Li, W. R., Hung, C. C., ... & Chan, C. H. (2015). Duration of Untreated Psychosis and Brain Function During Verbal Fluency Testing in First-Episode Schizophrenia: A Near-Infrared Spectroscopy Study. *Scientific Reports*, *5*(18069), 1-9. doi: 10.1038/srep18069
- Cocco, K. M., & Carey, K. B. (1998). Psychometric Properties of the Drug Abuse Screening Test in Psychiatric Outpatients. *Psychological Assessment*, *10*(4), 408-414. doi: 10.1037/1040-3590.10.4.408
- Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H. (1985). Measuring the Functional Components of Social Support. In I. G. Sarason & B. R. Sarason (Eds.), *Social Support: Theory, Research and Application* (pp. 73-94). The Hague, The Netherlands: Martinus Nijhoff.
- Coldham, E. L., Addington, J., & Addington, D. (2002). Medication Adherence of Individuals with a First Episode of Psychosis. *Acta Psychiatrica Scandinavica*, *106*(4), 286-290. doi: 10.1034/j.1600-0447.2002.02437.x

- Compton. M. T. Age at Onset and Mode of Onset of Psychosis: Two Prognostic Indicators in the Early Course of Schizophrenia. *Medscape*. July 15, 2010. http://www.medscape.com/viewarticle/724817_3
- Compton, M.T., & Broussard, B. (2011). Conceptualizing the Multifaceted Determinants of the Duration of Untreated Psychosis. *Current Psychiatry Reviews*, 7, 1-11. doi: 10.2174/157340011795945865
- Compton, M. T., Carter, T., Bergner, E., Franz, L., Stewart, T., Trotman, H., ... & McGorry, P. D. (2007). Defining, Operationalizing and Measuring the Duration of Untreated Psychosis: Advances, Limitations and Future Directions. *Early Intervention in Psychiatry*, 1(3), 236-250. doi: 10.1111/j.1751-7893.2007.00036.x
- Compton M. T., Chien V. H., Leiner A. S., Goulding S. M., Weiss P. S. (2008). Mode of Onset of Psychosis and Family Involvement in Help-Seeking as Determinants of Duration of Untreated Psychosis. *Social Psychiatry & Psychiatric Epidemiology*, 43, 975–82. doi: 10.1007/s00127-008-0397-y
- Connell, M., Schweitzer, R., & King, R. (2015). Recovery from First-Episode Psychosis: A Dialogical Perspective. *Bulletin of the Menninger Clinic*, 79, 70-90.
- Craney, T. A., & Surlis, J. G. (2002). Model-Dependent Variance Inflation Factor Cutoff Values. *Quality Engineering*, 14(3), 391-403. doi: 10.1081/QEN-120001878
- Crumlish, N., Whitty, P., Clarke, M., Browne, S., Kamali, M., Gervin, M., ... & O'Callaghan, E. (2009). Beyond the Critical Period: Longitudinal Study of 8-Year Outcome in First-Episode Non-Affective Psychosis. *British Journal of Psychiatry*, 194, 18-24. doi: 10.1192/bjp.bp.107.048942
- Davidson, L., O'Connell, M. J., Tondora, J., Staeheli, M., & Evans, A. C. (2005). In: Davidson L, Harding CM, Spaniol L, eds. Recovery in Serious Mental Illness: Paradigm Shift or Shibboleth. *Recovery from Severe Mental Illnesses: Research Evidence and Implications for Practice*. Boston, MA: Centre for Psychiatric Rehabilitation of Boston University.

- Dell'Osso, B., Glick, I. D., Baldwin, D. S., & Altamura, A. C. (2012). Can Long-Term Outcomes be Improved by Shortening the Duration of Untreated Illness in Psychiatric Disorders? A Conceptual Framework. *Psychopathology*, *46*, 14-21.
- de Koning, M., Bloemen, O., van Amelsvoort, T., Becker, H., Nieman, D., van der Gaag, M., & Linszen, D. H. (2009). Early Intervention in Patients at Ultra High Risk of Psychosis: Benefits and Risks. *Acta Psychiatrica Scandinavica*, *119*, 426–442. doi:10.1111/j.1600-0447.2009.01372.x
- de Wet, A., Swartz, L., & Chiliza, B. (2015). Hearing their Voices: The Lived Experience of Recovery from First-Episode Psychosis in Schizophrenia in South Africa. *International Journal of Social Psychiatry*, *61*, 27-32. doi: 10.1177/00207640-14535753
- Drake, R. E., Noel, V. A., & Deegan, P. E. (2015). Measuring Recovery as an Outcome. *Die Psychiatrie*, *12*, 174-149.
- Drapalski, A. L., Medoff, D., Unick, G. J., Velligan, D. I., Dixon, L. B., & Bellack, A. S. (2012). Assessing Recovery of People with Serious Mental Illness: Development of a New Scale. *Psychiatric Services*, *63*, 48-53. doi: 10.1176/appi.ps.201100109
- Edwards, J., & McGorry, P. D. (2002). Implementing Early Intervention in Psychosis: A Guide to Establishing Psychosis Services. *London: Martin Dunitz*.
- Ehmann, T. S., Tee, K. A., Macewan, G. W., Dalzell, K. L., Hanson, L. A., Smith, G. N., ... & Honer, W. G. (2014). Treatment Delay and Pathways to Care in Early Psychosis. *Early Intervention in Psychiatry*, *8*(3), 240-246. doi:10.1111/eip.12051
- Eisenstadt, P., Monteiro, V. B., Diniz, M. J., & Chaves, A. C. (2012). Experience of Recovery from a First-Episode Psychosis. *Early Intervention in Psychiatry*, *6*(4), 476-480. doi: 10.1111/j.1751-7893.2012.00353.x

- ElTayebani, M., ElGamal, M., Roshdy, R., & Al-Khadary, S. (2014). Gender Difference in Affective and Nonaffective Psychosis. *Egyptian Journal of Psychiatry*, 35, 45-55. doi: 10.4103/1110-1105.127281
- Emsley, R., Chiliza, B., & Schoeman, R. (2008). Predictors of Long-Term Outcome in Schizophrenia. *Current Opinion in Psychiatry*, 21(2), 173-177. doi: 10.1097/Y-CO.0b013e3282f33f76
- Evensen, J., Røssberg, J. I., Barder, H., Haahr, U., ten Velden Hegelstad, W., Joa, I., ... & Rund, B. R. (2012). Apathy in First Episode Psychosis Patients: A Ten Year Longitudinal Follow-Up Study. *Schizophrenia Research*, 136, 19-24. doi: 10.1016/j.sch-res.2011.12.019
- Faber, G., Smid, H. G., Van Gool, A. R., Wunderink, L., Wiersma, D., & van den Bosch, R. J. (2011). Neurocognition and Recovery in First Episode Psychosis. *Psychiatry Research*, 188, 1-6. doi: 10.1016/j.psychres.2010.11.010
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1995. Structured Clinical Interview of DSM-IV Axis I (SCID-1) Disorders: Clinical Version. Biometrics Research Department; New York State Psychiatric Institute, New York
- Flanagan, P., & Compton, M. T. (2012). A Comparison of Correlates of Suicidal Ideation Prior to Initial Hospitalization for First-Episode Psychosis with Prior Research on Correlates of Suicide Attempts Prior to Initial Treatment Seeking. *Early Intervention in Psychiatry*, 6(2), 138-144. doi: 10.1111/j.1751-7893.2011.00320.x
- Franz, L., Carter, T., Leiner, A. S., Bergner, E., Thompson, N. J., & Compton, M. T. (2010). Stigma and Treatment Delay in First-Episode Psychosis: A Grounded Theory Study. *Early Intervention in Psychiatry*, 4, 47-56. doi: 10.1111/j.1751-7893.2009.00155.x
- French, P., Smith, J., Shiers, D., Reed, M., & Rayne, M. (Eds.). (2010). *Promoting Recovery in Early Psychosis: A Practice Manual*. John Wiley & Sons.

- Friis, S., Melle, I., Johannessen, J. O., Røssberg, J. I., Barder, H. E., Evensen, J. H., ... & Larsen, T. K. (2015). Early Predictors of Ten-Year Course in First-Episode Psychosis. *Psychiatric Services, 67*(4), 438-443. doi: 10.1176/appi.ps.201400558
- Gee, B., Hodgekins, J., Fowler, D., Marshall, M., Everard, L., Lester, H., ... & Freemantle, N. (2016). The Course of Negative Symptom in First Episode Psychosis and the Relationship with Social Recovery. *Schizophrenia Research, 174* (1-3), 165-171. doi: 10.1016/j.schres.2016.04.017
- Gitlin, M., Nuechterlein, K., Subotnik, K. L., Ventura, J., Mintz, J., Fogelson, D. L., Bartzokis, G., Aravagiri, M. (2001). Clinical Outcome Following Neuroleptic Discontinuation in Patients with Remitted Recent-Onset Schizophrenia. *American Journal of Psychiatry, 158*(11): 1835-1842. doi:10.1176/appi.ajp.158.11.1835
- Gumley, A. I., Schwannauer, M., Macbeth, A., Fisher, R., Clark, S., Rattrie, L., ... & Birchwood, M. (2014). Insight, Duration of Untreated Psychosis and Attachment in First-Episode Psychosis: Prospective Study of Psychiatric Recovery Over 12-month Follow-up. *British Journal of Psychiatry, 205*, 60-67. doi: 10.1192/bjp.-bp.113.126722
- Gureje, O., Aderibigbe, Y. A., Olley, O., & Bamidele, R. W. (1994). Premorbid Functioning in Schizophrenia: A Controlled Study of Nigerian Patients. *Comprehensive Psychiatry, 35*(6), 437-440. doi: 10.1016/0010-440X(94)90226-7
- Harris, A., Brennan, J., Anderson, J., Taylor, A., Sanbrook, M., Fitzgerald, D., ... & Gordon, E. (2005). Clinical Profiles, Scope and General Findings of the Western Sydney First Episode Psychosis Project. *Australian & New Zealand Journal of Psychiatry, 39*(1-2), 36-43. doi: 10.1111/j.1440-1614.2005.01517.x
- Harris, M. G., Henry, L. P., Harrigan, S. M., Purcell, R., Schwartz, O. S., Farrelly, S. E., ... & McGorry, P. D. (2005). The Relationship between Duration of Untreated

Psychosis and Outcome: An Eight-Year Prospective Study. *Schizophrenia Research*, 79, 85-93. doi: 10.1016/j.schres.2005.05.024

Harrison, G., Hopper, K. I. M., Craig, T., Laska, E., Siegel, C., Wanderling, J., ... & Holmberg, S. K. (2001). Recovery from Psychotic Illness: A 15- and 25-Year International Follow-Up Study. *British Journal of Psychiatry*, 178(6), 506-517. doi: 10.1192/bjp.178.6.506

Harvey, P. D., & Bellack, A. S. (2009). Toward a Terminology for Functional Recovery in Schizophrenia: Is Functional Remission A Viable Concept? *Schizophrenia Bulletin*, 35(2), 300–306. doi: 10.1093/schbul/sbn171

Hill, M., Crumlish, N., Clarke, M., Whitty, P., Owens, E., Renwick, L., ... & Waddington, J. L. (2012). Prospective Relationship of Duration of Untreated Psychosis to Psychopathology and Functional Outcome Over 12 Years. *Schizophrenia Research*, 141(2), 215-221. doi: 10.1016/j.schres.2012.08.013

Hui, C. L., Tang, J. Y., Leung, C. M., Wong, G. H., Chang, W. C., Chan, S. K., ... & Chen, E. Y. (2013). A 3-Year Retrospective Cohort Study of Predictors of Relapse in First-Episode Psychosis in Hong Kong. *Australian & New Zealand Journal of Psychiatry*, 47(8), 746-753. doi: 10.1177/0004867413487229

Ichinose, H., Nakane, Y., Nakane, H., Kinoshita, H., Ohta, Y., Honda, S., & Ozawa, H. (2010). Nagasaki Schizophrenia Study: Relationship between Ultralong-Term Outcome (After 28 years) and Duration of Untreated Psychosis. *Acta Medica Nagasakiensia*, 54(3), 59-66. doi: 10.11343/amn.54.59

Ienciu, M., Romoșan, F., Bredicean, C., & Romoșan, R. (2010). First Episode Psychosis and Treatment Delay—Causes and Consequences. *Psychiatria Danubina*, 22(4), 540-543.

Iyer, S. N., Boeckstyn, L., Cassidy, C. M., King, S., Joobor, R., & Malla, A. K. (2008). Signs and Symptoms in the Pre-Psychotic Phase: Description and Implications for

Diagnostic Trajectories. *Psychological Medicine*, 38(8), 1147-1156. doi: 10.1017/S0033291708003152

Jaracz, K., Górna, K., Kiejda, J., Grabowska-Fudala, B., Jaracz, J., Suwalska, A., & Rybakowski, J. K. (2015). Psychosocial Functioning in Relation to Symptomatic Remission: A Longitudinal Study of First Episode Schizophrenia. *European Psychiatry*, 30(8), 907-913. doi: 10.1016/j.eurpsy.2015.08.001

Johnson, S. L., Winett, C. A., Meyer, B., Greenhouse, W. J., & Miller, I. (1999). Social Support and the Course of Bipolar Disorder. *Journal of Abnormal Psychology*, 108(4), 558-566. doi: 10.1037/0021-843X.108.4.558

Jones, C., Hacker, D., Cormac, I., Meaden, A., & Irving, C. B. (2012). Cognitive Behaviour Therapy Versus Other Psychosocial Treatments for Schizophrenia. *Schizophrenia Bulletin*, 38, 908-910. doi: 10.1002/14651858.CD008712.pub2.

Jørgensen, R., Zoffmann, V., Munk-Jørgensen, P., Buck, K. D., Jensen, S. O., Hansson, L., & Lysaker, P. H. (2015). Relationships Over Time of Subjective and Objective Elements of Recovery in Persons with Schizophrenia. *Psychiatry Research*, 228, 14-19. doi: 10.1016/j.psychres.2015.03.013

Kam, S. M., Singh, S. P., & Upthegrove, R. (2015). What Needs to Follow Early Intervention? Predictors of Relapse and Functional Recovery following First-Episode Psychosis. *Early Intervention In Psychiatry*, 9(4), 279-283. doi: 10.1111/eip.12099

Karahalios, A., Baglietto, L., Carlin, J. B., English, D. R., & Simpson, J. A. (2012). A Review of the Reporting and Handling of Missing Data in Cohort Studies with Repeated Assessment of Exposure Measures. *BMC Medical Research Methodology*, 12(96), 1-7. doi: 10.1186/1471-2288-12-9

Keks, N., & Blashki, G. (2006). The Acutely Psychotic Patient: Assessment and Initial Management. *Australian Family Physician*, 35(3), 90-94.

- Kenny, D. A., Kashy, D., & Bolger, N. (1998). Data Analysis in Social Psychology. In D. Gilbert, S. T. Fiske, & G. Lindzey (Eds.), *Handbook of Social Psychology* (4a ed., Vol. 1, pp. 233-265). New York: McGraw-Hill.
- Keshavan, M. S., Haas, G., Miewald, J., Montrose, D. M., Reddy, R., Schooler, N. R., & Sweeney, J. A. (2003). Prolonged Untreated Illness Duration from Prodromal Onset Predicts Outcome in First Episode Psychoses. *Schizophrenia Bulletin*, *29*(4), 757-769.
- Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of Onset of Mental Disorders: A Review of Recent Literature. *Current Opinion in Psychiatry*, *20*(4), 359-364. doi:10.1097/YCO.0b0-13e32816ebc8c
- Kinoshita, H., Nakane, Y., Nakane, H., Ishizaki, Y., Honda, S., Ohta, Y., & Ozawa, H. (2005). Nagasaki Schizophrenia Study: Influence of the Duration of Untreated Psychosis on Long-Term Outcome. *Acta Medica Nagasakiensia*, *50*, 17-22. doi: 0.11343/amn.50.17
- Kirkbride, J. B., Fearon, P., Morgan, C., Dazzan, P., Morgan, K., Tarrant, J., ... & Mallett, R. M. (2006). Heterogeneity in Incidence Rates of Schizophrenia and Other Psychotic Syndromes: Findings from the 3-Center AeSOP Study. *Archives of General Psychiatry*, *63*(3), 250-258. doi: 10.1001/archpsyc.63.3.250
- Køster, A., Lajer, M., Lindhardt, A., & Rosenbaum, B. (2008). Gender Differences in First Episode Psychosis. *Social Psychiatry & Psychiatric Epidemiology*, *43*(12), 940-946. doi: 10.1007/s00127-008-0384-3
- Kukla, M., Lysaker, P. H., & Roe, D. (2014). Strong Subjective Recovery as a Protective Factor against the Effects of Positive Symptoms on Quality of Life Outcomes in Schizophrenia. *Comprehensive Psychiatry*, *55*(6), 1363-1368. doi: 10.1016/j.comppsy.2014.04.022

- Lam, M. M., Pearson, V., Ng, R. M., Chiu, C. P., Law, C. W., & Chen, E. Y. (2010). What Does Recovery from Psychosis Mean? Perceptions of Young First-Episode Patients. *International Journal of Social Psychiatry*, *57*(6), 580-587. doi: 10.1177/0020764010374418
- Lauridsen, J., & Mur, J. (2006). Multicollinearity in Cross-Sectional Regressions. *Journal of Geographical Systems*, *8*(4), 317-333. doi: 10.1007/s10109-006-0031-z
- Law, H., Shryane, N., Bentall, R. P., & Morrison, A. P. (2015). Longitudinal Predictors of Subjective Recovery in Psychosis. *British Journal of Psychiatry*, *209*, 48-53. doi: 10.1192/bjp.bp.114.158428
- Leclerc, E., Noto, C., Bressan, R. A., & Brietzke, E. (2015). Determinants of Adherence to Treatment in First-Episode Psychosis: A Comprehensive Review. *Revista Brasileira de Psiquiatria*, *37*(2), 168-176. doi: 10.1590/1516-4446-2014-1539
- Liberman, R. P., & Kopelowicz, A. (2005). Recovery from Schizophrenia: A Concept in Search of Research. *Psychiatric Services*, *56*(6), 735-742. doi: 10.1176/appi.ps.56.6.735
- Little R. J. A., Rubin D.B. (2002). *Statistical Analysis with Missing Data*. Hoboken, New Jersey: John Wiley & Sons, Inc.
- Lloyd, C., King, R., & Moore, L. (2010). Subjective and Objective Indicators of Recovery in Severe Mental Illness: A Cross-Sectional Study. *International Journal of Social Psychiatry*, *56*(3), 220-229. doi: 10.1177/0020764009105703
- Lyne, J., Renwick, L., Grant, T., Kinsella, A., McCarthy, P., Malone, K., ... & Clarke, M. (2013). Scale for the Assessment of Negative Symptoms Structure in First Episode Psychosis. *Psychiatry Research*, *210*(3), 1191-1197. doi: 10.1016/j.psychres.2013.09.008
- Lysaker, P. H., Taylor, A., Miller, A., Beattie, N., Strasburger, A., Davis, L.W. (2006). The Scale to Assess Narrative Development: Associations with Other Measures of

Self and Readiness for Recovery in Schizophrenia Spectrum Disorders. *Journal of Nervous Mental Disease*, 194(3), 223–225. doi: 10.1097/01.nmd.0000-202512.54587.34

MacKinnon, D. P., Krull, J. L., & Lockwood, C. (2000). Mediation, Confounding, and Suppression: Different Names for the Same Effect. *Prevention Science*, 1, 173-181.

Mackrell, L., & Lavender, T. (2004). Peer Relationships in Adolescents Experiencing a First Episode of Psychosis. *Journal of Mental Health*, 13(5), 467-479. doi: 10.1080/09638-230400006775

Maddigan, W. J. (2011). *A Mixed Methods Study of Recovery Among Individuals in an Early Psychosis Program: Implications for Psychiatric/Mental Health Nurses*. University of Calgary.

Major, B. S., Hinton, M. F., Flint, A., Chalmers-Brown, A., McLoughlin, K., & Johnson, S. (2010). Evidence of the Effectiveness of a Specialist Vocational Intervention Following First Episode Psychosis: A Naturalistic Prospective Cohort Study. *Social Psychiatry & Psychiatric Epidemiology*, 45, 1-8. doi: 10.1007/s00127-009-0034-4

Malla, A. K., Norman, R. M. G., Manchanda, R., Ahmed, M., Scholten, D., Harricharan, R., ... & Takhar, J. (2002). One Year Outcome in First Episode Psychosis: Influence of DUP and Other Predictors. *Schizophrenia Research*, 54(3), 231-242. doi:10.1016/S0920-9964(01)00254-7

Malla, A. K., Norman, R. M. G., McLean, T., Scholten, D., & Townsend, L. (2003). A Canadian Programme for Early Intervention in Non-Affective Psychotic Disorders. *Australian & New Zealand Journal of Psychiatry*, 37(4), 407-413. doi: 10.1046/j.1440-1614.2003.01194.x

Malla, A. K., Norman, R. M. G., Scholten, D., Manchanda, R., & McLean, T. (2005). A Community Intervention for Early Identification of First Episode Psychosis.

Social Psychiatry & Psychiatric Epidemiology, 40(5), 337-344. doi:
10.1007/s00127-005-0901-6

- Malla, A. K., Norman, R. M. G., Bechara-Evans, L., Schmitz, N., Manchanda, R., & Cassidy, C. (2008). Factors Influencing Relapse During A 2-year Follow-up of First-Episode Psychosis in a Specialized Early Intervention Service. *Psychological Medicine*, 38(11), 1585-1593. doi: 10.1017/S0033291707002656
- Manchanda, R., Norman, R. M. G., Malla, A. K., Harricharan, R., & Northcott, S. (2008). EEG Abnormalities and 3-Year Outcome in First Episode Psychosis. *Acta Psychiatrica Scandinavica*, 117(4), 277-282. doi: 10.1111/j.1600-0447.2007.01120.x
- Mansfield, E. R., & Helms, B. P. (1982). Detecting Multicollinearity. *The American Statistician*, 36(3a), 158-160. doi: 10.1080/00031305.1982.10482818
- Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., Croudace, T. (2005). Association between Duration of Untreated Psychosis and Outcome in Cohorts of First-Episode Patients: A Systematic Review. *Archives of General Psychiatry*, 62(9), 975–983. doi: 10.1001/archpsyc.62.9.975
- Marshall, M., & Rathbone, J. (2011). Early Intervention for Psychosis. *Schizophrenia Bulletin*, 37(6), 1111–1114. doi:10.1093/schbul/sbr110
- McGlashan, T. H. (1999). Duration of Untreated Psychosis in First-Episode Schizophrenia: Marker or Determinant of Course? *Biological Psychiatry*, 46(7), 899-907. doi: 10.1016/S0006-3223(99)00084-0
- McGlashan, T. H. (2006). Schizophrenia in Translation: Is Active Psychosis Neurotoxic? *Schizophrenia Bulletin*, 32(4), 609-613. doi: 10.1093/schbul/sbl032
- McGlashan, T. H., Levy, S.T., (1977). Sealing-Over in Therapeutic Community. *Psychiatry*, 40, 55–65.

- McGorry, P. D., Killackey, E., & Yung, A. R. (2007). Early Intervention in Psychotic Disorders: Detection and Treatment of the First Episode and the Critical Early Stages. *Medical Journal of Australia*, *187*(7 Suppl), S8-S10.
- McGorry, P. D., Killackey, E., & Yung, A. (2008). Early Intervention in Psychosis: Concepts, Evidence and Future Directions. *World Psychiatry*, *7*(3), 148-156. doi: 10.1002/j.2051-5545.2008.tb00182.x
- Miller, R., Ream, G., McCormack, J., Gunduz-Bruce, H., Sevy, S., & Robinson, D. (2009). A Prospective Study of Cannabis Use as a Risk Factor for Non-Adherence and Treatment Dropout in First-Episode Schizophrenia. *Schizophrenia Research*, *113*(2), 138-144. doi: 10.1016/j.schres.2009.04.018
- Minas, I., Stuart, G. W., Klimidis, S., Jackson, H. J., Singh, B. S., & Copolov, D. L. (1992). Positive and Negative Symptoms in the Psychoses: Multidimensional Scaling of SAPS and SANS Items. *Schizophrenia Research*, *8*(2), 143-156.
- Mishra, A., Ojha, S. P., Chapagain, M., & Tulachan, P. (2014). Prevalence of Substance Use in First Episode Psychosis and its Association with Socio-Demographic Variants in Nepalese Patients. *Journal of Psychiatrists' Association of Nepal*, *3*, 16-22. doi: 10.3126/jpan.v3i1.11347
- Monte, R. C., Goulding, S. M., & Compton, M. T. (2008). Premorbid Functioning of Patients with First-Episode Non-affective Psychosis: A Comparison of Deterioration in Academic and Social Performance, and Clinical Correlates of Premorbid Adjustment Scale Scores. *Schizophrenia Research*, *104*, 206-213. doi: 10.1016/j.schres.2008.06.009
- Morgan, C., Abdul-Al, R., Lappin, J. M., Jones, P., Fearon, P., Leese, M., ... & Leff, J. (2006). Clinical and Social Determinants of Duration of Untreated Psychosis in the AESOP First-Episode Psychosis Study. *British Journal of Psychiatry*, *189*(5), 446-452. doi: 10.1192/bjp.bp.106.021303

- Morland, T. (2007). *The Predictive Factors of Subjective Recovery in First-Episode Psychosis*. Doctoral dissertation, University of London.
- Morrison, A. P., Shryane, N., Beck, R., Heffernan, S., Law, H., McCusker, M., & Bentall, R. P. (2013). Psychosocial and Neuropsychiatric Predictors of Subjective Recovery from Psychosis. *Psychiatry Research*, 208(3), 203-209. doi: 10.1016/j.psychres.2013.05.008
- Munguía, T., & Armando, J. (2014). Comparison of Imputation Methods for Handling Missing Categorical Data with Univariate Pattern. *Revista de Métodos Cuantitativos para la Economía y la Empresa*, 17, 101-120.
- Naggara, O., Raymond, J., Guilbert, F., Roy, D., Weill, A., & Altman, D. G. (2011). Analysis by Categorizing or Dichotomizing Continuous Variables is Inadvisable: An Example from the Natural History of Unruptured Aneurysms. *American Journal of Neuroradiology*, 32(3), 437-440. doi: 10.3174/ajnr.A2425
- Nakagawa, S., & Freckleton, R. P. (2008). Missing Inaction: The Dangers of Ignoring Missing Data. *Trends in Ecology & Evolution*, 23(11), 592-596. doi: 10.1016/j.tree.2008.06.014
- Nakai, M., & Ke, W. (2011). Review of the Methods for Handling Missing Data in Longitudinal Data Analysis. *International Journal of Mathematical Analysis*, 5, 1-13.
- Ng, R. K. M., Pearson, V., Lam, M., Law, C. W., Chiu C. P. Y., & Chen, E. Y. H. (2008). What Does Recovery from Schizophrenia Mean? Perceptions of Long-Term Patients. *International Journal of Social Psychiatry*, 54(2), 118-130. doi: 10.1177/0020764007084600
- Norman, R. M. G. (2014). Are the Effects of Duration of Untreated Psychosis Socially Mediated? *Canadian Journal of Psychiatry*. 59(10), 518-522.

- Norman, R. M. G., Lewis, S. W., & Marshall, M. (2005). Duration of Untreated Psychosis and its Relationship to Clinical Outcome. *British Journal of Psychiatry*, *187*(48), s19-s23. doi: 10.1192/bjp.187.48.s19
- Norman, R. M. G., & Malla, A. K. (2001). Duration of Untreated Psychosis: A Critical Examination of the Concept and its Importance. *Psychological Medicine*, *31*(3), 381-400. doi: 10.1017/S0033291701003488
- Norman, R. M. G., & Malla, A. K. (2002). Course of Onset and Relapse Schedule: Interview and Coding Instruction Guide. Prevention and Early Intervention for Psychosis Program: London, Ontario, Canada.
- Norman, R. M.G., Malla, A. K., & Manchanda, R. (2007). Early Premorbid Adjustment as a Moderator of the Impact of Duration of Untreated Psychosis. *Schizophrenia Research*, *95*, 111-114. doi: 10.1016/j.schres.2007.06.007
- Norman, R. M. G., Malla, A. K., Manchanda, R., Harricharan, R., Takhar, J., & Northcott, S. (2005). Social Support and Three-Year Symptom and Admission Outcomes for First Episode Psychosis. *Schizophrenia Research*, *80*(2), 227-234. doi: 10.1016/j.schres.2005.05.006
- Norman, R. M.G., Malla, A. K., Manchanda, R., Windell, D., Harricharan, R., Takhar, J., & Northcott, S. (2007). Does Treatment Delay Predict Occupational Functioning in First-Episode Psychosis? *Schizophrenia Research*, *91*, 259-262. doi:10.1016/j.schres.2006.12.-024
- Norman, R. M.G., Manchanda, R., Malla, A. K., Windell, D., Harricharan, R., & Northcott, S. (2011). Symptom and Functional Outcomes for a 5 Year Early Intervention Program for Psychoses. *Schizophrenia Research*, *129*(2), 111-115. doi: 10.1016/j.schres.2011.04.006
- Norman, R. M. G., Manchanda, R., Windell, D., Harricharan, R., Northcott, S., & Hassall, L. (2012). The Role of Treatment Delay in Predicting 5-year Outcomes

in an Early Intervention Program. *Psychological Medicine*, 42(2), 223-233. doi: 10.1017/S0033291711001140

Norman, R. M. G., & Manchanda, R. (2016). Prevention and Early Intervention Program for Psychoses (PEPP). *Healthcare Quarterly (Toronto, Ont.)*, 18, 37.

Norman, R. M. G., Manchanda, R., Harricharan, R., & Northcott, S. (2015). The Course of Negative Symptoms Over the First Five Years of Treatment: Data from an Early Intervention Program for Psychosis. *Schizophrenia Research*, 169, 412-417. doi:10.1016/j.schres.2015.09.010

Norman, R. M. G., Windell, D., Lynch, J., & Manchanda, R. (2013). Correlates of Subjective Recovery in an Early Intervention Program for Psychoses. *Early Intervention in Psychiatry*, 7(3), 278-284. doi: 10.1111/j.1751-7893.2012.00371.x

O'Brien, R. M. (2007). A Caution Regarding Rules of Thumb for Variance Inflation Factors. *Quality & Quantity*, 41(5), 673-690. doi: 10.1007/s11135-006-9018-6

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. *Schizophrenia Research & Treatment*, Article ID 916198, 1-9. doi:10.1155/2012/916198

Pan, Y., & Jackson, R. T. (2008). Ethnic Difference in the Relationship between Acute Inflammation and Serum Ferritin in US Adult Males. *Epidemiology & Infection*, 136(3), 421-431. doi: 10.1017/S095026880700831X

Pardo, A., & Román, M. (2013). Reflections on the Baron and Kenny Model of Statistical Mediation. *Annals of Psychology*, 29(2), 614-623. doi: 10.6018/analesps.29.2.139241

Perala, J., Suvisaari, J., Saarni, S. I., Kuopasalmi, K., Isometsa, E., Pirkola, S., ... & Lonnqvist, J. (2007). Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population. *Archives of General Psychiatry*, 64, 19-28. doi: 10.1001/archpsyc.64.1.19

- Perkins, D. O., Gu, H., Boteva, K., Lieberman, J. A. (2005). Relationship between Duration of Untreated Psychosis and Outcome in First-Episode Schizophrenia: A Critical Review & Meta-Analysis. *American Journal of Psychiatry*, *162*(10), 1785–1804. doi: 10.1176/appi.ajp.162.10.1785
- Preacher K. J., & Hayes, A. F. (2008). Asymptotic and Resampling Strategies for Assessing and Comparing Indirect Effects in Multiple Mediator Models. *Behavior Research Methods* *40*(3), 879–891. doi: 10.3758/BRM.40.3.879
- Primavera, D., Bandecchi, C., Lepori, T., Sanna, L., Nicotra, E., & Carpiniello, B. (2012). Does Duration of Untreated Psychosis Predict Very Long Term Outcome of Schizophrenic Disorders? Results of a Retrospective Study. *Annals of General Psychiatry*, *11*, 1-6. doi: 10.1186/1744-859X-11-21
- Proctor, S. E., Mitford, E., & Paxton, R. (2004). First Episode Psychosis: A Novel Methodology Reveals Higher than Expected Incidence: A Reality-Based Population Profile in Northumberland, UK. *Journal of Evaluation in Clinical Practice*, *10*(4), 539-547. doi: 10.1111/j.1365-2753.2003.00474.x
- Rabinovitch, M., Bechara-Evans, L., Schmitz, N., Jooper, R., & Malla, A. K. (2009). Early Predictors of Nonadherence to Antipsychotic Therapy in First-Episode Psychosis. *Canadian Journal of Psychiatry*. *54*, 28-35. doi: 10.1177/070674370905400106
- Reay, R., Mitford, E., McCabe, K., Paxton, R., & Turkington, D. (2010). Incidence and Diagnostic Diversity in First-Episode Psychosis. *Acta Psychiatrica Scandinavica*, *121*(4), 315-319. doi: 10.1111/j.1600-0447.2009.01505.x
- Reed, S. I. (2008). First-Episode Psychosis: A Literature Review. *International Journal of Mental Health Nursing*, *17*(2), 85-91. doi: 10.1111/j.1447-0349.2008.00515.x
- Resnick, S. G., Rosenheck, R. A., & Lehman, A. F. (2004). An Exploratory Analysis of Correlates of Recovery. *Psychiatric Services*, *55*(5), 540-547. doi: 10.1176/appi.ps.55.5.540

- Robinson, D., Woerner, M. G., Alvir, J. M. J., Bilder, R., Goldman, R., Geisler, S., ... & Lieberman, J. A. (1999). Predictors of Relapse Following Response from a First Episode of Schizophrenia or Schizoaffective Disorder. *Archives of General Psychiatry*, *56*(3), 241-247. doi: 10.1001/archpsyc.56.3.241
- Roe, D., Mashiach-Eizenberg, M., & Lysaker, P. H. (2011). The Relation between Objective and Subjective Domains of Recovery among Persons with Schizophrenia-Related Disorders. *Schizophrenia Research*, *131*, 133-138. doi:10.1016/j.schres.2011.05.023
- Rubin, D. B. (1976). Inference and Missing Data. *Biometrika*, *63*(3), 581-592. doi: 10.1093/biomet/63.3.581
- Rund, B. R. (2014). Does Active Psychosis Cause Neurobiological Pathology? A Critical Review of the Neurotoxicity Hypothesis. *Psychological Medicine*, *44*(8), 1577-1590. doi: 10.1017/S0033291713002341
- Rund, B. R., Barder, H. E., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., ... & Opjordsmoen, S. (2015). Neurocognition and Duration of Psychosis: A 10-year Follow-up of First-Episode Patients. *Schizophrenia Bulletin*, *42*, 87-95. doi: 10.1093/schbul/sbv083
- Salvatore, P., Khalsa, H. M. K., Hennen, J., Tohen, M., Yurgelun-Todd, D., Casolari, F., ... & Baldessarini, R. J. (2007). Psychopathology Factors in First-Episode Affective and Non-Affective Psychotic Disorders. *Journal of Psychiatric Research*, *41*(9), 724-736. doi: 10.1016/j.jpsychires.2006.04.008
- Saravanan, B., Jacob, K. S., Johnson, S., Prince, M., Bhugra, D., & David, A. S. (2010). Outcome of First-Episode Schizophrenia in India: Longitudinal Study of Effect of Insight and Psychopathology. *British Journal of Psychiatry*, *196*(6), 454-459. doi: 10.1192/bjp.bp.109.068577
- Sariah, A. E., Outwater, A. H., & Malima, K. I. (2014). Risk and Protective Factors for Relapse among Individuals with Schizophrenia: A Qualitative Study in Dar es

Salaam, Tanzania. *BMC Psychiatry*, *14*, 240-252. doi: 10.1186/s12888-014-0240-9

- Sartorius, N., Gulbinat, W., Harrison, G., Laska, E., & Siegel, C. (1996). Long-term Follow-up of Schizophrenia in 16 Countries. *Social Psychiatry & Psychiatric Epidemiology*, *31*(5), 249-258.
- Schimmelmann, B. G., Huber, C. G., Lambert, M., Cotton, S., McGorry, P. D., & Conus, P. (2008). Impact of Duration of Untreated Psychosis on Pre-treatment, Baseline, and Outcome Characteristics in an Epidemiological First-Episode Psychosis Cohort. *Journal of Psychiatric Research*, *42*(12), 982-990. doi: 10.1016/j.jpsychires.2007.12.001
- Schmael, C., Georgi, A., Krumm, B., Buerger, C., Deschner, M., Nöthen, M. M., ... & Rietschel, M. (2007). Premorbid Adjustment in Schizophrenia—An Important Aspect of Phenotype Definition. *Schizophrenia Research*, *92*, 50-62. doi: 10.1016/j.schres.2007.01.016
- Schooler, N., Rabinowitz, J., Davidson, M., Emsley, R., Harvey, P. D., Kopala, L., ... & De Smedt, G. (2005). Risperidone and Haloperidol in First-Episode Psychosis: A Long-Term Randomized Trial. *American Journal of Psychiatry*, *162*(5), 947-953. doi:10.1176/appi.ajp.162.5.947
- Shanks, V., Williams, J., Leamy, M., Bird, V. J., Le Boutillier, C., & Slade, M. (2013). Measures of Personal Recovery: A Systematic Review. *Psychiatric Services*, *64*(10), 974-980. doi: 10.1176/appi.ps.005012012
- Shrivastava, A., Shah, N., Johnston, M., Stitt, L., Thakar, M., & Chinnasamy, G. (2010). Effects of Duration of Untreated Psychosis on Long-Term Outcome of People Hospitalized with First Episode Schizophrenia. *Indian Journal of Psychiatry*, *52*(2), 164-167. doi:10.4103/0019-5545.64583

- Shrout, P. E., & Bolger, N. (2002). Mediation in Experimental and Nonexperimental Studies: New Procedures and Recommendations. *Psychological Methods*, 7(4), 422. doi: 10.1037/1082-989X.7.4.422
- Silverstein, S. M., & Bellack, A. S. (2008). A Scientific Agenda for the Concept of Recovery as it Applies to Schizophrenia. *Clinical Psychology Review*, 28(7), 1108-1124. doi: 10.1016/j.cpr.2008.03.004
- Singh, S. P., (2007). Outcome Measures in Early Psychosis Relevance of Duration of Untreated Psychosis. *British Journal of Psychiatry Supplement*, 191, s58–s63. doi: 10.1192/bjp.191.50.s58
- Singh, S. P., & Fisher, H. L. (2005). Early Intervention in Psychosis: Obstacles and Opportunities. *Advances in Psychiatric Treatment*, 11, 71-78. doi: 10.1192/apt.11.1.71
- Skinner, H. A. (1982). The Drug Abuse Screening Test. *Addictive Behaviors*, 7(4), 363-371. doi: 10.1016/0306-4603(82)90005-3
- StataCorp. (2015). *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.
- Stefanescu, C., Macrea, R., Popescu, C., Ilies, D., & Miclutia, I. (2013). Factors Influencing the Relapse after the First Psychotic Episode. *Romanian Journal of Psychopharmacology*, 13, 114-119.
- Tang, J. Y. M., Chang, W. C., Hui, C. L. M., Wong, G. H. Y., Chan, S. K. W., Lee, E. H. M., ... & Pang, E. P. F. (2014). Prospective Relationship between Duration of Untreated Psychosis and 13-Year Clinical Outcome: A First-Episode Psychosis Study. *Schizophrenia Research*, 153, 1-8. doi:10.1016/j.schres.2014.01.022
- Thompson, K. N., McGorry, P. D., & Harrigan, S. M. (2003). Recovery Style and Outcome in First-Episode Psychosis. *Schizophrenia Research*, 62, 31-36. doi: 10.1016/S0920-9964(02)00428-0

- Thorup, A., Albert, N., Bertelsen, M., Petersen, L., Jeppesen, P., Le Quack, P., ... & Nordentoft, M. (2014). Gender Differences in First-Episode Psychosis at 5-Year Follow-Up—Two Different Courses of Disease? Results from the OPUS Study at 5-Year Follow-Up. *European Psychiatry, 29*, 44-51. doi: 10.1016/j.eurpsy.-2012.11.005
- Tosato, S., Lasalvia, A., Bonetto, C., Mazzoncini, R., Cristofalo, D., De Santi, K., ... & Lamonaca, D. (2013). The Impact of Cannabis Use on Age of Onset and Clinical Characteristics in First-Episode Psychotic Patients: Data from the Psychosis Incident Cohort Outcome Study (PICOS). *Journal of Psychiatric Research, 47*(4), 438-444. doi: 10.1016/j.jpsycgires.2012.11.009
- UCLA: Statistical Consulting Group. Missing Data Techniques in Stata Part 1. Retrieved from: http://www.ats.ucla.edu/stat/stata/seminars/missing_data/Multiple_imputation/mi_in_stata_pt1_new.html (accessed May 26, 2016).
- Verma, S., Subramaniam, M., Abdin, E., Poon, L. Y., & Chong, S. A. (2012). Symptomatic and Functional Remission in Patients with First-Episode Psychosis. *Acta Psychiatrica Scandinavica, 126*(4), 282-289. doi: 10.1111/j.1600-0447.2012.01883.x
- Vittinghoff, E., Glidden, D. V., Shiboski, S. C., & McCulloch, C. E. (2011). *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. Springer Science & Business Media.
- Von Hippel, P. T. (2009). How to Impute Squares, Interactions, and Other Transformed Variables. *Sociological Methodology, 39*, 265-291. doi: 10.1111/j.1467-9531.2009.01215.x
- Wade, D., Harrigan, S., Edwards, J., Burgess, P. M., Whelan, G., & McGorry, P. D. (2006). Substance Misuse in First-Episode Psychosis: 15-Month Prospective Follow-Up Study. *British Journal of Psychiatry, 189*(3), 229-234. doi: 10.1192/bjp.bp.105.017236

- Wallcraft, J. (2012). Consumer Models of Recovery: Can they Survive Operationalism? *World Psychiatry, 11*(3), 166-167.
- White, I. R., Royston, P., & Wood, A. M. (2011). Multiple Imputation using Chained Equations: Issues and Guidance for Practice. *Statistics in Medicine, 30*(4), 377-399. doi: 10.1002/sim.4067
- White, C., Stirling, J., Hopkins, R., Morris, J., Montague, L., Tantam, D., & Lewis, S. (2009). Predictors of 10-Year Outcome of First-Episode Psychosis. *Psychological Medicine, 39*(9), 1447-1456. doi: 10.1017/S003329170800514X
- Wiersma, D., Nienhuis, F. J., Slooff, C. J., & Giel, R. (1998). Natural Course of Schizophrenic Disorders: A 15-year Follow Up of a Dutch Incidence Cohort. *Schizophrenia Bulletin, 24*, 75-85.
- Windell, D., & Norman, R. M. G. (2012). A Qualitative Analysis of Influences on Recovery Following a First Episode of Psychosis. *International Journal of Social Psychiatry, 59*(5), 493-500. doi: 10.1177/0020764012443751
- Windell, D., & Norman, R. M. G. (2013). A Qualitative Analysis of Influences on Recovery Following a First Episode of Psychosis. *International Journal of Social Psychiatry, 59*(5), 493-500. doi: 10.1177/0020764012443751
- Windell, D., Norman, R. M. G., & Malla, A. K. (2012). The Personal Meaning of Recovery among Individuals Treated for a First Episode of Psychosis. *Psychiatric Services, 63*(6), 548-553. doi: 10.1176/appi.ps.201100424
- World Health Organization (1992). Life Chart Schedule. *World Health Organization, Geneva*.
- Wunderink, L., Sytema, S., Nienhuis, F. J., & Wiersma, D. (2009). Clinical Recovery in First-Episode Psychosis. *Schizophrenia Bulletin, 35*(2), 362-369. doi: 10.1093/schbul/sbn143

- Wyatt, R. J. (1991). Neuroleptics and the Natural Course of Schizophrenia. *Schizophrenia Bulletin*, *17*(2), 325-351. doi: 10.1093/schbul/17.2.325
- Yung, A. R., & McGorry, P. D. (1996). The Initial Prodrome in Psychosis: Descriptive and Qualitative Aspects. *Australian & New Zealand Journal of Psychiatry*, *30*(5), 587-599.
- Zhao, X., Lynch, J. G., & Chen, Q. (2010). Reconsidering Baron and Kenny: Myths and Truths about Mediation Analysis. *Journal of Consumer Research*, *37*, 197-210. doi: 10.1086/651257

Appendices

Appendix A: Synonyms for Duration of Untreated Psychosis & Subjective Recovery.

Duration of Untreated Psychosis	Subjective Recovery
<ul style="list-style-type: none"> - Treatment Delay - Delay in Treatment - Latency in Treatment - Duration of Initially Untreated Psychosis 	<ul style="list-style-type: none"> - Subjective Perceptions of Recovery - Subjective Perceived Recovery - Self-Rated Recovery - Self-Perceived Recovery - Self-Described Recovery - Personal Recovery - Subjective Judgments of Recovery from Psychosis - Perceived Recovery - Consumer-Defined Recovery - Self-Rated Perceptions of Recovery

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