An Exploration of Loneliness Across the Psychosis Spectrum

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Dedication

This work is dedicated to the memory of Neal deCathelineau and Benny Potatoes, who each taught me that the joy and gratitude of companionship transcends all bounds. This work is also dedicated to the memory of Helen Kivnick, whose relentless encouragement will never be forgotten.

Abstract

Background: Loneliness has been robustly associated with negative health and wellbeing outcomes and is a growing concern across the United States. Adolescents and people with psychosis spectrum diagnoses have been shown to be at greater risk of experiencing chronic loneliness than the general public. However, loneliness is not well understood within the psychosis spectrum. Research focused on loneliness within psychosis populations has shown that loneliness is strongly correlated with clinical and psychosocial factors of psychosis that are commonly associated with both clinical and functional impairment. However, the current body of research is limited, and many questions remain about the potential causes and consequences of loneliness in both general and early psychosis populations. The three studies included in this dissertation aim to explore and identify causal relations between loneliness and common factors of psychosis in three distinct psychosis populations.

Methods: The participants recruited for each of the three studies were categorically different from one another. Participants in the first study were categorized as a general psychosis spectrum sample, while participants in the second study were categorized as an early psychosis spectrum sample. Participants in the third study were categorized as a first-episode psychosis sample and included people with schizophrenia spectrum disorders only. The participants in each of the three studies were also engaged in some form of psychosis intervention. Studies one and two explored data over a six-month period, while study three explored data over a one-year treatment period. Causal discovery methods were used in each of the three studies to identify preliminary causal structures of loneliness across each of three datasets. Each causal analysis was exploratory and uncontrolled. Study one included a more traditional linear mixed model analysis that allowed for a comparison between associational and causal discovery methods. Studies two and three each

included post-hoc analyses examining change over time among the variables included in each respective preliminary causal model.

Results: The linear mixed model comparison in study one revealed that internalized stigma, self-reported depression, and rater-rated negative symptoms were the strongest predictors of loneliness. However, the preliminary causal model in study one showed that loneliness was the primary cause of loneliness over the six-month period. There were ambiguous relationships between loneliness and self-reported motivation to engage in activities at both baseline and four-months. Loneliness was shown to causally influence internalized stigma, self-reported depression, self-reported social pleasure, and rater-rated motivation at the four-month timepoint. In study two, the preliminary causal model indicated loneliness was a possible cause and consequence of self-reported depression at baseline and six-months; an ambiguous edge was observed between these two variables at baseline. Loneliness was also shown as a possible causal influence of self-rated discrimination experiences at baseline and rater-rated depression at six-months. In the third study, the preliminary causal model indicated that loneliness was the primary cause of loneliness over the year-long period. Internalized stigma was indicated as a possible cause of loneliness at three-months and as a direct causal influence of loneliness at six-months. Loneliness causally influenced both social functioning and recovery attitudes at six-months; loneliness was shown to causally influence social functioning at one year.

Conclusions: Overall, several initial patterns were observed across the preliminary causal models. First, loneliness may have a causal relationship with specific types of self-reported motivation. Second, loneliness may have stronger causal relations with self-reported versus rater-rated clinical or functional measures. Third, loneliness may not be a primary consequence of typical psychosis treatment targets, but loneliness may have a causal influence on common

psychosis treatment targets. Fourth, loneliness did not appear to change along with its known clinical or functional correlates in the context of research or clinical intervention. Fifth, loneliness appeared to be largely self-sustaining. And lastly, causal relations were detected between loneliness and internalized stigma/perceived discrimination across all three studies. While current clinical intervention paradigms do not typically include loneliness as a treatment target, the overall patterns detected across these three studies suggest the following implications for clinical practice. Loneliness should be assessed at baseline and monitored throughout the course of treatment for those enrolled in clinical programs. Cognitive interventions and coordinated specialty care did not appear to have a large impact on loneliness or internalized stigma/perceived discrimination during the analysis periods. Additional intervention approaches are likely needed to address loneliness for those enrolled in traditional or coordinated-specialty care.

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CHAPTER 1: AN INTRODUCTION TO LONELINESS AND PSYCHOSIS

Loneliness is a complex experience that arises from the emotional pain of social isolation or rejection (Cacioppo et al., 2006). A recent Surgeon General's Advisory reported that loneliness is an ongoing and urgent public health issue in the United States (United States Department of Health and Human Services (HHS), 2023). Prior to the COVID-19 pandemic, several large surveys were published showing almost 50% of Americans reported recent experiences of loneliness (Bruce et al., 2019; Shovestul et al., 2020). When the experience of loneliness becomes enduring or persistent, it is typically referred to as chronic loneliness (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010). Research has shown that up to 30% of the general population has endorsed the experience of chronic loneliness (Hawkley & Cacioppo, 2010), which is a number that has continued to rise over the past few decades (Bruce et al., 2019; Jeste et al., 2020). Chronic loneliness has been theorized to be a self-reinforcing experience (Cacioppo et al., 2006; Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010), and it is a significant concern across the globe.

The impact of chronic loneliness is pernicious and cumulative. Chronic loneliness has been shown to increase risk of physical health problems, cognitive problems, mental health problems, and early death (Bruce et al., 2019; Hawkley & Cacioppo, 2010; HHS, 2023). The groups at the greatest risk for chronic loneliness are older adults (age 80+) (Beam & Kim, 2020), adolescents and young adults (Beam & Kim, 2020; Shovestul et al., 2020), and those with mental health disorders (Bruce et al., 2019; Hawkley & Cacioppo, 2010; Jeste, et al., 2020; Wang et al., 2018). While loneliness is clearly an issue of significant concern among the general population, it tends to be more common and more severe among populations with serious mental illness

(Jeste et al., 2020; Wang et al., 2018) such as psychosis spectrum disorders (Badcock et al., 2020a; Lim et al., 2018; Stain et al., 2012).

Psychosis

Psychosis generally refers to an episodic condition that causes disruptions in perception, which may interfere with someone's ability to accurately gauge aspects of reality (National Institute of Mental Health (NIMH), 2023). Symptoms of psychosis are generally categorized in the following ways: 1) positive symptoms, which refer to new or increasingly worsened symptoms such as hallucinations and delusions, 2) negative symptoms, which decrease a person's capacity for motivation, pleasure, or emotional expression 3) cognitive symptoms, which are changes in thinking abilities, such as processing speed or remembering information. (American Psychological Association (APA), 2023; Kahn et al., 2015).

The term psychosis spectrum disorder describes both non-affective and affective psychosis. Non-affective psychoses typically refer to diagnoses from within the schizophrenia spectrum (e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, etc.). Affective psychosis includes diagnoses from the mood spectrum (e.g., major depressive disorder, bipolar affective disorder) that include psychotic features. While psychosis typically has a much lower base rate than mental health conditions such as depression and anxiety, studies have shown psychosis is associated with disproportional mortality risks. Researchers have shown that people diagnosed with psychosis or schizophrenia spectrum disorders have significantly lower life expectancy rates, across all ages, when compared to the general population (Ali et al., 2022; Laursen et al., 2014). Increased mortality for people with schizophrenia specifically has been strongly associated with often preventable physical health concerns, antipsychotic medication

side effects (such as metabolic issues), less access to resources due to barriers to financial security, and increased instances of suicide (Laursen et al., 2014).

Loneliness and Psychosis

The risk of experiencing loneliness, or chronic loneliness, also appears to be elevated for people who have experienced psychosis. A large survey of people with psychosis found that approximately 80% of respondents endorsed feeling lonely, and 69% of respondents reported no participation in any social activity over the past year (Stain et al., 2012). Research has also shown that people with psychosis who endorse greater levels of loneliness access health services at more than double the rate of people with psychosis who do not report loneliness (Badcock et al., 2020b). We do not know whether the risk factors associated with loneliness and chronic loneliness pose an additive risk to the already elevated health and mortality risk faced by those within the psychosis spectrum.

Theory of Loneliness

A widely accepted theoretical model, generally referred to as the social cognitive model of loneliness, explains loneliness in an evolutionary context (Cacioppo et al., 2006; Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010) (Appendix A). In this model, temporary loneliness is viewed as largely adaptive and critical to the survival of human species (Cacioppo et al., 2006; Cacioppo and Hawkley, 2009; Hawkley & Cacioppo, 2010). Because human beings, as a collective species, cannot survive or thrive in isolation, the pain of temporary loneliness is believed to provide the motivation necessary to reconnect with or form new relationships with others (Cacioppo et al., 2006; Cacioppo and Hawkley, 2009; Hawkley & Cacioppo, 2010). Additional research has also shown that people experiencing temporary loneliness are more

likely to engage in collaborative behavior, show interest in pursuing new relationships, and view others positively (Vanhalst et al., 2017).

The social cognitive model of loneliness also asserts that the experience of chronic loneliness increases hypervigilance for social threats which, in turn leads to the interpretation of the social environment as threatening (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010). The interpretation of the social world as threatening increases negative reactions to social exclusion, leading to cognitive biases toward negative experiences that may also influence how one behaves in the company of others (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010). The result of negative expectations and associated interactions prompts the active avoidance of the social world and cautious/avoidant reactions to social inclusion. This reinforces the distress and pain (stress, anxiety, depression, emotional dysregulation, low self-esteem, general pessimism) associated with social disconnection (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010). The social cognitive model of chronic loneliness, as proposed by Cacioppo and Hawkley (2009), is a self-maintaining negative feedback loop that has a deleterious effect on health and wellbeing over time.

Theoretical Frameworks of Loneliness and Psychosis

While the social cognitive theory of loneliness appears to be a generally accepted model of loneliness in the literature, it has not been well studied among populations with psychosis. Thus, it is currently unclear if the social cognitive model of loneliness applies to persons with psychosis spectrum disorders. However, there have been two models of loneliness proposed specifically in the specific context of psychosis.

The first model, a theoretical framework of loneliness in psychosis, was proposed by Lim et al. (2018) (Appendix B). This model is focused on clinical and psychosocial factors associated

with loneliness. Their framework was created using findings from a systematic review (Lim et al., 2018), which was based on a limited body of predominantly correlational research focused on loneliness and psychosis. According to the proposed model, loneliness is shown to have reciprocal (bidirectional) relationships with factors belonging to the larger domains of mental health (psychosis, depression, anxiety), social support (structural, functional), well-being (recovery, quality of life), societal perception (internalized stigma, perceived discrimination), and self-constructs (self-esteem, self-efficacy) (Lim et al., 2018). Importantly, this model lacks specificity regarding directionality, and possible interactions between factors/domains, because these relationships are not well understood in psychosis-specific populations currently.

The second model was proposed by Badcock et al. (2020a) (Appendix C). This conceptual model suggests that the experience of psychosis contributes to greater experiences of internalized stigma (referred to as self-stigma in their model (Badcock et al., 2020a). Internalized stigma contributes to increased social avoidance or withdrawal, which is theorized to contribute to greater loneliness (Badcock et al., 2020a). In this model, loneliness then leads to more symptoms of psychosis, which in turn may reinforce, or increase, the experience of internalized stigma leading to more social withdrawal, loneliness, and psychosis symptoms (Badcock et al., 2020a). The model proposed by Badcock et al. (2020a) highlights the prevalence and potential importance of negative self-directed thoughts and attitudes in sustaining loneliness among people who experience psychosis.

The frameworks proposed by Lim et al. (2018) and Badcock et al. (2020a) provide initial conceptual contexts regarding the possible relationships between loneliness and factors commonly observed in psychosis specific populations. As such, both models contain similar, but not identical, variables. Both models were based on findings from the available literature on

loneliness and psychosis. However, the relationships between loneliness and factors commonly observed in psychosis are proposed in a fundamentally different manner. In the model proposed by Lim et al. (2018), loneliness is shown to have bidirectional relationships with every included variable within each domain, and it is centered within the model. The Lim et al. (2018) model does not propose a particular process of loneliness, and there are no directional arrows between any of the non-loneliness variables in the model. Alternatively, the Badcock et al. (2020a) model proposes a specific process of LN in the context of psychosis, and it does so by clearly identifying the proposed relationships between both the non-loneliness and loneliness variables included in the model. The Badcock et al. (2020a) model is more parsimonious than the Lim et al. (2018) model, and because it identifies a process, it is also more similar to the general theory of loneliness proposed by Cacioppo and Hawkley (2009).

Overview of the Loneliness and Psychosis Literature

The current literature focused on loneliness and psychosis has produced the following results. People within the psychosis spectrum report significantly higher levels of loneliness than do control participants (Chrostek et al., 2016; Ludwig et al., 2020a). The relationship between loneliness and depression among people with psychosis spectrum disorders has been reported to be similar to what has been found in the general population (Cacioppo et al., 2006; Culbreth et al., 2021; Ludwig et al., 2020a), meaning they are strongly associated yet do not fully explain the presence or severity of the other.

Loneliness has been shown to be positively associated with depressive symptoms (Culbreth et al., 2021; Lim et al., 2020; Ludwig et al., 2020a; Sundermann et al., 2014), negative symptoms of psychosis (Culbreth et al., 2021), positive symptoms of psychosis (Angell & Test, 2002; Badcock et al., 2015; Culbreth et al., 2021; Steenkamp et al., 2022; Switaj et al., 2014),

and internalized stigma (Chrostek et al., 2016; Switaj et al., 2014; Switaj et al., 2021). Loneliness has also been shown to be negatively associated with social functioning (Chrostek et al., 2016; Culbreth et al., 2021; Ludwig et al., 2020a), social support (Chrostek et al., 2016; Sundermann et al., 2014), and self-constructs like self-esteem (Ludwig et al., 2020a). Loneliness has been associated with lower performance on a singular task of general cognition (Badcock et al., 2015). Very few studies have examined the relationship between loneliness and social cognition, and the reported results of these studies have been mixed (Tremeau et al., 2016; Ludwig et al., 2020a).

Preliminary evidence in this domain shows that loneliness is associated with many of the same factors that contribute to clinical and functional impairments among people with psychosis spectrum disorders. Most of the published research examining loneliness among those with psychosis is cross-sectional. The majority of research in this area is associational. Much of this research recruited and studied samples best described as a general psychosis population, meaning most of these samples consisted of people with prolonged psychosis experiences and mean ages over age 30. There are few qualitative studies, and there is an absence of published participatory research studies.

Because most of our knowledge is based on the general population and *preliminary* evidence from within the psychosis spectrum, there are significant gaps in the literature regarding the role of loneliness in psychosis populations. The cross-sectional nature of the research has established relationships likely exist at one timepoint, yet the relationships between loneliness and clinical, psychosocial, or cognitive variables over time is not well understood. Further, the correlational nature of this research body allows us to better understand variables that may predict or signal the presence of loneliness, though we have very limited knowledge

about the specific causes or consequences of loneliness in psychosis populations. It is incredibly important to examine the role of loneliness among general or prolonged psychosis populations. However, because adolescents, young adults, and those with serious mental illness are at high risk for chronic loneliness, more research is needed examining loneliness among early or first-episode psychosis populations specifically.

Overall, the state of research exploring loneliness among psychosis spectrum populations has established that loneliness is a relevant issue among people with psychosis spectrum disorders. This body of research has shown that further study is needed to better understand loneliness within the broader population of people who experience psychosis, but also within sub-populations such as early or first-episode psychosis. Initial research findings have established that loneliness is correlated with frequent targets of intervention (e.g., positive and negative symptoms, depression, etc.) within this population; however, the strength and direction of those relationships are not well understood.

Research Questions

This dissertation includes three distinct studies, each of which aims to address specific gaps in the literature. These three studies share some important similarities. First, all three studies are exploratory in nature. All three studies are uncontrolled explorations using data collected during randomized controlled trials (RCTs) or an ongoing measurement-based care (MBC) study. Each study includes an outpatient sample of people with confirmed psychosis spectrum diagnoses; however, each study sample is intentionally different regarding aspects of psychosis classification. Finally, each of the three studies include some shared methodology to assist with the intended comparisons across the produced models. The research questions for each of the three studies are as follows:

1) What are the relationships between loneliness and psychosocial, clinical, and social cognitive factors over time among a *generalized psychosis (GP)* sample of people with psychosis spectrum disorders?
2) What are the relationships between loneliness, psychosocial, and clinical factors over the first six-months of treatment among a sample of people with *early psychosis (EP)* diagnoses?
3) What are the relationships between loneliness and psychosocial, clinical, and cognitive factors over the first year of treatment among a sample of people with *first-episode psychosis (FEP)* diagnoses?

Study Descriptions

The first study, ***Predictors and Possible Causes of Loneliness Within a General Psychosis Spectrum Sample***, explores loneliness in the context of a generalized psychosis (GP) sample. The term *generalized psychosis (GP)* in this dissertation refers to an adult only sample (age 18+) that have confirmed diagnoses within the broader psychosis spectrum. A GP sample could therefore include people with initial episodes of psychosis and people with prolonged psychosis. The GP sample used in this study does not share the same age demographic characteristics as the early or first-episode samples, which is not uncommon. As a result, most of this GP sample has experienced psychosis for greater than five years. This study explores the relationships between loneliness and psychosocial, clinical, and social cognitive factors in two separate analyses. The first analysis explores predictors of loneliness using a comparison of linear mixed models. The second analysis explores causes and consequences of loneliness using causal discovery analysis (CDA) methods. The data were obtained from a recently completed RCT and contain three timepoints over a duration of six-months.

The second study, ***An Initial Causal Structure of Loneliness Among People with Early Psychosis Enrolled in Coordinated Specialty Care***, explores loneliness in the context of an early psychosis (EP) sample. The term *early psychosis (EP)* in this dissertation refers to a sample between the ages of 15-40 years that have confirmed psychosis spectrum diagnoses within an onset period of less than five years. This study explores the causes and consequences of loneliness using causal discovery analysis (CDA) methods. The data were obtained from an ongoing measurement-based care (MBC) study of coordinated specialty care (CSC) programs in Minnesota and captures the first six-months of CSC treatment.

The third study, ***Uncovering a Preliminary Causal Model of Loneliness within a First-Episode Psychosis Sample Over the First Year of Treatment***, explores loneliness in the context of a first-episode psychosis (FEP) sample. The term *first-episode psychosis (FEP)* in this dissertation refers to a sample between the ages of 15-40 years that have confirmed schizophrenia spectrum diagnoses with only one total episode of psychosis allowed. This study explores the causes and consequences of loneliness using causal discovery analysis (CDA) methods. This is a secondary analysis of data obtained from a large national RCT and captures the first year of treatment.

Causal Discovery Methods

To address gaps in the current literature, causal discovery methods were used across the three studies. As previously mentioned, the statistical methods used in the majority of the current literature are associational, and therefore not informed by causal theory. It is commonly believed that experimental research, such as a randomized controlled trial (RCT), is the only way in which causal effects can be accurately estimated. In the context of clinical mental health research, there are many barriers to conducting RCTs. For example, RCTs are not always feasible or ethical,

particularly because studies of this type normally rely on human or animal research participants. Another major barrier to conducting RCTs in clinical mental health research is that a causal model is necessary, but we frequently do not know the causal order of our variables of interest. Clinical mental health researchers have historically relied upon correlational statistical methods when RCTs were not possible. Unfortunately, correlational research is notoriously inaccurate in distinguishing causal from non-causal correlates, which has greatly contributed to underwhelming treatment outcomes and limited insight into the causes and consequences of mental health issues (Saxe et al., 2022).

When thinking of loneliness in the context of psychosis, the current literature has not shed much insight into what factors are causes or consequences of loneliness, which means we are also limited in our understanding of how psychosis specific interventions may impact loneliness. Causal discovery methods are particularly advantageous in situations where we aim to gain insight into causal relationships without knowing exactly which variables are causal influences on other variables (e.g., exploratory studies). Causal discovery is an innovative approach to data analysis that allows us to identify *probable causes* of our variable(s) of interest (e.g., loneliness).

While there are many causal discovery algorithms with different assumptions and purposes, they generally blend statistics, graph theory, and machine learning to create plausible causal models from observational datasets (Eberhardt, 2017; Nogueira et al., 2022; Spirtes et al., 2000). Causal discovery algorithms clearly identify models that are simultaneously causal and statistical, and then map those data to the model that most accurately represents the *process* that generated the data (Anderson et al., 2023; Ogarrio et al., 2016). In contrast, instead of describing

the data generating process, traditional statistical approaches (e.g., associational/predictive) describe the data itself (Anderson et al., 2023).

Causal discovery analysis (CDA) approaches have been shown to perform better than traditional associational/predictive statistical methods in multiple simulation studies (Glymour et al., 2019; Shen et al., 2020). One such statistical method is structural equation modeling (SEM), which identifies structural relationships between measured and latent variables. When using SEM to test a causal structure, the model must be fit a priori, and while several models may be fit, they all require fine tuning by the researcher(s). If the causal structure used to fit the SEM models was not accurate, then the effect size estimates are also inaccurate. Alternatively, CDA searches the entire space of possible SEMs and returns the model that is most correct, statistically (Ogarrio et al., 2016). Therefore, causal models produced by CDA are statistically strong and provide a more complete set of causal relationships than traditional predictive approaches (Ogarrio et al., 2016; Shen et al., 2020).

Causal discovery methods are of particular interest because they may allow us to illuminate the underlying causal structure of loneliness (and related factors), which may provide valuable information about how the underlying system might behave in the context of later intervention development or implementation. In other words, because the majority of the literature describes variables that may predict or associate with loneliness, CDA was used in this dissertation to identify variables that are part of the causal structure of loneliness. The variables that are part of the causal network (which includes loneliness) signify key targets for intervention in the context of loneliness in psychosis.

There are two primary assumptions of the causal discovery algorithm used across the three studies. The first, known as the Causal Markov Condition, states that when conditioned on

its direct causes, a node is probabilistically independent of every other node in the graph (Saxe et al., 2022; Spirtes et al., 2000). The second, known as the Faithfulness Condition, states that the independencies detected through the Causal Markov Condition are the only independencies found in the graph (Saxe et al., 2022; Spirtes et al., 2000). Provided the Causal Markov and Faithfulness assumptions are upheld, the resulting graph (causal model) represents the causal structure found in the given dataset (Saxe et al., 2022; Spirtes et al., 2000).

CHAPTER 2: PREDICTORS AND POSSIBLE CAUSES OF LONELINESS WITHIN A GENERAL PSYCHOSIS SPECTRUM SAMPLE

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Abstract

Background: Loneliness has been shown to affect people with psychosis at disproportionately higher rates than the general public. However, the relationship between loneliness and common clinical, psychosocial, and cognitive issues in psychosis is not well understood.

Methods: Two uncontrolled, exploratory longitudinal analyses were performed. A linear mixed model comparison was used to determine primary predictors of loneliness for 99 participants. Causal discovery methods were used to identify a preliminary causal structure of loneliness across 61 participants with complete data.

Results: The mixed model comparison showed that internalized stigma, depression, and negative symptoms of psychosis were the strongest predictors of loneliness. The preliminary causal model showed the following: 2) loneliness was the primary cause of loneliness, 2) loneliness causally influenced self-rated internalized stigma, depression, and social pleasure at four-months, 3) loneliness causally influenced rater-rated motivation at four-months, and 4) loneliness and motivation to engage in activities had ambiguous causal relations at baseline and four-months.

Conclusions: Our preliminary causal model showed that loneliness may not be the consequence of psychosis symptoms, outside of possibly self-rated motivation to engage in activities and social pleasure. However, loneliness may causally influence important clinical and psychosocial issues, and loneliness may also maintain itself without interruption in psychosis populations. These preliminary findings suggest the causal structure of loneliness in psychosis populations may be somewhat different than models developed from correlational literature. Overall, our preliminary findings suggest that loneliness is likely a relevant issue in need of greater attention and understanding across research and clinical settings.

Introduction

Loneliness has been defined as the subjective experience of feeling socially disconnected from others (Cacioppo et al., 2006). Importantly, loneliness is an unwanted experience. Loneliness is a significant public health issue that disproportionately affects people who experience psychosis. Previous research studies have shown that people with psychosis report greater levels of loneliness when compared to the general public and research control groups (Badcock et al., 2015; Culbreth et al., 2021; Lim et al., 2018; Stain et al., 2012). Yet, loneliness does not appear to be well understood within psychosis populations.

Previous research in this area has shown correlations between loneliness and factors frequently targeted for intervention in psychosis populations. The relationship that appears best understood currently is the association between loneliness and depression. Strong positive correlations have been reported between loneliness and depression in multiple studies using samples with psychosis (Lim et al., 2018; Ludwig et al., 2020a; Suman et al., 2023). The association between loneliness and depression found among psychosis populations also appears consistent with results found in different clinical populations (Leathem et al., 2021; Meltzer et al., 2013; Wang et al., 2018), as well as what has been found in the general population (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010; Park et al., 2020).

A meta-analysis found that loneliness was moderately associated with psychosis symptoms across 13 studies with wide-ranging psychosis populations representing more than 15,000 participants (Michalska da Rocha et al., 2018). While this is a clinically valuable finding, it does not allow us to understand specific associations between loneliness and the positive, negative, and cognitive symptoms of psychosis. Research examining associations between

loneliness and the positive/negative symptoms of psychosis within generalized psychosis samples has revealed mixed results.

Several studies have found that loneliness was correlated with positive symptoms such as disordered thinking (Badcock et al., 2015), suspiciousness/persecution (Ludwig et al., 2020a), and paranoia (Ludwig et al., 2020a) while others have found no correlation between loneliness and positive symptoms (Culbreth et al., 2021; Jaya et al., 2016; Switaj et al., 2014). Similarly, Jaya et al. (2016) found that loneliness was correlated with negative symptoms more broadly, while other studies have found associations with a limited range of negative symptom such as anhedonia (Badcock et al., 2015), emotional withdrawal (Ludwig et al., 2020a), passive social withdrawal (Ludwig et al., 2020a), and active social avoidance (Ludwig et al., 2020a). However, some studies have shown no correlation between loneliness and rater-rated negative symptoms (Culbreth et al., 2021; Switaj et al., 2014). Interestingly, Culbreth et al. (2021) found that loneliness was correlated with self-reported negative symptoms (motivation and pleasure items only).

The relationship between loneliness and motivation has been less studied among psychosis populations. Motivation plays a key role in negative symptom severity (Barch & Dowd, 2010; Dowd & Barch, 2010; Green et al., 2018; Kahn et al., 2015; Kring & Barch, 2014; Llerena et al., 2013) and functional outcomes (Abplanalp et al., 2021; Barch & Dowd, 2010; Dowd & Barch, 2010; Gard et al., 2009; Green et al., 2018; Kring & Barch, 2014) for people with psychosis experiences. Another core negative symptom is anhedonia, or difficulty experiencing pleasure (Dowd & Barch, 2010; Green et al., 2018; Llerena et al., 2013); however, much research has indicated that anhedonia is likely the result of specific motivational difficulties among populations that experience psychosis (Barch & Dowd, 2010; Dowd & Barch,

2010; Gard et al., 2007; Kring & Barch, 2014). Motivation has been strongly associated with psychosocial functioning (e.g., social functioning) among people who experience psychosis (Abplanalp et al., 2021), as well as ongoing disability (Green et al., 2018).

Like loneliness and motivation, the relationship between loneliness and social functioning in psychosis populations is unclear. Research has shown that loneliness has also been shown to play a role in social functioning in the general population and among those who experience psychosis (Chrostek et al., 2016; Culbreth et al., 2021; Green et al., 2018; Stain et al., 2012). More studies are needed to better understand the relationship between loneliness, rater-rated negative symptoms, motivation and pleasure, and social functioning among populations that experience psychosis.

A few studies have examined the relationship between loneliness and both general and social cognition. One study conducted by Badcock et al. (2015) found that people with higher levels of loneliness had lower general cognition, as measured by a digit symbol coding task. Regarding social cognition, Ludwig et al. (2020a) found no relationship between loneliness and social cognition, which was measured using a variety of validated and psychometrically sound measures of social cognition in psychosis-specific populations. Tremeau et al. (2016) reported participants displayed social cognitive difficulties in self-reported measures but did not show those impairments in social cognition tasks. However, a limitation of the Tremeau et al. (2016) study is that the tasks of social cognition were not validated for use among psychosis-spectrum populations (Pinkham et al., 2014).

While there is clearly much more to learn regarding loneliness and common treatment targets of psychosis, the relationship between loneliness and clinically relevant psychosocial issues is also in need of greater understanding. Research has shown that negative symptoms and

social functioning among general psychosis populations tends to be worsened by psychosocial issues such as internalized stigma (Firmin et al., 2019; Lysaker et al., 2007; Yanos et al., 2008) and defeatist beliefs (Grant and Beck, 2009; Couture et al., 2011). Studies have also shown that loneliness tends to have strong positive correlations with internalized stigma (Chrostek et al., 2016; Switaj et al., 2014; Switaj et al., 2021). There is virtually no literature expressly examining the relationship between loneliness and defeatist beliefs in psychosis spectrum populations. Defeatist beliefs have been associated with asocial beliefs and social avoidance among people with psychosis (Granholm et al., 2018), which is congruent with the widely accepted theoretical model of loneliness proposed by Cacioppo and Hawkley (2009).

Two additional theoretical models of loneliness have been proposed regarding psychosis populations specifically. A broad framework was proposed by Lim et al. (2018), which was based on findings from their systematic review of the literature at that time. The authors proposed that loneliness may be operating reciprocally with clinically and socially relevant issues pertaining to psychosis. A smaller and more specific negative feedback loop model was proposed by Badcock et al. (2020a) suggesting cyclical relationships between psychosis symptoms, stigma, social withdrawal, and loneliness. Both theoretical models propose that loneliness is a clinically and socially significant issue impacting people with psychosis; however, both models need clarification and/or replication from additional studies.

The majority of research published on loneliness in various contexts of psychosis is cross-sectional and correlational. The cross-sectional nature of the literature limits our ability to understand how loneliness operates over time among people with psychosis, either independently or in conjunction with meaningful clinical or social issues frequently faced by this population. The correlational nature of the current literature is also clinically useful in that it

allows us to better understand possible predictors of loneliness in this population. However, correlational research does not allow us to understand the potential causal relationships of loneliness, which thereby poses a significant limitation regarding possible treatment approaches or interventions targeting loneliness. For example, does loneliness change along with its known correlates in various treatment scenarios?

The aims of this uncontrolled and explorational study are two-fold. The first aim is to examine which common clinical, psychosocial, and cognitive factors are strongly predictive of loneliness in a generalized sample of people with confirmed psychosis spectrum diagnoses. Linear mixed model comparisons will then be performed to determine the strongest predictors of loneliness in the study population through the most parsimonious lens. The second aim is to explore and identify the causal cascade of loneliness in this specific sample by using causal discovery analysis (CDA) methods. The same factors used in the predictive analysis will be entered into the causal model to allow for greater comparison of findings between the two methods.

Causal discovery methods were chosen because most of the current literature on loneliness and psychosis is predictive (correlational), meaning it lends little insight into the causal relationships between loneliness and common issues observed in psychosis. CDA is particularly well-suited to explorational research that aims to identify plausible causal models in the absence of such models identified through causal inference (experiments).

Materials and Methods

Methods

This study is an uncontrolled analysis of data collected as part of a randomized-controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT02782442). The original study examined the

remote delivery of a motivation enhancement application in conjunction with either targeted cognitive training (TCT) or computer games (CG) among a general psychosis spectrum population (Fisher et al., 2023). All participants received the motivation enhancement intervention, regardless of treatment condition assignment (Fisher et al., 2023). Participants were confirmed to have a psychosis spectrum diagnosis at the outset of the study and completed measures at baseline, four-, and six-months. This study was approved by the University of Minnesota Institutional Review Board (IRB).

Sampling Procedure

Participants met the following eligibility criteria: between the ages of 18-60 years, confirmed psychosis spectrum diagnosis, no known neurological disorder diagnoses, good general physical health, minimum of one-month outpatient status prior to participation, minimum of one month stability with psychiatric medications prior to participation, fluency in English, and consistent access to a computer and smartphone (Fisher et al., 2023). Participants were excluded if they did not meet the criteria above, had a severe substance use history within three-months, or received significant cognitive training in the past three years (Fisher et al., 2023). There were no geographic inclusion/exclusion criteria due to the remote nature of the study.

Measures

Loneliness

Loneliness was assessed using the original version of the UCLA Loneliness Scale (ULS). The ULS is a 20-item self-report scale that assesses subjective feelings of loneliness and social isolation (Russell et al., 1978).

Internalized Stigma

Internalized stigma was assessed using the Internalized Stigma of Mental Illness Scale – Abbreviated (ISMI). The ISMI is a 10-item scale comprised of the strongest two items from each of the five original subscales (alienation, discrimination experience, social withdrawal, stereotype endorsement, and stigma resistance) (Boyd et al., 2014).

Defeatist Beliefs

Defeatist beliefs were assessed using the Dysfunctional Attitudes Scale – Form B, Defeatist Beliefs Subscale (DBS). The DBS contains 14-items that ask respondents to rate their experience of self-directed defeatist thoughts/attitudes (Granholm et al., 2017; Luther et al., 2016).

Motivation

Motivation was assessed using 1) the Motivation and Pleasure Scale – Self Report (MAPS-SR) and 2) the Intrapsychic Foundations subscale of the Abbreviated Quality of Life Scale (AQLS). The MAPS-SR is a 15-item self-report scale specifically designed to assess experiences of motivation and pleasure in the psychosis spectrum (Llerena et al, 2013). The MAPS-SR has four-subscales: social pleasure (SP), recreational or work pleasure (RWP), motivation for close relationships (MCR), and motivation to engage in various activities (MEA). The MAPS-SR has shown little affiliation with positive symptoms, depression, and anxiety (Llerena et al., 2013).

The Intrapsychic Foundations subscale includes six-items of the AQLS, which is a rater-rated assessment of functioning, and combines intrapsychic foundations and common place objects subscales (Bilker et al., 2003). The Intrapsychic Foundations (MOT) subscale reflects aspects of the motivational deficits commonly found in the psychosis spectrum; experts have

recommended using the term *motivation* for this subscale since it is better understood in research and clinical contexts (Mueser et al., 2017).

Depression

Depression was assessed using the Beck Depression Inventory (BDI-II). The BDI-II consists of 21-items and asks respondents to rate the severity of depression symptoms (Beck et al., 1996).

Functioning

Functioning was assessed in two domains using the remaining subscales of the AQLS. The AQLS is a nine-item measure rated by a trained interviewer (Bilker et al., 2003). Each of the nine items were derived from the Quality of Life Scale (QLS) (Heinrichs et al., 1984). Social functioning (SF) is assessed using two items that comprise the interpersonal relations subscale, and occupational role functioning (OF) is composed of a single item on the AQLS (Bilker et al., 2003).

Emotion Recognition

Emotion recognition was assessed using the emotion recognition task (ER-40) from the Social Cognition battery within the Penn Computerized Neurocognitive Battery (Penn CNB) (Gur et al., 2010). Emotion recognition is one important aspect of social cognition (Pinkham et al., 2018). Scores for correct responses and reaction time for correct responses were included in the analysis.

Psychosis Symptoms

Psychosis symptoms were assessed using the Quick Scale for the Assessment of Positive and Negative Symptoms (QSAPS/QSANS). The QSAPS/QSANS are rated by interviewers

trained to evaluate both the positive and negative symptom domains of psychosis (Andreason, 1984; Andreason, 1989).

Demographic Variables

Demographic variables of interest included age, age at first symptoms, total hospitalizations, racial background, ethnicity, sex, and diagnostic information. Treatment group assignment from the original study was also included.

Analyses

Participant Baseline Differences

Independent samples t-tests (continuous measures) and chi-square tests (categorical variables) were used to discern whether baseline characteristics predicted differences among participants who completed measures at all timepoints and those that did not. The drop-out analysis was conducted in R Studio (Core Team, 2015).

Linear Mixed Effects Models (LMM)

Participants completed self-report, interview, and cognitive tasks at intervals of baseline, four-, and six-months. The R package *lme4* (Bates et al., 2007) was used to estimate all linear mixed effect models (LMM). Since measurement timepoints were at approximate intervals, the effect of time was initially coded as a factor. Time was included in separate models as a continuous predictor. Due to the possibility of collinearity, each variable was initially examined separately (univariate models), which was followed by a comparison of model fits.

A random effect at the participant level was included in each model. Corrections for multiple tests are not typically incorporated into model comparison analyses. However, due to the multiple comparisons necessary for this analysis, variables were selected for the initial "full" model using a cutoff p-value of <0.001 for each univariate model. Models were fit using

maximum likelihood (ML). Full and reduced models were compared using analysis of variance (ANOVA) in R Studio (Core Team, 2015).

Causal Discovery Analysis (CDA)

After identifying predictors of loneliness using LMM, an exploratory causal discovery analysis (CDA) was performed to estimate the causal relationships between the variables included in the analysis. The same measurement variables were used in both the LMM and CDA analyses. Tetrad version 7.5.0-0 (Ramsey et al., 2018) was used to conduct the causal discovery analysis. The Greedy Fast Causal Inference (GFCI) algorithm was used to estimate the causal relationship between the variables of interest at all three timepoints. Background knowledge was included prior to running the GFCI algorithm and specified that four- and six-month variables could not cause baseline variables (and that six-month variables could not cause 4-month variables). Model parameters include a Bayesian Information Criterion Score that was set to the default discount value of two, and a Fisher Z test set to the default alpha value of 0.01.

The GFCI algorithm is a causal algorithm that allows for the possibility of latent confounding variables, and it has also been shown to provide accurate results on smaller sample sizes when compared to many alternative algorithms (Ogarrio et al., 2016). GFCI requires complete cases and continuous data for analysis (Ogarrio et al., 2016). To accommodate the need for continuous data we created numeric binary variables for our categorical data.

The GFCI algorithm uses a two-step process to determine causal relationships. In step one, the algorithm searches the space of penalized likelihood scores for all possible acyclic causal relationships among the variables. Initial variable pairs are established as conceivably causally related. During this initial step, the algorithm assumes there are no latent common causes of the observed variables. In step two, GFCI sharpens its search by dropping the

assumption that there are no latent common causes and executes conditional independence tests to find and remove statistical inconsistencies between the searches. The graph produced in step one is revised during step two (Anker et al., 2019; Chickering, 2002; Miley et al., 2021; Ogarrio et al., 2016; Ramsey, 2015). GFCI output is displayed graphically as a Partial Ancestral Graph (PAG) (Anker et al., 2019; Ogarrio et al., 2016). Due to statistical equivalence, causal relationships are typically not fully resolved from an observational dataset, so the PAG denotes a set of causal graphs that are congruent with the identified relationships in the data under the Markov and Faithfulness assumptions. The resulting PAG may contain four types of edges (Table 2.1).

The presence of a directed edge (-->) in a PAG means that all possible causal models that did not contain this edge were removed in one of the two steps executed in the GFCI algorithm. The stability of the PAG was evaluated by running GFCI on 1,000 bootstrapped datasets. The bootstrapped graphs compute the percentage of edges from the original PAG that were reproduced during the resampling procedure.

To estimate causal effects, a Mixed Ancestral Graph (MAG) was created from the original PAG output. A MAG is an acyclic graph that has directed (-->) and undirected (<->) edges chosen from the equivalence class of the PAG to display (Tetrad Manual, 2023; Malinsky & Spirtes, 2016). The MAG disregards latent variables, preserves the conditional independence relationships among the measured variables, and displays one causal structure that is in the equivalent structure of the PAG (Malinsky & Spirtes, 2016). The MAG shows one instantiation of the PAG without ambiguous (o-o or o->) edges, which allowed us to estimate causal effects. Raw and standardized effect sizes (ES, std.ES) of the causal relationships identified in the model were estimated by fitting a linear SEM to the MAG. Standardized effect sizes (std.ES) are

reported within the graph output. The R package *lavaan* 0.6-15 was used for this analysis (Rosseel, 2012). Each directional relationship was represented as a regression path, while non-directional relationships were represented as covariances in the path model.

Results

Participants

Overall, 108 participants completed baseline measures and were randomized to their respective treatment group. Nine participants were dropped due to missing data. The remaining 99 participants completed all measures at baseline, with 56 participants completing measures at all three timepoints. Data was imputed for six people who had partially incomplete data at either timepoint two or three. Imputed scores for these six participants were their individual mean scores, which were derived from their completed measures at timepoints one and two/three, respectively. Table 2.2 shows the baseline demographic characteristics, and Table 2.3 shows the baseline clinical characteristics for those included in this study.

Participants with complete data had significantly lower baseline mean scores on the BDI-II (19.375) than participants with incomplete data (25.52) ($t = -2.16$, $p = 0.033$). There were no other statistically significant baseline differences for continuous or categorical variables between participants who completed measures at all timepoints and those that did not.

Mixed Model Comparison

The LMM models included 99 unique participants with 233 observations. The univariate models that were significant at the pre-determined cutoff level ($p < 0.001$) were: internalized stigma (ISMI), defeatist beliefs (DBS), depression (BDI-II), MAPS-SR social pleasure (SP), MAPS-SR motivation for close relationships (MCR), MAPS-SR recreational/work pleasure

(RWP), and MAPS-SR motivation to engage in activities (MEA), negative symptoms (QSANS), and the AQLS intrapsychic foundations (MOT) subscale.

Emotion recognition correct responses ($p = 0.125$) and reaction time for correct responses ($p = 0.130$) were not significant predictors for loneliness. Positive symptoms of psychosis (QSAPS) were not significant ($p = 0.297$), nor was the AQLS occupational role functioning subscale (OF) ($p = 0.750$). The AQLS social functioning (SF) model was significant ($p = 0.037$), however it was not significant at the cutoff threshold and therefore was not included in the full model. Demographic (age, sex, race, ethnicity, diagnosis, age of first symptoms, total hospitalizations) and treatment condition variables were not significant predictors of loneliness in the univariate models. Time was not significant in any univariate model (as a factor or continuous variable).

A full model was constructed using time plus the variables that were significant at the cutoff threshold ($p<0.001$) in the univariate models. Significant positive main effects were found for the ISMI ($\beta = 0.72$, SE = 0.17, CI [0.38, 1.05], $p = < .001$), BDI-II ($\beta = 0.26$, SE = 0.07, CI [0.12, 0.40], $p = < .001$), and QSANS ($\beta = 0.11$, SE = 0.05, CI [0.01, 0.21], $p = 0.026$). The marginal R^2 for the full model is 0.429, meaning approximately 43% of the variance in loneliness can be explained by the fixed effects. The conditional R^2 is 0.786, meaning about 79% of the variance in loneliness can be explained by the total model (fixed and random effects) (Table 2.4). Multicollinearity within the full model was measured using the variance inflation factor (VIF) from the R package *usdm* 1.1-18 (Naimi et al., 2014). The VIF was below three which indicates low multicollinearity in the model.

A reduced model was created by removing the non-significant variables from the full model, which included time. Significant positive main effects remained for the ISMI ($\beta = 0.79$,

SE = 0.16, CI [0.47, 1.10], p = < .001), BDI-II (β = 0.31, SE = 0.06, CI [0.19, 0.43], p = < .001), and QSANS (β = 0.11, SE = 0.04, CI [0.04, 0.19], p = 0.003). Multicollinearity was again assessed, and the VIF was less than 1.5 for all variables in the model. The marginal R^2 for the final reduced model is 0.408, meaning approximately 41% of the variance in loneliness can be explained by the fixed main effects. The conditional R^2 remained at 0.786, meaning about 79% of the variance in loneliness can be explained by the total model (Table 2.4).

A model comparison was conducted using an ANOVA to compare the models and select the model that best predicts loneliness. The unconditional random intercept model, the full model, and reduced model were included in the ANOVA. The reduced model (loneliness predicted by stigma, depression, and negative symptoms only) was identified as the preferred model ($X^2(3) = 97.7388$, $p<0.001$).

Causal Discovery Analysis (CDA)

The exploratory GFCI analysis included 62 participants with complete cases. The graph shows results from the original PAG combined with our MAG results. The color of the edge is determined by the relationship found in the original PAG. The line-type indicates the stability of each edge determined by the bootstrap resampling procedure. Standardized effect sizes are displayed on each respective edge throughout the graph. Standardized and raw effect sizes were obtained from the MAG, which is just one possible instantiation of the PAG. Variables that were significantly outside the network shown were not included in the graphic output to assist with clarity. Causal connections were included from the broader network provided they were somewhat close in proximity to the loneliness network. In this section, we will focus on results from the direct and indirect loneliness network.

The preliminary causal model produced by GFCI is displayed in Figure 2.1. An ambiguous edge (o-o) is shown between baseline self-reported motivation to engage in activities (MEA) and baseline loneliness (ULS). An ambiguous edge of this type indicates that this relationship may be influenced by unmeasured common causes. The MAG oriented the edge to show baseline MEA as a causal influence of baseline ULS, which would have a standardized effect size of -0.56 under the assumption that this relationship is unconfounded. The standardized effect size indicates that a one standard deviation increase in MEA results in a -0.56 unit change in ULS while holding other variables constant.

Baseline MEA appears to be the epicenter of several ambiguous (o-o) relationships such as baseline stigma (ISMI), baseline self-reported depression (BDI-II), and self-reported motivation for close relationships (MCR), Additional ambiguous (o-o) relationships are present between baseline MCR and self-reported social pleasure (SP), baseline MCR and baseline rater-rated social functioning (SF), and baseline SF and baseline negative symptoms (QSANS). The ambiguous (o-o) edges between these baseline nodes creates plenty of uncertainty regarding their potential influence on the loneliness network.

Baseline ULS converged with negative symptoms (QSANS) at four-months to causally influence rater-rated motivation (MOT) at four-months (std.ES = -0.32). Baseline ULS was the sole causal influence of ULS at four-months (std.ES = 0.74). The edge between ULS at four-months and MEA at four-months is ambiguous, signified by a o-> edge (-0.24), indicating that ULS at four-months is a cause of MEA at four-months, or an unmeasured common cause has a causal influence on ULS and MEA at four-months, or both.

Loneliness (ULS) at four-months causally influenced four additional variables. Social pleasure (SP) at four-months was causally influenced by both baseline SP (std.ES = 0.58) and

ULS at four-months (std.ES = -0.36). Depression (BDI-II) at four-months was causally influenced by both baseline BDI-II (std.ES = 0.37) and ULS at four-months (std.ES = 0.3). Internalized stigma (ISMI) at four-months was causally influenced by both baseline ISMI (std.ES = 0.36) and ULS at four-months (std.ES = 0.51). Notably, the causal influence of ULS at four-months on ISMI at four-months had a larger effect than did baseline ISMI on ISMI at four-months. Loneliness (ULS) at four-months was the sole cause of ULS at six-months (std.ES = 0.82).

At four-months, BDI-II was shown to contribute causally to QSANS at six-months (std.ES = 0.38). The BDI-II at four-months was also shown as the sole causal influence of BDI-II at six-months (std.ES = 0.83). At four-months, ISMI was shown as the sole causal influence on ISMI at six-months. Notably, QSANS at baseline and six-months are relatively distant from the direct loneliness network.

Defeatist beliefs (DBS), self-reported recreation or work pleasure (RWP), rater-rated occupational role functioning (OF), emotion recognition as measured by the ER-40 (correct responses and reaction time for correct responses), positive symptoms (QSAPS), demographic variables (age, age at first symptoms, total hospitalizations, racial background, ethnicity, sex, diagnostic category), and treatment group assignment were not causal influences, or close causal influences, of loneliness at any timepoint and were therefore not displayed in the graph output.

Graph Stability

Graph stability was assessed in Tetrad version 7.5.0-0 by conducting a bootstrap of 1,000 resamples of the data. A table of complete bootstrap results is located in Appendix D. The causal relationship between ULS nodes at baseline, four-, and six-months appeared relatively stable. The causal relationship from baseline ULS to four-months was replicated in about 55% of

bootstrap resamples, while the causal relationship from ULS at four- to six-months was replicated approximately 91% of the time.

The bootstrap procedure showed some edges below 50% replication, along with several dropped edges within the direct and extended loneliness network. The causal edges between 1) baseline MEA and baseline loneliness, 2) baseline loneliness and MOT at four-months, 3) loneliness at four-months and internalized stigma at four-months, 4) loneliness at four-months and depression at four-months, and 5) loneliness at four-months and MEA at four-months were not replicated in the bootstrap procedure. When looking only at the direct loneliness network, the dropped edges indicate the network depicted in this preliminary causal model was relatively unstable, except for the causal relationships between ULS ratings across the six-month period of assessment.

Discussion

This analysis included a mixed model comparison and preliminary exploration of causal relationships using data collected as part of a RCT examining cognitive and motivational interventions among a generalized psychosis population. We analyzed data collected at baseline, four-, and six-month timepoints with two aims. The first aim was to examine which factors were the strongest predictors of loneliness using a linear mixed model comparison approach. The second aim was to explore and identify a preliminary causal model of loneliness using CDA methods.

The univariate mixed models showed that numerous common clinical and functional variables were significantly correlated with loneliness. The model comparison allowed us to get a better understanding of the coefficients with the strongest signals. Within this specific sample, self-reported depression (BDI-II), internalized stigma (ISMI), and rater-rated negative symptoms

(QSANS) were the strongest predictors of loneliness. These findings are consistent with results from other studies examining correlates or predictors of loneliness (Chrostek et al., 2016; Culbreth et al., 2021; Lim et al., 2020; Ludwig et al., 2020; Sundermann et al., 2014; Switaj et al., 2014; Switaj et al., 2021). While functional variables (AQLS) were significant predictors of loneliness in our univariate models, they did not survive in the full model. Emotion recognition was not a significant predictor of loneliness, which is consistent with results from Ludwig et al. (2020). No demographic variables were predictors of loneliness in any model; participants had an average age of 33.4 (SD 10.8) and were mostly white (66.7%), female (59%), with predominant diagnoses of schizophrenia (39.4%) or schizoaffective disorder (40.4%).

Since correlation does not equal causation, a causal discovery approach was used to attempt to better understand the network of causal relationships concerning loneliness. Because the GFCI algorithm requires complete cases for analysis, we were only able to include 61 participants for the causal analysis. Regarding the various causally ambiguous (o-o) relationships (particularly at baseline), our causal graph had directionality added from the MAG (which basically forces directionality by preserving conditional independence relationships after disregarding latent variables). The directionality provided by the MAG is only one possible instantiation of the ambiguous relationship, as there are multiple possibilities for every ambiguous edge in the PAG.

Given the constrained data, the ULS, BDI-II, and ISMI at baseline all had ambiguous (o-o) edges with baseline motivation to engage with activities (MEA), meaning those relationships could be confounded. While depression (BDI-II) was shown to be a strong predictor of loneliness in the mixed model, our preliminary causal graph showed that depression was not causally influencing loneliness at any timepoint. However, BDI-II was shown to be causally influenced

by loneliness at four-months. Similarly, internalized stigma (ISMI) scores were not shown to causally influence loneliness at any timepoint, but ISMI was shown to be causally influenced by loneliness at four-months. The causal effect of loneliness at four-months was larger for ISMI at four-months than for BDI-II at four-months.

Despite our mixed model findings, rater-rated negative symptoms (QSANS) were not a direct cause or consequence of loneliness at any timepoint. The causal graph showed baseline QSANS scores having ambiguous (o-o) relationships with MOT and SF at baseline, while QSANS at 4-months also showed an ambiguous (o-o) relationship with SF at four-months. At the four-month timepoint, QSANS was shown to have an ambiguous (o->) relationship with MOT at four-months, which was also causally influenced by ULS at four-months. At six-months, QSANS was shown to causally influence MOT at six-months. The variables sharing edges with QSANS in this causal graph were also all significant predictors of ULS in the univariate linear mixed models.

Interestingly, self-reported motivation and pleasure variables were collected by the MAPS-SR, which was originally derived from the rater-rated Clinical Assessment Interview for Negative Symptoms (CAINS) (Llerena et al., 2013). The MAPS-SR has been shown to have good internal consistency, convergent validity with the CAINS motivation and pleasure scale, and good discriminant validity regarding depression, anxiety, and symptoms of psychosis (Llerena et al., 2013). Essentially, instead of relying upon trained assessors, the MAPS-SR allows participants to rate their own experiences of motivation and pleasure on a scale consistent with the CAINS subscale. The preliminary causal model showed that self-rated MEA at baseline may be the cause of baseline ULS, but this relationship may be confounded. At four-months, our model showed that ULS had an ambiguous edge (o->) with MEA, indicating that ULS causally

influenced MEA, a latent variable causally influenced ULS and MEA, or both. Social pleasure (SP) at four-months was shown to be causally influenced by loneliness at four-months (and baseline SP).

These initial results may suggest that while rater-rated negative symptoms were generally predictive of loneliness, perhaps the specific expression of such symptoms were more relevant to the experience of loneliness among these study participants. For example, the self-reported variables of motivation to engage in activities (MEA) and social pleasure (SP) were directly involved in the loneliness cascade, while rater-rated negative symptoms were more distal. While our results are preliminary, more research is needed to clarify 1) whether specific types of motivation and pleasure difficulties are causes or consequences of loneliness, and 2) whether self-ratings of such experiences are more causally related to loneliness than ratings provided by trained assessors.

The conceptual model of loneliness proposed by Lim et al. (2018) suggests that depression and internalized stigma may have a bidirectional relationship with loneliness. The causal graph in this study shows loneliness as a causal influence of depression and stigma, but not the reverse. The conceptual model proposed by Badcock et al. (2020) suggests a cycle where psychosis symptoms lead to internalized stigma, then social withdrawal, followed by loneliness, which in turn exasperates psychosis symptoms. We do see an initial ambiguous (o-o) relationship between MEA (which could be akin to social withdrawal) at baseline, with loneliness having a possible causal influence on MEA at four-months. Positive symptoms of psychosis were not causal influences of loneliness or internalized stigma at any timepoint (nor was it a predictor in our mixed model at any point); however, motivation, which is a prominent negative symptom, was shown to be a possible causal influence or outcome of loneliness in our model. This is not to

suggest that bidirectional/cyclical causal relationships are not possible. The GFCI algorithm is acyclic; therefore, we would not be able to corroborate bidirectional/cyclical relationships as a natural limitation associated with the choice of algorithm.

Outside of ULS at baseline *possibly* being causally influenced by baseline MEA, ULS did not appear to be a direct consequence of psychosis symptoms or other common psychosis treatment targets over the six-months of the study. However, ULS was shown as a possible causal influence on common psychosis treatment targets (e.g., depression, motivation/pleasure). Importantly, our preliminary causal model showed that 1) ULS was the primary causal influence of later ULS over the six-month study period, and 2) the observed causal effect of ULS on later ULS was large for both edges (e.g., baseline to four-months, four-months to six-months).

What happened with these variables in the original study? To better understand the causal network shown in our findings, we examined results from the RCT (Fisher et al., 2023). There were no statistically significant differences reported between the TCT and CG group regarding average use of the motivation enhancement application (PRIME), meaning both groups appeared to have relatively equal participation in the supportive online community provided by PRIME. The MAPS-SR variables of SP, RWP, and MEA significantly improved over time for both groups. Scores for the BDI-II and QSAPS improved significantly over time for both groups, while the QSANS improved at trend-level across the sample ($p = 0.09$). The AQLS variables of MOT, SF, and OC did not significantly improve over time. The ISMI results were not reported in Fisher et al. (2023), but the ISMI did not significantly improve for either group. Lastly, loneliness (ULS) ratings did not significantly change over time across the original study sample (Fisher et al., 2023).

Several variables that were directly involved in the loneliness causal network improved over the six-month period of the original study. Self-reported variables such as MEA and depression improved significantly. Rater-rated negative symptoms, which was a strong predictor of loneliness in our mixed models but was more distal to loneliness in our causal graph, also improved somewhat. Rater-rated AQLS variables, internalized stigma, and loneliness did not improve significantly over the six-month period. Our preliminary model suggests that baseline MEA *may* causally influence baseline loneliness, but that loneliness was the primary cause of loneliness over time.

While these findings are preliminary, they initially suggest that loneliness may not change in the same manner as several of its predictors/correlates. For example, as depression and self-reported motivation and pleasure variables improved, loneliness appeared somewhat static. However, given the data, loneliness was shown to have a large causal effect on later loneliness, and those causal edges were shown to be relatively stable. This could suggest that 1) loneliness may not improve when it is not a specific target of intervention, and 2) it may self-perpetuate in the absence of direct intervention or other interruption within a general psychosis population. Similarly, internalized stigma did not improve over time; however, loneliness appeared to causally contribute to internalized stigma at four-months. This could suggest that 1) the experience of internalized stigma may not improve without specific targeted intervention, and 2) that if left uninterrupted, loneliness may contribute to the maintenance of internalized stigma over time among a generalized psychosis population.

This study has several limitations. Sample size is a frequent issue in clinical research with psychosis specific foci, and it is a real limitation for our exploratory causal discovery analysis. The population included in the GFCI analysis was quite constrained and was shown in our

dropout analysis to have significantly lower mean BDI-II scores at baseline, which could influence the causal network. Further, while GFCI has been shown to work well with smaller samples, our sample was small enough that it is possible the algorithm was unable to discern directionality in the causal relationships. For example, it is possible that with a larger sample we may have observed fewer ambiguous relationships in the PAG, particularly at baseline. However, the ambiguous edges in our causal graph could be the result of unmeasured common causes.

It is also possible that due to the limited sample size in this study, the algorithm could have difficulty discerning true directionality in causal edges. For example, it is possible that while we see loneliness at four-months as a causal influence of stigma at four-months, the same analysis with a larger sample may show that stigma at four-months is a causal influence on loneliness at four-months. Additionally, the bootstrap analysis revealed that some of the edges in our causal graph were unstable; a larger sample may improve the stability of the overall graph output.

In conclusion, we examined and identified predictors of loneliness from among common treatment targets. Our reduced model showed that self-reported internalized stigma, self-reported depression, and rater-rated negative symptoms were our strongest predictors of loneliness. Because loneliness is not typically assessed or measured in traditional clinical care for psychosis, it may be useful for researchers and clinicians to consider loneliness among those in clinical situations in the presence of these predictors. This is, to our knowledge, one of the first causal discovery analysis aimed at uncovering a causal network centered on loneliness within a general psychosis population. While our findings are preliminary and should be interpreted with caution, our model suggests that loneliness may be self-sustaining without interruption. In a clinical context, our results suggest that loneliness may not improve in conjunction with common

treatment targets, including predictors and correlates of loneliness, and may worsen experiences such as internalized stigma, depression, motivation to engage in activities, and generalized motivation. Lastly, if we have a goal to enhance the social functioning of people who experience psychosis, we may need to regularly assess and measure loneliness at the outset of treatment, as well as research specific targeted interventions to address loneliness among our participants who endorse the experience.

Table 2.1

Partial Ancestral Graph (PAG) Edge Types

Edge Type	Present Relationships	Absent Relationships
A --> B	A is a cause of B. It may be a direct or indirect cause that could include other measured variables. There could also be an unmeasured confounder of A and B.	B is not a cause of A.
A <-> B	There is an unmeasured variable (L) that is a cause of A and B. There may be measured variables along the causal pathway from L to A or from L to B.	A is not a cause of B. B is not a cause of A.
A o-> B	Either A is a cause of B (-->), or there is an unmeasured confounder of A and B (<->), or both.	B is not a cause of A.
A o-o B	One of the following is true: 1) A is a cause of B, 2) B is a cause of A, 3) there is an unmeasured confounder of A and B, 4) both 1 and 3, 5) both 2 and 3.	

Note: Adapted from *Tetrad Manual* (2023), Center for Causal Discovery, Retrieved from:

https://cmu-phil.github.io/tetrad/manual/.

Table 2.2

Demographic Characteristics at Baseline

Baseline Demographics	(n=99)	
	M or %	*(SD)*
Age (years)	33.4	(10.8)
Education (years)	15.5	(2.8)
Sex		
Female	59%	
Male	41%	
Racial background		
Asian	12.1%	
Native Hawaiian or Other Pacific Islander	2%	
Black or African American	13.1%	
White	66.7%	
More than one Race	5.1%	
Declined to answer	1%	
Ethnicity: Hispanic or Latino	10%	
Diagnosis		
Schizophrenia	39.4%	
Schizoaffective	40.4%	
Schizophreniform	3%	
Psychosis NOS	3%	
Bipolar	9.1%	
MDD with Psychotic Features	5.1%	

Table 2.3

Clinical Characteristics at Baseline

Baseline Clinical Characteristics	(n=99)	
	M or %	*(SD)*
Age of first symptoms	19.4	(7.4)
Total hospitalizations	4.3	(5.7)
Treatment group assignment (TCT)	48.5%	
UCLA Loneliness Scale-3	33.9	(15.01)
Internalized Stigma of Mental Illness Scale	22.3	(5.6)
Beck Depression Index-II	22.4	(15.03)
Defeatist Beliefs (DAS subscale)	45.6	(16.5)
Quick Scale for the Assessment of Negative Symptoms	31.5	(20.4)
Quick Scale for the Assessment of Positive Symptoms	16.9	(12.4)
Motivation and Pleasure Scale		
Social Pleasure	6.1	(3.1)
Recreation and Work Pleasure	6.4	(3.2)
Motivation for Close Relationships	6.5	(3.05)
Motivation to Engage in Activities	11.3	(5.9)
Abbreviated Quality of Life Scale (QLS)		
Intrapsychic Foundations	3.9	(0.9)
Social Functioning	3.1	(1.7)
Occupational Functioning	3.5	(2.1)
Environmental Engagement	5.6	(0.6)

Table 2.4

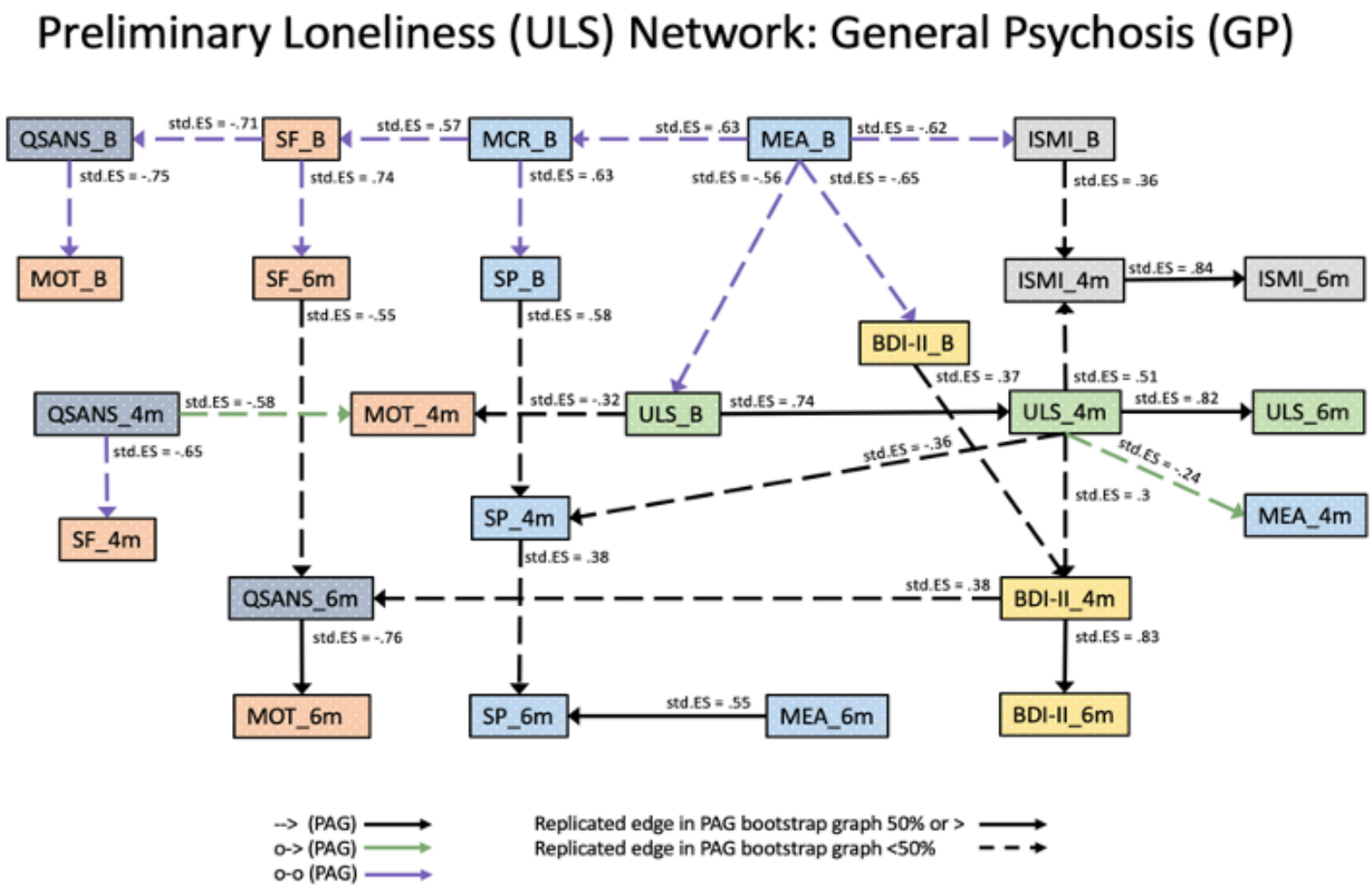
Comparison of Full and Reduced Linear Mixed Models

Effect	Estimate	*SE*	95% CI		Statistic	*p*	Estimate	*SE*	95% CI		Statistic	*p*
			LL	*UL*					*LL*	*UL*		
Fixed Effects	Full						Reduced					
(Intercept)	11.12	7.56	-3.78	26.02	1.47	0.143	6.02	3.26	-0.41	12.45	1.85	0.066
time2	0.58	1.15	-1.68	2.83	0.50	0.616						
time3	0.68	1.18	-1.65	3.00	0.57	0.566						
ISMI	0.72	0.17	0.38	1.05	4.22	**<0.001**	0.79	0.16	0.47	1.10	4.93	**<0.001**
DBS	-0.01	0.06	-0.12	0.11	-0.10	0.920						
BDI-II	0.26	0.07	0.12	0.40	3.73	**<0.001**	0.31	0.06	0.19	0.43	5.25	**<0.001**
MAPS (SP)	-0.33	0.30	-0.93	0.27	-1.08	0.283						
MAPS (MCR)	0.15	0.28	-0.39	0.70	0.55	0.581						
MAPS (RWP)	0.25	0.32	-0.37	0.88	0.80	0.427						
MAPS (MEA)	-0.34	0.19	-0.72	0.03	-1.80	0.073						
QSANS	0.11	0.05	0.01	0.21	2.24	**0.026**	0.11	0.04	0.04	0.19	2.95	**0.003**
MOT	0.20	1.04	-1.85	2.24	0.19	0.851						
Random Effects												
σ^2 (within)	44.45						44.66					
τ_{00} (between)	74.17_{ID}						79.05_{ID}					
ICC	0.63						0.64					
$N_{Individual}$	99						99					
Observations	233						233					
Marginal R^2/	0.429/						0.408/					
Conditional R^2	0.786						0.786					
AICc	1737.67						1724.07					

Note. CI = confidence interval; LL = lower limit; UL = upper limit; AICc = Akaike information criterion, corrected for multiple tests; ICC = intraclass correlation coefficient.

Figure 2.1

Preliminary Causal Model of Loneliness in a General Psychosis Sample



CHAPTER 3: AN INITIAL CAUSAL STRUCTURE OF LONELINESS AMONG PEOPLE WITH EARLY PSYCHOSIS ENROLLED IN COORDINATED SPECIALTY CARE

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Abstract

Background: Loneliness is a convincing public health concern that carries risks for an array of negative health outcomes. Research has shown that people within the psychosis spectrum tend to endorse greater levels of loneliness than what has been observed in the general public. While the experience of loneliness is broadly under researched in psychosis populations, little is known about the causes and consequences of loneliness among people experiencing early psychosis.

Methods: Data was collected from the Minnesota hub of the Early Psychosis Intervention Network (EPINET) initiative, which is a large, collaborative study of coordinated specialty care (CSC) in the United States. Causal discovery methods were used to explore a preliminary causal model of loneliness for 80 participants enrolled in CSC for early psychosis. Multivariate imputation for chained equations was used to address missing data; causal discovery was performed for each imputed dataset for variables at baseline and six-months. Results for each imputed dataset were pooled and summarized in the final causal model.

Results: The pooled preliminary causal model showed that loneliness had a causal relationship with self-reported depression at baseline and six-months, where loneliness was shown as both a cause and consequence of self-reported depression. Two different ambiguous edge-types were observed at baseline between loneliness and self-reported depression and discrimination experiences. Behavioral inhibition was shown as a possible causal influence of loneliness at six-months, while rater-rated depression was shown as a possible consequence of loneliness at six-months.

Conclusions: This pooled preliminary model suggests that loneliness and self-reported depression may have a causal relationship, while the relationship between loneliness and rater-rated depression was questionable. Loneliness was shown as a possible causal influence of self-

reported discrimination experiences, which is consistent with findings from correlational studies showing strong relationships between loneliness and internalized stigma/perceived discrimination. This preliminary model showed that loneliness was not a direct consequence of functional impairment, symptom distress, anxiety, motivation variables (outside of possibly behavioral inhibition), or measures of time spent with others. Overall, our findings suggest that loneliness might not merely be a consequence of psychosis symptoms and may need additional attention in treatment settings.

Introduction

Public health officials have expressed heightened concern about the rising levels of loneliness reported in large surveys of the general population (Bruce et al., 2019; Shovestul et al., 2020, United States Department of Health and Human Services (HHS), 2023). The primary reason for the public health concern is that loneliness has been shown to be associated with an array of negative health outcomes (Bruce et al., 2019; Hawkley & Cacioppo, 2010; HHS, 2023). Research has shown that loneliness disproportionately impacts those with mental illness (Hawkley & Cacioppo, 2010; Bruce et al., 2019; Wang et al., 2018) and those within adolescent/young adult developmental stages (Beam & Kim, 2020; Shovestul et al., 2020).

While research studies focused on loneliness within psychosis populations have increased in recent years, loneliness remains an understudied issue among psychosis populations more broadly. More specifically, loneliness is not well-understood in early psychosis populations, which is significant based on what has been widely reported about populations with heightened risk. Additionally, studies of general psychosis populations have repeatedly shown that loneliness is endorsed at rates above what has been reported among the general public (Badcock et al., 2015; Chrostek et al., 2016; Culbreth et al., 2021; Lim et al., 2018; Stain et al., 2012). Importantly, it has been suggested that loneliness may be more active and dynamic in adolescence and early adulthood than what is seen among those who are middle-aged or older (Beam & Kim, 2020). The experience of chronic loneliness among adolescents and young adults in the general population has been shown to significantly impact motivation, emotion regulation, and social functioning (Vanhalst, et al. 2017), which are already well-known issues impacted by psychosis.

Early psychosis populations typically include adolescent and young adult populations (National Institute of Mental Health (NIMH), 2023). Further, the five-year period following an initial psychosis experience is considered a "critical period" for early intervention (Birchwood et al., 1998, p.53; McGorry et al., 2008). This five-year period is critical because psychosis-related issues develop rapidly during this time, but show high levels of plasticity, meaning early interventions are essential to improving long-term functional outcomes (Birchwood et al., 1998; McGorry et al., 2008). It is therefore crucial to increase our scientific knowledge and understanding of loneliness among early psychosis populations.

There is a limited body of literature examining loneliness in early psychosis; however, a notable limitation of this literature is the small sample sizes. Sundermann et al. (2014) found that loneliness was associated with lower perceived social support, paranoia, anxiety, and depressive symptoms among 38 participants with first-episode psychosis; this study also found that participants reported high levels of loneliness and approximately 33% of those participants reported having no confidant. A small pilot study of 12 participants with early psychosis found depression and psychological well-being were both strongly correlated with loneliness (Lim et al., 2020a), which is congruent with research from generalized psychosis samples (Lim et al., 2018; Ludwig et al., 2020a; Roe et al., 2011; Suman et al., 2023). Lim et al. (2020a) found evidence that loneliness improved over time for some participants, which was also observed at modest levels at the six-week point in a small feasibility study of 19 participants with first-episode psychosis (Ludwig et al., 2020b). Importantly, Lim et al. (2020a) and Ludwig et al. (2020b) were both examining the efficacy of an online social platform aimed at improving or maintaining gains made during formal early psychosis treatment experiences.

A much larger randomized controlled trial (RCT) performed using the same online social platform found no statistically significant improvements in loneliness in either treatment group (Horyzons = 86, treatment as usual (TAU) = 84) over the 18-month period of the study (Alvarez-Jimenez et al., 2021). One study has been published examining loneliness, among other treatment outcomes, in the context of coordinated specialty care (CSC) for first-episode psychosis in the United States (Pennsylvania). Outcomes from this study showed no statistically significant changes in loneliness over the first year of CSC treatment (Westfall et al., 2020); however, researchers did note a non-statistically significant improvement in loneliness was observed between baseline and six-months (Westfall et al., 2020). The Westfall et al. (2021) study is quite unique because loneliness was formally measured as an outcome variable for CSC treatment; loneliness does not appear to be expressly measured or monitored in typical CSC programs.

Theoretically, much of what has been proposed about loneliness has been derived from the general population or from general psychosis populations. The social cognitive framework of loneliness, proposed by Cacioppo and Hawkley (2009), is a broad evolutionary model suggesting that the experience of temporary loneliness was (and is) crucial to the survival of the human species. This model also proposes that numerous consequences are associated with prolonged experiences of loneliness, such as changes in the ability to detect social threats (Cacioppo & Hawkley, 2009). A framework of loneliness specific to general psychosis populations has been proposed by Lim et al. (2018) showing bidirectional relationships between loneliness and a number of clinical or socially important domains. Importantly, Lim et al. (2018) report more research is needed on their model to determine the strength and direction of these relationships.

Ultimately, what is known about loneliness and psychosis is predominantly based on correlational research among generalized psychosis populations. Additional research is needed to clarify the relationships between loneliness and clinical factors, as well as the relationship between loneliness and social factors, such as experienced discrimination. In a path-analysis study using a generalized psychosis sample, Chrostrek et al. (2015) found that participant reported discrimination experiences had a direct path to increased feelings of reported loneliness, which had an additional path to loneliness mediated by self-esteem. Additional research is needed to clarify relationships between loneliness and perceived discrimination (e.g., threat detection) among people with early psychosis experiences.

This study aims to address gaps in the current literature by conducting a preliminary exploration into the causal relationships of loneliness among an early psychosis sample receiving CSC treatment in Minnesota. Clinical variables of interest include both self-rated and rater-rated depression, along with self-reported clinical issues such as anxiety, motivation, suicidal ideation, symptom distress and functional impairment. Psychosocial variables of interest include self-reported ratings of experienced discrimination and anticipated discrimination. The relationship between the primary variables of interest and loneliness will be examined using causal discovery methods over the first six-months of CSC treatment within a naturalistic sample with confirmed early psychosis diagnoses.

We selected causal discovery methods for this analysis to address specific gaps in the current literature. Causal discovery is a novel method of data analysis that links graph theory and statistics with machine learning to construct credible causal models from observational data (Eberhardt, 2017; Nogueira et al., 2022; Spirtes et al., 2000). Causal discovery methods are especially helpful when we lack enough experimental data to identify causal relations between

variables of interest. Another advantage of causal discovery over traditional associational approaches to data analysis is that causal discovery analysis (CDA) allows us to incorporate more variables into the analysis than what would typically be feasible in predictive models.

Methods

Study Design

This is an exploratory analysis of data collected as part of a large ongoing research project. The Early Psychosis Intervention Network (EPINET) initiative is supported by the National Institute of Mental Health (NIMH) and aims to improve early psychosis interventions by engaging in collaborative, practice-based research (nationalepinet.org, n.d.). The EPINET research collective consists of eight regional hubs across the United States – one regional hub is in Minnesota (EPI-MINN) and includes six coordinated specialty care (CSC) programs. This study will conduct a preliminary examination of the data collected from participants enrolled in the EPI-MINN Measurement Based Care (MBC) protocol. This is an active MBC study and is approved by the University of Minnesota Institutional Review Board (IRB).

The data for this preliminary and exploratory analysis was collected from the Minnesota hub of the Early Psychosis Intervention Network (EPINET) initiative. While the Minnesota hub of EPINET (EPI-MINN) has several ongoing projects, the primary aim is focused on measurement-based care (MBC) in local CSC for EP programs. The MBC project is a large and ongoing protocol focused on participant- and program-level outcomes in real-world clinical settings.

Participants

Participants included in this study were enrolled in the EPI-MINN MBC research study. The MBC protocol requires that all included participants have authorized the study team to

access their clinical data for research purposes. However, there are no additional tasks required of participants enrolled in the MBC study. Because the goal of the MBC study is to examine participant- and program-level outcomes in real-world clinical settings, the assessments completed by participants are part of their clinical care. Participants are not compensated for attending clinical appointments or completing assessments in the MBC study. Participants may choose to enroll in the EPI-MINN MBC study at any point during the EP treatment experience. Participants are eligible to enroll in the EPI-MINN MBC study provided they are receiving CSC services at a participating EP treatment program site, have a psychosis spectrum diagnosis, and are between the ages of 15-40 years. There are no exclusion criteria for the MBC study. Participants are scheduled to complete clinical assessments at intervals of approximately six-months during their course of their treatment.

Measures

Loneliness (LN). Loneliness was captured in this study by using items from the Modified Colorado Symptom Index (CSI). The CSI has been shown to be a reliable and valid 14-item measurement (Conrad et al., 2001). The two CSI items used to assess loneliness were: 1) "How often have you felt lonely" and 2) "How often did you feel out of place or like you did not fit in?" Both items ask participants to rate their subjective experiences with 1) loneliness and 2) feeling left out or isolated by others. These items were rated from zero (not at all) to four (at least every day).

Intersectional Discrimination Index (InDI). The InDI assesses anticipated and enacted social discrimination experiences in an attribution-free manner (Scheim & Bauer, 2019). The InDI uses the language, "because of who I am," to avoid specific ascriptions to race, gender, mental illness, etc. The InDI uses three scales to assess 1) anticipated discrimination, 2) day-to-

day discrimination, and 3) major discrimination (Scheim & Bauer, 2019). The anticipated discrimination (InDI-A) and day-to-day discrimination (InDI-D) scales were used for this study. The nine-items on each respective scale are rated from one (strongly disagree) to five (strongly agree). Higher scores on each of these scales indicate higher levels of anticipated or day-to-day discrimination experiences. The InDI has been shown to be a reliable and valid measure of discrimination experiences (Scheim & Bauer, 2019).

Minnesota Symptom Severity Checklist (MSSC). The MSSC was used to assess self-reported depression, motivation, and anxiety. The MSSC contains 27-items that assess 18 symptom domains that commonly occur across numerous categorical diagnoses. The MSSC is modeled after the Adult DSM-5 Cross-Cutting Symptom Measure, but it has additional domains deemed important for clinical care and progress tracking. The MSSC contains all the original domains of the Adult DSM-5 Cross-Cutting Symptom Measure (American Psychological Association (APA), 2023) with the following additions or changes: 1) functioning, rumination, motivation, and impulsivity domains were added, and 2) repetitive thoughts and repetitive behaviors are their own unique domains. Depression (DEP) consists of two items: 1) "Little interest or pleasure in doing things," and 2) "Feeling down, depressed, or hopeless?" Anxiety (ANX) includes three items: 1) Feeling nervous, anxious, frightened, worried, or on edge," 2) "Feeling panic or being frightened," and 3) "Avoiding situations that make you anxious?" Motivation (MOT) includes one item, "Lack of motivation or pleasure?" Each item is self-rated from 0 (not at all) to four (nearly every day), with higher scores indicated greater severity.

Calgary Depression Scale for Schizophrenia (CDSS). The CDSS is a nine-item measure administered and scored by a trained rater (Addington et al., 1996). The CDSS was developed to evaluate depressive symptoms specifically within psychosis spectrum populations –

meaning this scale is intended to distinguish depression from negative and positive symptoms (Addington et al., 1996; Addington et al., 2014). The CDSS was rated from one (absent) to four (severe), and it has been shown to be a reliable and valid measure of depression among populations experiencing psychosis (Addington et al., 2014). Psychometrists conducting CDSS interviews received training from experienced CDSS raters and were determined to have adequate inter-rater reliability prior to conducting assessments with study participants.

Behavioral Inhibition and Behavioral Activation Scale (BIS/BAS). The BIS/BAS is a reliable and valid 24-item measure that assesses two general motivational systems thought to inhibit or activate behavior (Carver & White, 1994; Jorm et al., 1998). The behavioral inhibition system (BIS) is thought to contribute to avoidant behaviors, while the behavioral activation system (BAS) is thought to regulate goal-directed behavior (e.g., appetitive motivation) (Carver & White, 1994). The BIS/BAS is rated from one (very true for me) to four (very false for me) and is scored on four scales: BIS, BAS Drive, BAS Fun Seeking, BAS Reward Responsiveness.

Life Events Checklist for DSM-5 (LEC-5). The LEC-5 is a self-report screening tool that asks participants about their exposure to 16 types of events associated with significant distress and/or post-traumatic stress disorder (PTSD) (Weathers et al., 2013; Gray et al., 2004). The 16 events were rated from one (Happened to me) to five (Does not apply). This assessment was intended to assess participants for exposure to potentially traumatic events and not PTSD specifically. The LEC has been shown to have adequate psychometric properties when used to assess exposure to traumatic events (Gray et al., 2004).

Illness Management and Recovery Scale – Client Version (IMR). The IMR scale is a reliable and valid scale containing 15-items developed to assess progress toward recovery domains while receiving treatment (Salyers et al., 2007). Each item is behaviorally anchored and

self-rated from one to five, with a higher item score indicating greater recovery for that specific item (Salyers et al., 2007). The IMR items used for this study include: 1) contact with people outside of family (IMR-OC) – "In a normal week, how many times do you talk to someone outside of your family (like a friend, co-worker, classmate, roommate)," 2) time in structured roles (IMR-TSR) – "How much time do you spend working, volunteering, being a student, being a parent, taking care of someone else or someone else's house or apartment? That is, how much time do you spend doing activities for or with another person that are expected of you," 3) symptom distress (IMR-SD) – "How much do your symptoms bother you," and 4) impairment of functioning (IMR-FI) – "How much do your symptoms get in the way of you doing things that you would like to do or need to do?"

Demographic Information. The demographic variables of age at program entry, duration of untreated psychosis (DUP), racial background, ethnicity, and gender (as identified by participants) were included in our analysis. Diagnostic information was obtained by clinicians or clinic psychometrists using the Mini International Neuropsychiatric Interview 7.0.02 (MINI). Clinician or clinic psychometrists also collected participant self-reports on suicidal ideation and whether friends were included in the participant identified natural support system.

Age at program entry and DUP were log-transformed due to skewness. Categorical variables with more than two-levels such as racial background, ethnicity, and gender required transformation to numeric binary variables for analysis.

Analysis

Multivariate Imputation by Chained Equations (MICE)

Prior to analysis, data was reviewed for the first year of treatment. The review showed baseline was the most complete timepoint, with the incompleteness of data increasing

significantly at six- and 12-month timepoints. The general incompleteness of the dataset is likely a reflection of the real-world and flexible nature of the larger study design. The 12-month timepoint was significantly incomplete for the primary variables of interest in this study and was ultimately dropped from the analysis. The remaining data represented baseline and six-month timepoints for people enrolled in EP treatment programs. Participants with less than 60% of measures complete at the six-month timepoint were also removed from the analysis.

The missingness of the dataset was examined visually using the *visdat* 0.6.0 package (Tierney, 2017) in R Studio (Core Team, 2015). The remaining six-month dataset was 87% complete. The percentage of missingness for each of the included variables ranging from 0-30%. Missing data was imputed using the Multivariate Imputation by Chained Equations (*mice*) method in R (van Buuren & Groothuis-Oudshoorn, 2011).

MICE is a flexible and advanced imputation method that uses regressions to model missing data conditional on other variables found within the dataset (Azur et al., 2011; van Buuren & Groothuis-Oudshoorn, 2011; Madley-Dowd et al., 2019). The specific procedure followed by MICE varies somewhat by the specific imputation method selected, but generally MICE replaces missing values by identifying probable values drawn from the distribution modeled for each missing value of a specific variable (Azur et al., 2011; van Buuren & Groothuis-Oudshoorn, 2011). Simulation studies have consistently shown that data with missingness exceeding 25% can be effectively imputed using MICE procedures (Madley-Dowd et al., 2019).

The R package *mice* 3.16.0 (van Buuren & Groothuis-Oudshoorn, 2011) allows users to select the number of datasets they would like to create (the default is m = 5), as well as how many regression iterations they would like the package to run for each dataset. For this study, the

number of iterations for each imputed dataset was set to 50. The total number of imputed datasets was set to m = 10. Predictive mean matching (PMM, type one), which is the MICE default, was used to impute continuous variables. The number of random donor values used for imputation was also the MICE default in R, which is d = 5. Logistic regression was used to impute binary variables.

PMM creates an initial set of coefficients by estimating linear regressions for cases with no missing data. The regression procedure, in the case of PMM, is used to create a system for matching missing data with similar instances where the data are present (Allison, 2015; van Buuren, 2018). Next, a new coefficient is generated by randomly selecting coefficients from the set formed in the initial procedure. Using the new pool of coefficients, PMM creates predicted values for variables with complete and missing data (Allison, 2015). In each instance of missing data, PMM pinpoints cases with observed values where the predicted values are similar to the predicted value for the instance with missing data. The cases that PMM pinpoints in this step are called donor cases (d = 5 was used in this study). Using the donor cases PMM pinpoints, one is chosen, and its observed value is substituted for the missing value (Allison, 2015; van Buuren, 2018). This process is then repeated for all missing values for each imputed dataset. The process PMM uses for imputation ensures that values are probable, and values selected will always be within the range of values possible for the specific dataset (van Buuren, 2018).

Typically, MICE imputed datasets are analyzed and then the results are pooled within the *mice* package. Due to the nature of this analysis, we were not able to analyze data and pool results within the *mice* package. To keep our process consistent with generally accepted MICE procedures, all 10 imputed datasets were analyzed separately. Results were then pooled and summarized across the 10 respective datasets.

Causal Discovery Analysis

To estimate the causal relationships among variables, we conducted a causal discovery analysis. All causal discovery analyses were performed in Tetrad version 7.5.0-0 (Ramsey et al., 2018). The Greedy Fast Causal Inference (GFCI) algorithm was used to explore and assess the preliminary network of loneliness and associated variables at baseline and six-months for the 10 imputed datasets separately. GFCI works by using a combination of score-based and constraint-based methods to create a Partial Ancestral Graph (PAG). In general, causal relationships cannot be fully resolved from observational data due to statistical equivalence. The GFCI algorithm outputs a PAG which represents a set of causal graphs that are consistent with the statistical relationships observed in the data under the Markov and Faithfulness assumptions.

To create a PAG, the GFCI algorithm first searches the space of all possible models, identifies directly dependent variables, and then augments model scores (BIC scores) until it finds the best penalized likelihood score. During this stage, the algorithm creates a graph with the assumption there are no unmeasured common causes. As a result, the first graph may have inaccurate edges and orientations (Chickering, 2002; Jabbari & Cooper, 2020; Miley et al., 2021; Ogarrio et al., 2016; Ramsey, 2015). In the next phase, GFCI no longer assumes that there are no unmeasured common causes. The algorithm uses conditional independence tests and mathematical decision-making rules to check for all the possible statistical discrepancies or irregularities that may have been produced by unmeasured common causes; incorrect edges from the first phase are removed and PAG edge orientations are revised and improved. (Chickering, 2002; Jabbari & Cooper, 2020; Miley et al., 2021; Ogarrio et al., 2016; Ramsey, 2015). The resulting PAG is the best model of causal relationships, given the specific data used in the analysis (Chickering, 2002; Ogarrio et al., 2016; Ramsey, 2015). The procedure used by GFCI

has been confirmed to be asymptotically correct, and the PAG output has been generally shown to have excellent accuracy in simulation studies (Ogarrio et al., 2016).

The PAG contains nodes (variables) and edges. The orientation of an edge that connects two nodes depicts the type of causal relationship identified by GFCI. There are several types of edges that can be shown in a PAG **(**Table 3.1).

To estimate causal effects, Mixed Ancestral Graphs (MAGs) were obtained from each of the original PAGs created from the 10 imputed datasets. A MAG is one causal structure that is in the equivalent structure of the PAG. A MAG maintains the conditional independence relationships from among the measured variables in the PAG (Tetrad Manual, 2023; Malinsky & Spirtes, 2016). Essentially, in the case of ambiguous causal edges (o-o or o->) shown in a PAG, the MAG shows a forced choice of either a causal (-->) or undirected (<->) relationship, given the data. In this case, a MAG gives us just one possible outcome of a PAG containing ambiguous edge types, enabling causal effect estimation. Effect sizes (raw, standardized) were obtained by fitting a linear SEM to each of the 10 MAGs using the R package *lavaan* 0.6-15 (Rosseel, 2012). In the path model, non-directional relationships were represented as covariances while directional relationships were represented as a regression path. The results of the SEM analyses were pooled and standardized effect size (std.ES) ranges were reported for each of the graph edges.

To summarize the results over the 10 imputed datasets and assess the stability of the results across the 10 imputed datasets, we analyzed each PAG separately and created count tallies for observed edge types among sets of nodes. The results for each of the 10 PAGs were pooled; an edge was determined to be sufficiently represented if it was present in the pooled output at a threshold of 30% or more. After identifying PAG edges present at least 30% of time, the MAGs

were then analyzed in the exact same manner as the PAGs. A final graph was then constructed. Edges that were considerably outside the loneliness network, along with nodes with no edges, were not incorporated into the final graph.

To assess the stability of the results associated with applying causal discovery analysis to each of the 10 imputed datasets, a bootstrap resampling procedure was performed. The bootstrap procedure used GFCI on 1,000 resamples of the data to assess the stability of all 10 PAGs. The proportion of edges present in the bootstrap resamples were then pooled and a final average proportion was used to determine stability.

Post-hoc Analysis

Following the GFCI analysis, a series of t-tests were performed to assist with understanding aspects of the relationships observed among the nodes in the causal graph. These analyses were conducted for each of the 10 imputed datasets. The results were pooled and averaged for each respective variable included in these additional analyses.

Results

Participants

Eighty participants were included in this analysis. Table 3.2 shows the baseline demographic and pooled average clinical characteristics for participants across the 10 imputed datasets.

GFCI

Our GFCI results will first be presented as a single graph, which presents outcomes for one randomly selected imputed dataset. Next, we will present the pooled findings for all 10 imputed datasets in one graph. Both causal graphs incorporate data from the original PAG(s) and MAG(s). The type of causal relationship found in the original PAG(s) is represented by the color

of the edge. The bootstrap stability of the edges in both causal graphs are depicted by line-type. The pooled causal graph displays the total count for each edge in both the PAG(s) and MAG(s); the PAG totals appear in parentheses while the MAG totals are shown without. If multiple edge types between two nodes were detected at the 30% threshold in the original PAG(s), the color of the edge in the pooled graph reflects the edge type with the greatest count total. Standardized effect sizes are shown along the edge in each causal graph; the pooled graph displays the standardized effect size range for the specific edge. For both causal graphs, the effect sizes were obtained from the MAG(s), meaning the standardized effect size(s) only reflect the possible effect size for edges that are not directly causal in the PAG(s).

GFCI Results from One Imputed Dataset

The causal graph shown in Figure 3.1 displays results for one randomly selected instantiation of the imputed datasets. An ambiguous edge (o-o) is shown between baseline self-reported depression (DEP) and baseline loneliness (LN). The ambiguous edge signifies that confounding variables could be influencing this relationship. In the MAG chosen by Tetrad, the edge was oriented to show baseline self-reported DEP as a causal influence of baseline loneliness. Assuming that there is no confounding in the baseline DEP and LN relationship, the effect size is 0.63 (i.e., increasing DEP by one standard deviation results in a 0.63 unit change in LN while holding other variables constant).

The edge between baseline LN and baseline daily discrimination experiences (InDI-D) is also ambiguous, signified by a o-> edge, (std.ES = 0.37), where baseline LN is a cause of InDI-D, or a latent variable has a causal influence on LN and ratings of baseline InDI-D (or both). Trauma exposure (LEC-5) at baseline converges with baseline LN as an ambiguous (o->) causal influence on ratings of InDI-D at baseline (std.ES = -0.55). Baseline ratings of InDI-D are shown

to causally influence baseline anticipation of discrimination (InDI-A) (std.ES = 0.65) and ratings of InDI-D at six-months (std.ES = 0.53).

Baseline LN also appeared to causally influence DEP at six-months (std.ES = 0.28). Self-reported motivation (MOT) at six-months converged with baseline LN as a causal influence on DEP at six-months (std.ES = 0.66). At six-months, LN was causally influenced by both DEP (std.ES = 0.76) and behavioral inhibition (BIS) (std.ES = 0.15).

Diagnostic groupings, behavioral activation (BAS) variables, friends as natural supports, outside contacts (IMR-OC), and time in structured roles (IMR-TSR) were significantly outside the loneliness cascade and therefore were not included in the causal graph. No demographic variables (log age, log DUP, race, gender) were shown to have a causal influence on loneliness. Race was the only demographic variable shown to have a causal influence on any variable included in the causal graph; race was shown to have an ambiguous (o->) causal influence on baseline anxiety (ANX).

Individual Graph Stability

Edges determined to be relatively stable are shown as a solid line-type in the graph. Overall, the loneliness network shown in Table 3.1 is relatively unstable. Several edges were dropped during the bootstrap resample procedure: the ambiguous edge (o-o) between baseline DEP and LN, the ambiguous edge (o-o) between baseline DEP and baseline CDSS, the ambiguous edge (o->) between baseline LN and InDI-D, the causal edge between baseline LN and DEP at six-months, and the causal edge between BIS at six-months and LN at six-months. A full bootstrap outcomes table for the individual PAG is located in Appendix E.

GFCI Results Pooled over Ten Imputed Datasets

Figure 3.2 shows the pooled findings across the 10 imputed datasets. There is an ambiguous edge (o-o) between baseline DEP and baseline LN. The ambiguous edge between baseline DEP and LN was observed in 90% of the PAGs. In all 10 MAGs, the orientation of this edge showed baseline DEP as a causal influence of baseline LN with a standardized effect size range of 0.61 to 0.68, indicating a potentially large causal effect of DEP on LN, assuming no hidden confounding. The discrepancy between the PAG and MAG edge counts is due to one causal edge being identified in the PAG. A full table of PAG and MAG edge counts is located in Appendix F.

An ambiguous edge (o->) was shown from baseline LN and baseline InDI-D in 80% of the PAGs, and a direct causal relationship between these nodes was shown in 100% of the MAGs (std.ES = 0.32, 0.46). In 80% of the PAGs, there was also an ambiguous (o->) causal influence observed between baseline LEC-5 and baseline InDI-D; the edge was oriented to a direct causal relationship in 80% of the MAGs (std.ES = -0.51, -0.59). Baseline InDI-D was shown to have a direct causal influence on baseline InDI-A (std.ES = 0.58, 0.65) (80% of PAGs, 100% of MAGs) and InDI-D at six-months (std.ES = 0.53, 0.54) (30% of PAGs and MAGs).

Baseline LN causally influenced self-reported DEP at six-months in 30% of PAGs, while a direct causal relationship was shown in 40% of MAGs (std.ES = 0.24, 0.4). Two additional nodes converged with baseline LN to causally influence DEP at six-months: 1) self-reported functional impairment (IMR-FI) at six-months (3 PAGs, 4 MAGs, std.ES = -0.36, -0.54) and 2) self-reported MOT at six-months (50% of PAGs/MAGs, std.ES = 0.56, 0.76). Self-rated DEP at six-months was shown to causally influence both MOT at six-months (3 PAGs, 4 MAGs, std.ES = 0.48, 0.8) and LN at six-months (60% of PAGs, 70% of MAGs, std.ES = 0.52, 0.76).

Behavioral inhibition (BIS) converged with DEP at six-months as a causal influence of LN at six-months in 30% of PAGs and 40% of MAGs (std.ES = 0.14, 0.33).

Rater-rated depression (CDSS) scores at six-months were causally influenced by LN at six-months in 30% of the PAGs and 40% of the MAGs (std.ES = 0.53, 0.63). CDSS scores were shown as a causal influence of suicidal ideation (SI) at six-months (30% of PAGs/MAGs, std.ES = -0.33, -0.4) and ANX at six-months (30% of PAGs/MAGs, std.ES = 0.31, 0.46).

The demographic variables included in this analysis were not shown to be direct causes or consequences of loneliness at the minimum threshold for inclusion (30%). Race was the only demographic variable shown to have a potential causal influence on any node included in the graph; race was shown to have an ambiguous (o->) causal influence on baseline ANX (8 PAGs, 10 MAGs, std.ES = -0.25, -0.4). Diagnostic category, BAS variables, friends as self-reported natural supports, IMR-OC, and IMR-TSR were located significantly outside the loneliness causal network and were therefore not shown in the pooled causal graph.

Pooled Graph Stability

Regarding consistency across the 10 imputed datasets for the direct LN network, a baseline relationship was detected between DEP and LN in all 10 imputed datasets, with nine edges being ambiguous (o-o). A relationship between baseline LN and InDI-D was present across all 10 imputed datasets, with eight edges being ambiguous (o->). For the relationship between baseline InDI-D and InDI-A, edges were observed across the 10 imputed datasets, with eight of those edges being shown as directly causal (-->). The relationship between baseline LN and DEP at six-months was only observed in four PAGS, with three edges being shown as directly causal (-->). At the six-month timepoint, the edge from DEP to LN was present in seven imputed datasets and was shown as directly causal (-->) for six of those imputed datasets. At the six-

month timepoint, an edge from BIS to LN was observed in four of the imputed datasets, with three of those edges shown as directly causal (-->). At the six-month timepoint, an edge from LN to CDSS was observed in four imputed datasets, with three being shown as directly causal (-->).

While the counts reported in the causal graph for both the PAGs and MAGs are an assessment of the stability of each edge, we conducted a bootstrap analysis using 1,000 resamples of the data for each of the 10 imputed datasets to assess overall edge stability. The proportion of each edge-type in the resamples were pooled and averaged for all relevant edges. A table of the pooled average bootstrap stability outcomes is found in Appendix G.

The bootstrap results showed several dropped edges within the direct loneliness network. The dropped edges include: 1) baseline LN to baseline InDI-D, 2) BIS at six-months to LN at six-months, 3) CDSS at six-months to ANX at six-months, and 4) CDSS at six-months to SI at six-months. Edges that were replicated in less than 50% of the bootstrap resamples are shown in the graph with dashed line-types. Overall, the pooled causal graph shows several unstable, or less than stable edges.

Post-hoc Analysis

The first relationship assessed was the ambiguous edge (o->) observed between race and baseline ANX. An independent samples t-test was used to assess baseline differences in ANX scores for participants who identified as Black, Indigenous, or Person of Color (BIPOC) or white. On average, baseline anxiety scores were significantly higher for participants who identified as white (mean = 6.89) when compared to BIPOC participants (mean = 4.22) ($p < 0.001$, 95% CI = 1.15823538, 4.16990325).

We were then curious about whether average mean scores changed significantly for the nodes included in the pooled causal graph between baseline and six-months. Paired t-tests were

used to determine whether average mean scores improved between baseline and six-months for the participants included in this study. Paired t-tests were run on each of the 10 imputed datasets separately; results were then pooled and averaged across all datasets. See Table 3.3 for the pooled results. The pooled paired t-test results showed that all variables included improved significantly at six-months, with the exception of InDI-D (trend-level, $p = 0.09$), InDI-A, BIS, and ANX (trend-level, $p = 0.08$).

Discussion

This analysis was a preliminary exploration of data collected during a large ongoing study examining measurement-based care (MBC) in real-world EP CSC programs. We analyzed data collected at baseline and six-month timepoints with the aim to explore and identify preliminary relationships of loneliness among a real-world clinical sample of people engaged in early psychosis treatment (CSC) programs in Minnesota. To address incompleteness in the dataset, we first removed measures, followed by participants, with exceptional amounts of missing data. For the remaining participants, we used MICE methods to create 10 imputed datasets.

The causal model obtained from the pooled PAGs revealed significant ambiguity in terms of causal relationships between baseline variables, which was not unexpected given the sample size and limited timepoints in our dataset. We created MAGs to provide some clarity regarding *possible* directionality and associated effect size when the algorithm is forced to choose a causal order (for ambiguous (o-o, o->) edges), given our specific dataset (meaning each MAG represents just one of many possibilities in the case of numerous ambiguous relationships).

The pooled causal model showed that self-reported depression (DEP) may be the cause of loneliness (LN) at treatment baseline, but this relationship may be confounded. LN at baseline

was shown to causally influence self-reported DEP at six-months, which was then shown to causally influence LN at six-months. The causal edge showing self-reported DEP at six-months as a direct causal contributor of LN at six-months was a robust preliminary finding, as reflected in the pooled edge counts, bootstrap outcomes, and standardized effect size range. Both LN and DEP mean scores were shown in the post-hoc analyses to significantly improve between baseline and six-months, so we may assume the edges between LN and DEP at baseline and six-months aren't simply the result of static data. Generally, depression and loneliness have been shown to have strong positive correlations in the literature (Culbreth et al., 2021; Lim et al., 2020; Ludwig et al., 2020; Sundermann et al., 2014), and the relationship between loneliness and depression is supported by theory (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010) and psychosis-specific conceptual models (Lim et al., 2018).

While rater-rated depression (CDSS) was not shown to have an edge with LN at baseline, CDSS scores were shown as a potential consequence of loneliness at six-months. The causal edge was only present in 30% of the PAGs, and given this dataset, it is possible the edge orientation is reversed at six-months. It is also possible that self-reported ratings of depression are more closely aligned with the subjective experience of loneliness than ratings provided by trained professionals. Perhaps the experience of depression, or loneliness, influences how one rates other phenomena or life areas; whereas structured interviews may not elicit responses to help decipher such linkages.

The pooled PAG findings indicated that baseline LN was either a cause of baseline daily discrimination experience (InDI-D) ratings, or that a latent variable was the cause of both LN and InDI-D (or both). While this edge was shown to be unstable in our pooled bootstrap analysis, it was present in 80% of the PAGs and 100% of the MAGs, which means GFCI produced an

initial edge from baseline LN to baseline InDI-D across all 10 PAGs. These preliminary findings add to a growing body of literature focused on the relationship between discrimination and loneliness. Discrimination experiences have been correlated with the intensity of loneliness feelings among people receiving treatment for schizophrenia spectrum diagnoses (Switaj et al., 2015). Researchers also found that participant endorsed discrimination experiences had a direct path to increased loneliness, but also indirectly through a path mediated by self-esteem (Switaj et al., 2015).

Our preliminary model suggests the possible presence of an unmeasured common cause in the causal pathway between baseline LN and ratings of daily discrimination experiences (InDI-D). Based on existing research, a hypothesis that either internalized stigma or self-esteem (or both) is causally influencing InDI-D ratings and/or loneliness would be reasonable. Recent research has shown that self-esteem is a strong predictor of loneliness among a general psychosis sample (Ludwig et al., 2020; Switaj et al., 2015). Research has also shown that internalized stigma is strongly and positively correlated with loneliness (Switaj et al., 2014). The experience of stigma and/or reduced self-esteem is highly common across different psychosis spectrum populations (Cunningham & Luckstead, 2017; DeTore et al., 2021; Firmin et al., 2018; Ritsher et al., 2003; Switaj et al., 2014; Switaj et al., 2015; Switaj et al., 2021).

Our post-hoc tests also showed that while mean LN scores improved, neither InDI-D or InDI-A ratings improved significantly between baseline and six-months. While individual treatment participants and clinicians may work to improve experiences of loneliness or discrimination while engaged in clinical care, neither are explicit treatment targets in traditional or CSC models of early psychosis treatment. It is possible the relationship observed at baseline was not maintained at six-months due to observed improvements in loneliness mean scores at

six-months, while no significant mean changes were observed for InDI-D or InDI-A at six-months.

The observed causal relationships between LN, InDI-D ratings, and possible unmeasured common causes such as internalized stigma or self-esteem are consistent with aspects of current theories of loneliness. The conceptual model proposed by Lim et al. (2018) suggests bidirectional relationships between both internalized stigma and perceived discrimination with LN. However, our current preliminary model suggests that discrimination ratings may be causally influenced by LN. In their broader theory of loneliness, Cacioppo and Hawkley (2009) propose a self-maintaining cycle suggesting that ongoing loneliness biases our detection of social threats, which causes behavior that elicits unwanted social interactions thereby increasing the experience of social avoidance and loneliness. At baseline, the preliminary model shows loneliness (and possibly latent variables) causally influencing ratings of discrimination experiences, which increased ratings of anticipated discrimination at baseline. We also see that six-month ratings of InDI-D and InDI-A were influenced by same-measure baseline ratings, and that a stable edge showed anticipation of discrimination as a cause of anticipation of discrimination at six-months.

Correlations between motivation (which includes negative symptoms) and LN have been reported across a variety of loneliness studies (Culbreth et al., 2021; Lim et al., 2018; Vanhalst et al., 2018). This preliminary causal model of LN did not support direct causal relationships between LN and self-reported motivation (MOT) or the behavioral activation motivation system (BAS) (drive, fun-seeking, reward). We did see that MOT at six-months may be an indirect causal influence on LN at six-months (through DEP). However, the BAS variables were not a direct or indirect causal influence (or consequence) of LN at our cutoff threshold across all 10 datasets.

We did observe LN at six-months being causally influenced by behavioral inhibition (BIS) at six-months, although that causal relationship was unstable. Our post-hoc analyses also revealed that average BIS mean scores did not significantly improve during the first six-months of treatment ($p = 0.13$). One explanation of this preliminary finding could be that uninterrupted or ongoing avoidant behavior may have an increasing impact on the felt experience of loneliness over time, particularly in the context of other symptom improvement.

Notably, our preliminary model did not show causal relationships between LN and self-reported symptom distress; we did find a possible indirect causal influence at the six-month timepoint between self-reported functional impairment and DEP. We also did not find causal connections between self-reported outside contacts with other people, time spent in structured roles (e.g., work, school), or endorsed friendships. This is worth noting because research has consistently shown that relatively objective measures of social isolation do not always reflect the subjective experience of loneliness. However, it is interesting that the presence of friends as part of participants' natural support system was not causally linked to ratings of loneliness. We also did not observe direct causal relationship between anxiety and loneliness, although a possible indirect and unstable relationship was observed between CDSS scores at six-months (causally influenced by LN at six-months) and anxiety at six-months.

This study has several limitations. First, we needed to create a composite loneliness score instead of using a reliable and valid measure of loneliness, which of course is not ideal. The LN composite item was intentionally constructed using participant ratings of feeling lonely (subjective) and feeling left out socially (subjective), but it does not replace a validated measure. However, limited item scales have been shown to effectively assess loneliness in clinical populations (Hughes et al., 2004).

The sample size for this study was small, which reduces the ability to make generalized statements. Additionally, the GFCI algorithm may have difficulty determining the correct edge orientation with too few samples. The sample was also constrained due to the level of missing data; our sample is likely not representative of the full population of people receiving CSC for EP in Minnesota. This study was also limited by too few timepoints. While it is critical to understand causal relationships in the first six-months of treatment, data with three or more timepoints would likely yield more complete results.

The flexible and naturalistic nature of the larger study was likely reflected in our dataset, particularly in the context of missingness. The assessments used for this analysis are a part of clinical care, and therefore may or may not be fully completed prior to attending clinical appointments. If participants authorized access to their clinical information, they were not asked to attend their clinic appointments any differently than would be typical. The issues observed within our dataset reflected the real-world issues commonly experienced by community mental healthcare providers regarding appointment attendance and collection of participant- and/or clinician-level data.

Imputation with MICE methods was used to address missing data without further reducing our sample. We created 10 imputed datasets using predictive mean matching (PMM) and logistic regression imputation strategies. While PMM is a flexible and generally robust method for imputation, there are two specific limitations regarding its use with this specific dataset. Because PMM uses randomly selected donor cases for imputation, it is possible that one donor case value could be repeatedly randomly selected (e.g., unbalanced selections). The default value for donor values in the *mice* package was used for this study (d = 5), which is considered an adequate donor pool for a smaller dataset (van Buuren, 2018). Another possible

PMM limitation is that it may be less robust with small sample sizes; however, some of this concern may be alleviated due to the percent-missingness of this dataset (13% total was incomplete). Importantly, newer imputation methods, such as MICE, have shown superior results regarding bias when compared to using complete case analysis (Azur et al., 2011; Madley-Dowd et al., 2019; van Buuren, 2018).

Future Directions

Longitudinal research is needed to better understand the causal relationships of loneliness among people experiencing early psychosis, as this remains an under-researched area in the psychosis literature. Specific studies are needed to better determine the causal relations between loneliness, internalized stigma, discrimination, and self-esteem. Our preliminary causal model indicates the need for future studies to examine whether self-report or rater-rated assessments of depression have similar performance in the context of a causal model of loneliness.

While age was not relevant in our preliminary causal model, it is unclear if the developmental stage of participants influences causal relationships. Qualitative and mixed-method research approaches would likely help elucidate the potential role of development in the experience, meaning-making, and views of causes and consequences of loneliness among people who experience psychosis. Additional research is also needed to increase our understanding of causal relationships in the context of higher versus lower loneliness at the outset of treatment. Causal relationships could look different in the context of groups (or clusters) with higher or lower levels of loneliness at the outset of treatment, which could in turn impact treatment trajectories and/or intervention approaches during the course of treatment.

Clinical programs or clinicians providing services for EP populations may want to consider assessing and monitoring loneliness among treatment participants. Our preliminary

causal model indicates that reporting the presence of friends as supports, spending time with people other than family (or professional supports) and engaging in structured out-of-home activities is likely not overtly indicative of the presence or absence of loneliness. While it is well understood that clinics and clinicians are often overwhelmed with the many aspects of providing mental healthcare in typical community-based settings, there are short and informative measures of loneliness that can enhance clinical care. One example is the UCLA 3-Item Loneliness Scale, which has demonstrated adequate psychometric properties (Hughes et al., 2004).

Conclusion

To our knowledge, this is the first study to explore the causes and consequences of loneliness in an early psychosis population using causal discovery methods. While our findings should be interpreted with caution due to the preliminary nature of this study, we found possible causal relationships between loneliness, self-reported depression, discrimination experiences, rater-rated depression, and behavioral inhibition. We did not find causal relations between self-reported subjective loneliness experiences and measures of more objective social isolation.

Table 3.1

Partial Ancestral Graph (PAG) Edge Types

Edge Type	Present Relationships	Absent Relationships
A --> B	A is a cause of B. It may be a direct or indirect cause that could include other measured variables. There could also be an unmeasured confounder of A and B.	B is not a cause of A.
A <-> B	There is an unmeasured variable (L) that is a cause of A and B. There may be measured variables along the causal pathway from L to A or from L to B.	A is not a cause of B. B is not a cause of A.
A o-> B	Either A is a cause of B (-->), or there is an unmeasured confounder of A and B (<->), or both.	B is not a cause of A.
A o-o B	One of the following is true: 1) A is a cause of B, 2) B is a cause of A, 3) there is an unmeasured confounder of A and B, 4) both 1 and 3, 5) both 2 and 3.	

Note: Adapted from *Tetrad Manual* (2023), Center for Causal Discovery, Retrieved from:

https://cmu-phil.github.io/tetrad/manual/.

Table 3.2

EPI-MINN Demographic and Pooled Clinical Characteristics

	(n=80)	
	Mean or %	(SD)
Demographics		
Age at program entry (years)	22.63	(5.9)
Gender ("male")	58.75%	
Racal background		
White	56%	
Black, Indigenous, or Person of Color	44%	
Diagnosis (schizophrenia spectrum)	66%	
Baseline Variables		
Duration of untreated psychosis (DUP) (weeks)	22.33	(38.62)
Natural supports: Friends (yes)	53.8%	
Suicide ideation (yes)	46.2%	
Loneliness	4.6	(2.5)
Intersectional Discrimination Index		
Day-to-day discrimination experiences	16.6	(7.03)
Anticipated discrimination	22.3	(7.7)
BIS/BAS		
Behavioral Inhibition	21.1	(3.9)
Behavioral Activation: Drive	10.4	(2.7)
Behavioral Activation: Fun	11.7	(2.8)
Behavioral Activation: Reward	15.9	(2.9)
Minnesota Symptom Severity Checklist		
Depression	4.02	(2.6)
Anxiety	5.7	(3.6)
Motivation	2.2	(1.4)
Calgary Depression Scale for Schizophrenia	6.1	(4.9)
Life Events Checklist	62.4	(19.4)
Illness Management and Recovery Scale – Self Report		
Outside contacts	3.1	(1.3)
Time in structured activities	2.6	(1.5)
Symptom distress	2.4	(1.2)
Functional impairment	2.4	(1.2)

Note. BIS/BAS = Behavioral Inhibition System/Behavior Exhibition System Scale.

Figure 3.1

Preliminary Causal Model of Loneliness in an Early Psychosis Sample

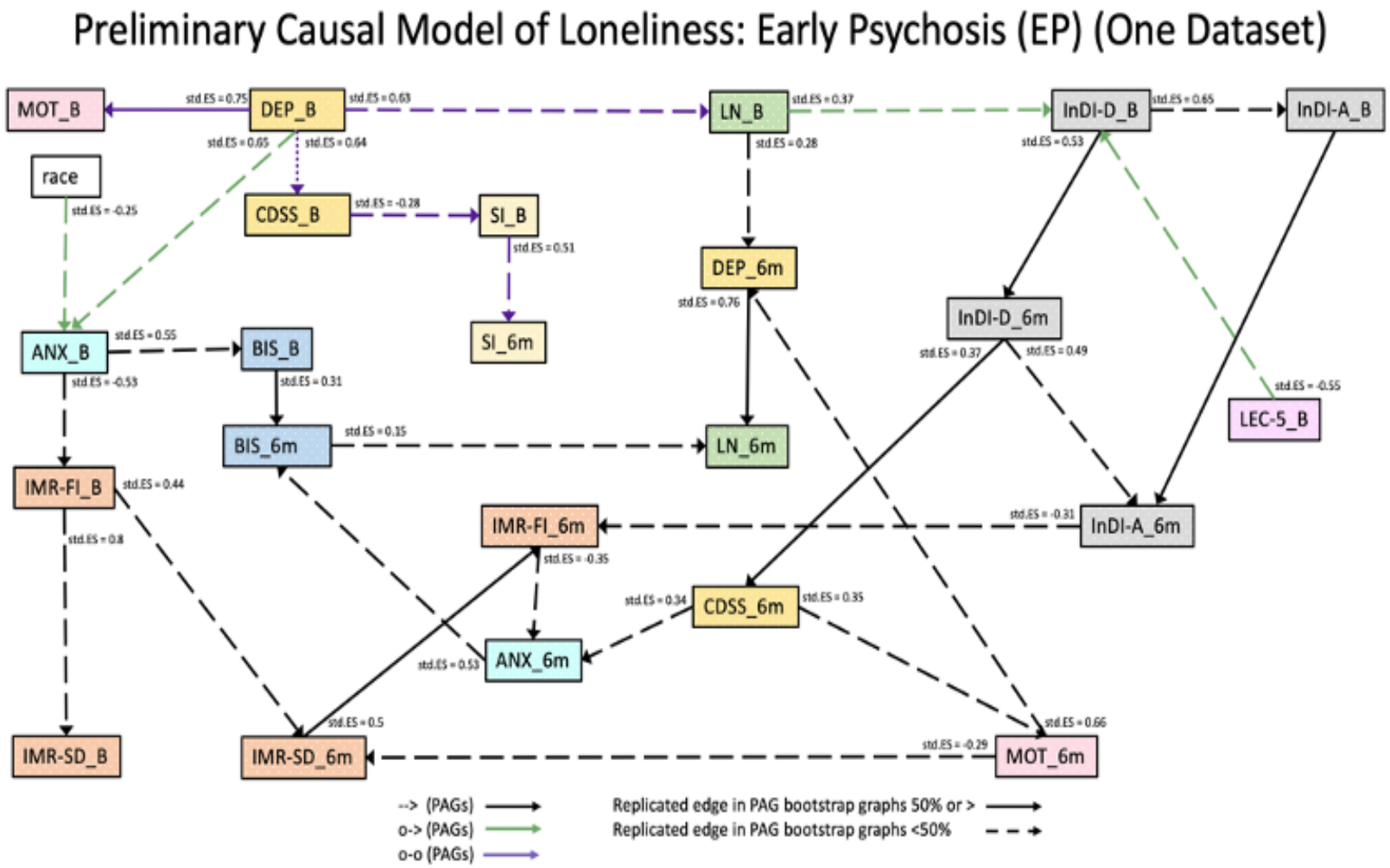

Figure 3.2

Preliminary Pooled Causal Model of Loneliness from an Early Psychosis Sample

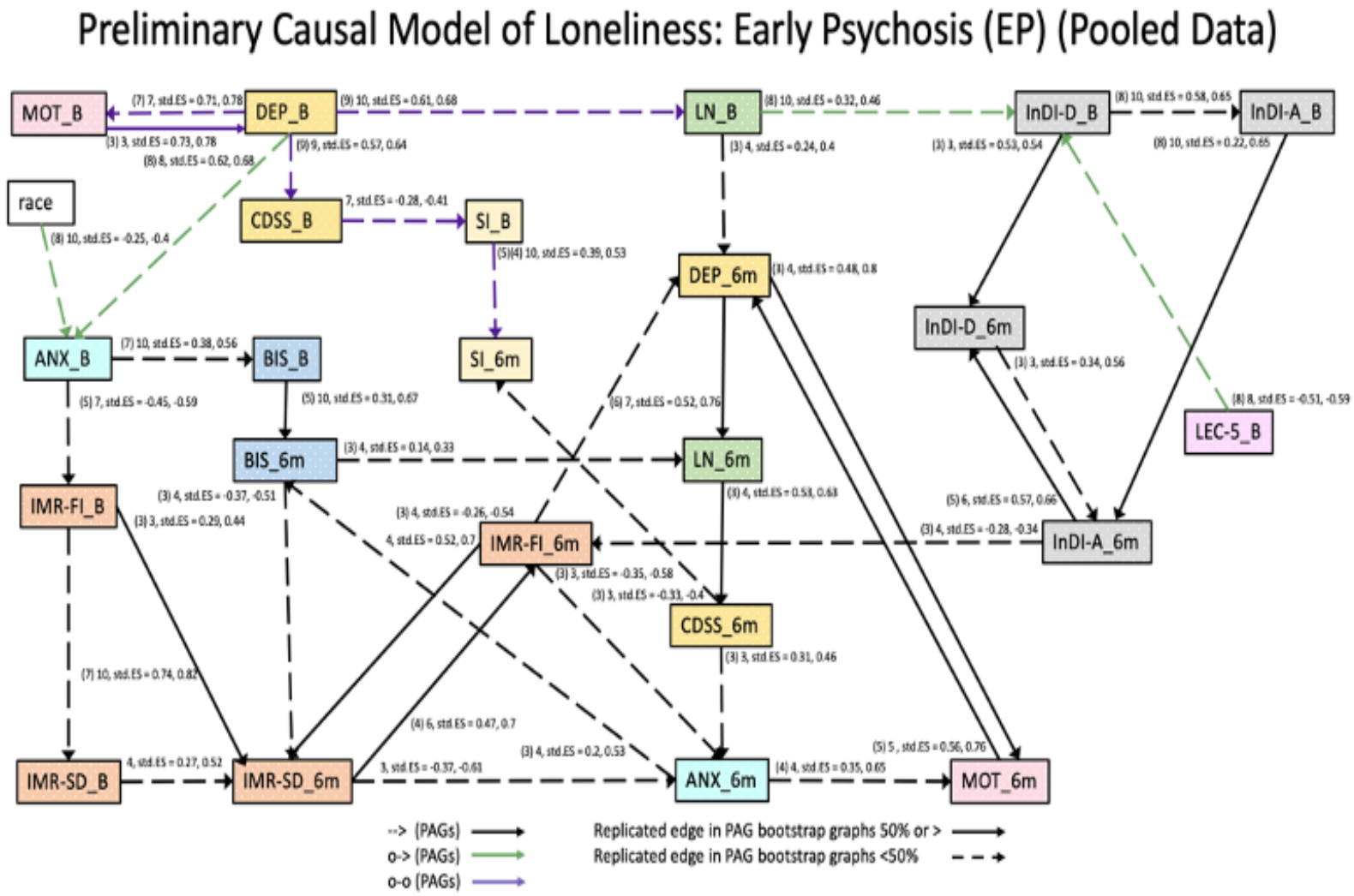

Table 3.3

Pooled Paired T-test Results for Baseline and Six-Month Average Mean Scores

Measure	Baseline		Six-months				95% CI	
	Mean	*(SD)*	Mean	*(SD)*	*t*	*p*	*LL*	*UL*
LN	4.567	2.504	3.227	2.283	4.77316	0.00004	0.78026	1.899738
DEP	4.019	2.56	3.109	2.421	3.0332	0.00424	0.31364	1.50886
CDSS	6.102	5.24	4.466	4.528	2.45943	0.03539	0.30639	2.97111
InDI-D	16.63	7.031	15.16	5.957	1.943544	0.09166	-0.03106	2.94356
InDI-A	22.28	7.693	20.66	8.221	2.032678	0.11262	0.02250	3.22499
BIS	22.06	3.851	21.31	4.491	1.793374	0.13291	-0.08121	1.64121
ANX	5.705	3.624	4.806	3.675	2.09798	0.08174	0.03537	1.76213
MOT	2.248	1.38	1.579	1.378	3.88638	0.00101	0.32553	1.01197
IMR-SD	2.368	1.153	3.016	1.402	-4.36157	0.00107	-0.94595	-0.35155
IMR-FI	2.45	1.202	3.184	1.297	-4.56575	0.00004	-1.05617	-0.41383

Note: LL = lower limit; UL = upper limit.

CHAPTER 4: UNCOVERING A PRELIMINARY CAUSAL MODEL OF LONELINESS WITHIN A FIRST-EPISODE PSYCHOSIS SAMPLE OVER THE FIRST YEAR OF TREATMENT

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Intended Journal: Psychological Medicine

Abstract

Background: Despite research showing that people with psychosis and adolescents/young adults are at high risk for chronic loneliness, which is a serious health issue, the causal relationships of loneliness are virtually unknown in early or first-episode psychosis populations.

Method: An uncontrolled, exploratory causal analysis was performed using the RAISE-ETP dataset. Causal discovery methods were used to identify a preliminary causal model of loneliness across the first year of treatment for 161 RAISE-ETP participants. We explored loneliness in the context of typical psychosis treatment targets, along with internalized stigma and recovery attitudes.

Results: The preliminary causal model showed that loneliness was the primary cause of loneliness. Internalized stigma was the only variable shown as a *possible* cause of loneliness at three-months, but it shown as a direct cause of loneliness at six-months. Loneliness was shown as a possible cause of mental health recovery attitudes at six-months and social functioning at six- and 12-months.

Conclusions: Loneliness was not shown to be the consequence of psychosis symptoms, rater-rated depression or anxiety, functional, or cognitive variables at any timepoint in the preliminary causal model. Internalized stigma was shown as the only potential cause of loneliness during the first six-months of treatment. Overall, loneliness appears to be primarily self-maintaining but could be exacerbated by internalized stigma. If left unaddressed, our preliminary model indicates that loneliness may negatively impact recovery attitudes and social functioning. Our preliminary findings indicate that loneliness may benefit from targeted assessment and intervention in first-episode psychosis populations.

Introduction

Loneliness is generally understood to be a highly subjective, unwanted, and distressing experience of social disconnection (Cacioppo et al., 2006; Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010). Loneliness has been identified as a public health concern largely because it has been associated with negative health outcomes, suicidality, and early death (Bruce et al., 2019; Hawkley & Cacioppo, 2010; HHS, 2023; Holt-Lunstad et al., 2015). The experience of psychosis has also been associated with broad negative health outcomes, including increased risk of preventable illness, suicidality, and early death (Ali et al., 2022; Laursen et al., 2014). For young people experiencing psychosis, the risk of experiencing loneliness may be disproportionately high because loneliness is more likely to impact adolescents and young adults (Beam & Kim, 2020; Shovestul et al., 2020), as well as persons with mental health disorders (Hawkley & Cacioppo, 2010; Bruce et al., 2019; Wang et al., 2018).

The increased risks associated with psychosis and loneliness for adolescents and young adults is notable. A first episode of psychosis would typically occur during adolescence/young adulthood (National Institute of Mental Health (NIMH), 2023). It is widely accepted that adolescence and young adulthood is a sensitive period for neurobiological (e.g., brain plasticity) and social development (e.g., social relationships, identity) (Larsen & Luna, 2018; Luciana & Collins, 2021). This sensitive period has been suggested as a critical period for the development of incentive-reward based motivation (e.g., anticipatory pleasure) (Luciana & Luna, 2018). It has also been widely accepted that the initial years after the onset of psychosis represent a critical period for both symptom expression and intervention efficacy (Birchwood et al., 1998; McGorry et al., 2008).

It is unclear how loneliness operates in the context of common research or clinical treatment targets of psychosis. Correlational research using general psychosis samples has shown that loneliness may be associated with rater-rated positive and/or negative symptom severity, but much of that research has presented mixed findings for both (Badcock et al., 2015; Culbreth et al., 2021; Jaya et al., 2016; Ludwig et al., 2020a; Michalska da Rocha et al., 2018; Switaj et al., 2014). In studies where the relationship between categorical symptom severity (positive/negative) was not statistically significant, researchers did find relationships between anhedonia and loneliness (Badcock et al., 2015), loneliness and social withdrawal/avoidance (Ludwig et al., 2020a), and loneliness and self-reported motivation and pleasure items (Culbreth et al., 2021).

The possible relationship between loneliness and anhedonia and motivation are significant because many believe that motivation, and relatedly anhedonia, are the driving features of negative symptoms (Barch & Dowd, 2010; Dowd & Barch, 2010; Green et al., 2018; Kahn et al., 2015; Kring & Barch, 2014; Llerena et al., 2013). Moreover, research has shown that anhedonia may be a direct result of difficulties with motivation and reward systems (Barch & Dowd, 2010; Dowd & Barch, 2010; Gard et al., 2007; Kring & Barch, 2014). Importantly, issues with motivation are commonly observed and studied among early and first-episode psychosis populations, and these issues have been strongly correlated with clinical outcomes (Breitborde et al., 2021; Chang et al., 2018; DeTore et al., 2021; Schlosser et al., 2014).

Motivation has also been associated with functional outcomes among early and first-episode psychosis populations (Abplanalp et al., 2021; Breitborde et al., 2012; Chang et al., 2019; DeTore et al., 2021; Fervaha et al., 2015). One specific functional outcome associated with motivation in these populations has been social functioning (Burton et al., 2019; Chang et al.,

2018; Chang et al., 2019; DeTore et al., 2021; Fulford et al., 2018; Fulford et al., 2013; Lutgens et al., 2017; Schlosser et al., 2015; Schlosser et al., 2014), which has been shown to be impacted by loneliness among adolescents and young adults in the general population (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010; Vanhalst et al., 2017). Social functioning difficulties are considered a core feature of psychosis, including early and first-episode psychosis populations (Burns & Patrick, 2007; Burton et al., 2019; Devoe et al., 2019; Griffiths et al., 2021; Malla and Payne, 2005). Difficulties with social functioning have been shown to be strongly correlated with disability across the psychosis spectrum (Addington et al., 2008; Alvarez-Jimenez, et al., 2012; Burton et al., 2019), meaning difficulties with social functioning, and relatedly motivation, clearly take a toll on those impacted.

Importantly, in addition to motivation/negative symptoms, an array of other factors have been associated with social functioning difficulties across the psychosis spectrum, including depression (Fulford et al., 2013; Gardner et al., 2019; Pruessner et al., 2011), social cognition (Addington & Addington, 2008; Vohs et al., 2014), internalized stigma (Lysaker et al., 2007; Mueser et al., 2020; Yanos et al., 2008), and loneliness (Chrostek et al., 2016; Culbreth et al., 2021; Stain et al., 2012). Loneliness has been shown to be correlated with social functioning difficulties in psychosis specific populations (Chrostek et al., 2016; Culbreth et al., 2021; Stain et al., 2012), but less is known about how loneliness may contribute to motivational or social functioning issues in early or first-episode psychosis populations. Additionally, more information is needed to determine how loneliness may contribute to depression, internalized stigma, social cognition and general cognition in early or first-episode psychosis populations.

Generally, loneliness has been strongly correlated with depression (Culbreth et al., 2021; Lim et al., 2020; Ludwig et al., 2020a; Sundermann et al., 2014) and internalized stigma

(Chrostek et al., 2016; Switaj et al., 2014; Switaj et al., 2021) in psychosis specific populations. Loneliness has also been negatively correlated with quality of life and self-reported recovery measures (Roe et al., 2011). Little is known about the relationship between loneliness and social cognition or general cognition. Two studies using general psychosis samples have reported mixed findings regarding loneliness and social cognition (Tremeau et al., 2016; Ludwig et al., 2020a), while one study has reported lower general cognition scores (based on a digit symptom coding task) were associated with greater loneliness (Badcock et al., 2015).

There are several theories, which are based on the available literature, that may allow us to better understand loneliness in the specific context of psychosis. Lim et al. (2018) conducted a systematic analysis and created a framework of loneliness using those results. They proposed that loneliness has bidirectional relationships with mental health symptoms (e.g., depression, anxiety, and psychosis), structural and functional social support, well-being (which includes quality of life and recovery measures), social perception (internalized stigma/discrimination), and self-constructs (Lim et al., 2018). The authors of this framework clearly articulate their belief that more research is needed to clarify the relationships between variables, as well as to better determine the strength and direction of the proposed relationships (Lim et al., 2018). A more parsimonious model was proposed by Badcock et al. (2020), which suggested psychosis symptoms lead to internalized stigma, which lead to social withdrawal, which then leads to loneliness. The authors proposed this negative feedback loop would continue if there were no interruptions or direct intervention (Badcock et al., 2020).

Overall, loneliness appears to be correlated with many factors that are highly related to clinical and functional outcomes, which includes quality of life, in psychosis populations. However, it is currently unclear what role, if any, loneliness may play in clinical or functional

outcomes for early or first-episode psychosis populations. To date, most of the research on loneliness in psychosis populations is cross-sectional and correlational. More research is needed to better understand how loneliness may operate over time. Further, more research is needed to determine the causes and consequences of loneliness in the context of commonly observed clinical, psychosocial, and cognitive issues in psychosis. The aim of this study is to perform a preliminary exploration into the causal relationships of loneliness among a clinical sample of people engaged in treatment for first-episode psychosis (FEP) using causal discovery methods.

Causal discovery methods are particularly well-suited to the aim of this study because we generally lack experimental data in this particular domain, meaning we do not have a strong understanding of what variables may be causes or consequences of loneliness. The algorithms used in causal discovery analysis (CDA) explicitly search the space of plausible causal models and identifies the best possible model, given the data (Ogarrio et al., 2016). CDA is commonly compared against structural equation models (SEM), and CDA has been shown to be superior in simulation studies (Ogarrio et al., 2016; Shen et al., 2020). Importantly, traditional predictive approaches provide a description of the data, while CDA can help us identify preliminary causal models because it illustrates the process that generated the data (Anderson et al., 2023).

Methods

This study was an uncontrolled, secondary analysis using data from the Recovery After an Initial Episode of Psychosis – Early Treatment Program (RAISE-ETP) study. The de-identified RAISE-ETP dataset was obtained from the National Institute of Mental Health National Database for Clinical Trials (https://data-archive.nimh.nih.gov/). The RAISE-ETP study was a large clinical trial that compared treatment as usual (TAU) against a multimodal coordinated specialty care (CSC) intervention for FEP (Kane et al., 2015). This specific

multimodal intervention for FEP is known as NAVIGATE (NAV) (Kane et al., 2015). The University of Minnesota Institutional Review Board (IRB) determined this study was exempt from human subjects research.

Participants

A total of 34 sites were enrolled into RAISE-ETP, which used a cluster randomization design to assign 17 sites to continue with TAU, while the other 17 sites provided NAV; the 34 clinical sites represented 21 states across the United States (Kane et al., 2015). RAISE-ETP participants were between the ages of 15-40 years and were confirmed to have schizophrenia spectrum diagnoses (using the Structured Clinical Interview for DSM-IV-SCID), only one total episode of psychosis, and antipsychotic medication use for six-months or less prior to study enrollment (Kane et al., 2015). Schizophrenia spectrum diagnoses included schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychosis not otherwise specified. Overall, the RAISE-ETP dataset included 404 participants with FEP. Participants from both trial groups (CSC, TAU) were included because the aim of this study was to explore loneliness among people with FEP who are enrolled in treatment. Participants included in this study had complete data for all included measures over their first of year of treatment (n = 161).

Assessments

Loneliness (LN) was assessed using a composite score created from the items on the Psychological Well-Being Scale (PWB) (Ryff, 1989). Two items were selected from the PWB to create the LN composite score: 1) “I often feel lonely because I have few close friends with whom to share my concerns,” and 2) “It seems to me that most other people have more friends than I do.” The first item asks participants to rate their subjective experience of loneliness based

on the presence of companionship. The second item asks participants to rate their perception of having less social support than their peers. The PWB items were self-rated on a scale from one (strongly disagree) to six (strongly agree).

The RAISE-ETP study did not measure LN, so a composite score was necessary, although not ideal. The LN composite items are congruent with items on brief scales shown to be reliable and valid measures of LN in clinical populations. For example, the UCLA 3-Item Loneliness Scale asks the following three questions: "How often do you feel that you lack companionship?", "How often do you feel left out?", and "How often do you feel isolated from others?" (Hughes et al., 2004).

Internalized stigma (IS) was assessed using the Self Rating Stigma Scale (SRSS), which is a seven-item version of the Stigma Scale (King et al., 2007) used in RAISE-ETP (Mueser et al., 2020). Participants were asked to rate perceptions of stigma due to mental illness; items were rated from zero (strongly disagree) to four (strongly agree).

Depression was assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1996). The CDSS is a commonly used nine-item scale administered and scored by trained raters (Addington et al., 1996). Trained raters scored the CDSS on a scale from one (absent) to four (severe). The CDSS is a well-accepted and psychometrically valid measure of depression within populations experiencing psychosis (Addington et al., 1996; Addington et al., 2014).

Motivation (MOT) was assessed using three-items taken from the Intrapsychic Foundations subscale of the Heinrichs-Carpenter Quality of Life Scale (QLS) (Heinrichs et al., 1984). Items 13 (sense of purpose), 14 (degree of motivation), and 15 (curiosity) were used to create the MOT score. These specific items shown convergent validity with other measures of

motivation, as well as have been used in numerous studies to examine motivation in psychosis specific populations (Fervaha et al., 2015; Mueser et al., 2017). All QLS items are rated by trained interviewers; functioning is rated using a scale from zero to six, with higher scores reflecting higher levels of functioning.

Socio-affective capacity (SAC), which is akin to social cognition, was assessed using items 20 (capacity for empathy) and 21 (capacity for engagement with the interviewer) from the QLS Intrapsychic Foundations subscale. Together, these items represent import aspects of social cognition (e.g., theory of mind, social perception) and assess participant abilities to perceive and respond to the emotions or situational perspectives of others (Miley et al., 2021).

Social functioning (SF) was assessed using items two, three, four, five, six, and seven from the Interpersonal Relations subscale of the Heinrichs-Carpenter Quality of Life Scale (QLS) (Heinrichs et al., 1984). This reduced item scale has been shown to specifically assess the inclination to seek out others in their broader social environment (Mueser et al., 2017).

Role functioning (RF) was assessed using the Instrumental Role Functioning scale of the Heinrichs-Carpenter Quality of Life Scale (QLS) (Heinrichs et al., 1984).

Psychosis symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS is scored by trained raters and is scored using the following three subscales: Positive Scale (POS), Negative Scale (NEG), and the General Psychopathology scale.

Anxiety (ANX) was assessed using a composite score generated from the rater-rated anxiety/tension items on the PANSS General Psychopathology subscale.

Mental health recovery (MHR) was assessed using a 15-item version of the Mental Health Recovery Measure (MHRM) (Young & Bullock, 2005). The MHRM is a self-report

measure designed to assess progress toward recovery in populations affected by serious mental illnesses, such as psychosis spectrum disorders. The MHRM was scored in the RAISE-ETP study on a scale from 1 (strongly disagree) to seven (strongly agree); higher scores indicate higher levels of recovery.

General cognition (GCog) was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). The BACS measures six-domains of cognition often associated with impairment and functional outcomes among people experiencing schizophrenia (Keefe et al., 2004). Participants completed the BACS yearly (e.g., baseline and 12-months); the six-domains assessed were: verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency. For this study, a composite standardized z-score was created to reflect GCog by using the total average score from the six-domains assessed.

Suicidal ideation (SI) was captured in the dataset at every six-month follow-up appointment after baseline. Trained CDSS raters asked participants whether they had experienced suicidal ideation since their last assessment. SI is technically assessed as part of the CDSS (item 8), and therefore was not scored separately at the baseline visit. The item was rated in the same manner as the CDSS.

Demographic information used in this analysis was provided by participants at baseline. The following variables were used in this analysis: age, age at first illness, duration of untreated psychosis (DUP), race, ethnicity, and sex (M/F). DUP was defined as time between first psychosis symptoms and the start of antipsychotic medication. Age and DUP variables were log-transformed due to skewness. Treatment group assignment was also included in the analysis to determine if there were causal effects of treatment type. We did not include specific diagnoses into the analysis because all RAISE-ETP participants were carefully assessed using the SCID-IV

and determined to have schizophrenia spectrum diagnoses (e.g., non-affective). The causal discovery algorithm used in this study requires continuous data; therefore, categorical variables were transformed into numeric binary variables for this analysis.

Analysis

Participant data over the first year of treatment was analyzed. There were variations in the cadence of assessments used in the analysis. The LN, IS, and MHR items were assessed at baseline, three-month, six-month, and one-year intervals. The SI variable was assessed at six-months and one-year. The GCog measure was completed at baseline and one-year. We only included participants who had complete data for the first year of treatment.

Baseline Differences

Independent samples t-tests and chi-square tests were used to determine whether participants included and excluded from this study differed significantly at baseline. Demographic and clinical characteristics were examined in R Studio (Core Team, 2015).

Causal Discovery Analysis

Causal discovery methods were used to estimate the causal relations of LN. The use of CDA in various mental health research paradigms has been increasing, largely due to the need to improve intervention outcomes (Anderson et al., 2023; Saxe et al., 2016). CDA identifies causal relations (through mathematical modeling) and creates causal models from observational datasets (Anderson et al., 2023; Eberhardt, 2017; Nogueira et al., 2022). All CDA algorithms aim to produce causal models that best describe the structure of the given data (Anderson et al., 2023; Eberhardt, 2017; Nogueira et al., 2022).

For this analysis, Greedy Fast Causal Inference (GFCI) was used in Tetrad version 7.5.0-0 (Ramsey et al., 2018) to explore and identify a causal model of LN from the RAISE-ETP

dataset. The GFCI algorithm uses a hybrid two-phase process to create causal models, which are output as a Partial Ancestral Graph (PAG). Generally, we are unable to completely determine causal relations from observational data because of statistical equivalence. The PAG signifies a set of causal graphs that correspond with the statistical relations detected in the dataset under the Markov and Faithfulness assumptions. The PAG includes nodes, which represent variables, and edges, which represent the type of causal relation between two nodes.

In the first stage, GFCI assumes there are no latent confounders and uses a score-based method to repetitiously add and remove edges within the large space of possible graphs until it finds the best possible model (typically based on BIC scores) given the data (Anderson et al., 2023; Chickering, 2002; Jabbari & Cooper, 2020; Miley et al., 2021; Ogarrio et al., 2016; Ramsey, 2015). The first stage of GFCI is based on the Greedy Equivalence Search (GES) algorithm, which has been proven to be asymptotically correct (Anderson et al., 2023; Jabbari & Cooper, 2020; Ogarrio et al., 2016). The second stage of GFCI, which uses a constraint-based approach (Fast Causal Inference, FCI), assumes the possibility of latent confounders. Stage two of GFCI uses conditional independence tests to remove irrelevant edges leftover from the first stage; a series of orientation rules are then used to orient the edges based on stage one results (Chickering, 2002; Jabbari & Cooper, 2020; Miley et al., 2021; Ogarrio et al., 2016; Ramsey, 2015). The resulting PAG may contain four different edge orientations (Table 4.1).

After obtaining the PAG, we generated a Mixed Ancestral Graph (MAG), which is one causal structure that is in the equivalent structure of the PAG, to estimate causal effects. The MAG preserves the conditional independence relationships in the PAG and disregards the potential for unmeasured common causes, which permits causal effect estimation by producing causal (-->) or undirected (<->) edges from ambiguous (o-o, o->) PAG edges (Tetrad Manual,

2023; Malinsky & Spirtes, 2016). To estimate causal effects (standardized, raw), a linear SEM was fitted to the MAG using the R package *lavaan* 0.6-15 (Rosseel, 2012), with directional relationships represented as regression paths and non-directional relationships represented as covariances.

The stability of the PAG was also examined by performing a bootstrap analysis in Tetrad version 7.5.0-0 (Ramsey et al., 2018). We used GFCI to run a bootstrap of 1,000 resamples of the data, which indicated the proportion of PAG edges that were corroborated during the procedure.

Post-hoc Analysis

We performed pairwise paired t-tests to assess whether the average mean scores for variables included in the causal model changed over the first year of treatment. Benjamini-Hochberg correction was used to adjust for multiple tests.

Results

Participants

A total of 161 people completed measures at all timepoints over the first year of treatment and were included in this analysis. Missing data resulted in the exclusion of 243 people. Table 4.2 shows the baseline demographic and clinical characteristics for included participants.

Results from the comparison analysis between included/excluded participants indicated several statistically significant baseline mean score differences. Excluded participants had significantly higher mean scores on the CDSS (t = 3.66, p-value = <.001) and ANX (t = 2.55, p-value = 0.011) measures. Excluded participants also had significantly lower baseline mean scores on the SAC (t = -2.2, p-value = 0.028) and GCog (z-score) (t = -2.2, p-value = 0.028) assessments.

Causal Discovery Analysis

The causal model generated by the GFCI analysis, presented in Figure 4.1, incorporates results from both the PAG and MAG. The color of each edge represents the type of causal relationship shown in the original PAG, while the line-type depicts the proportional stability of the PAG edge assessed in the bootstrap analysis. The MAG disregarded the possibility of latent confounders for both ambiguous edge-types (o-o, o->) and oriented o-o edges in a causal direction. Direct causal edges (-->) or undirected edges (<->) found in the PAG were not altered by the MAG. The ambiguous edges found in the PAG are essentially a qualitative finding; the MAG allowed us to quantify the effect size for a single causal outcome in the context of ambiguity. The graph contains the standardized effect size estimations for each included edge. Nodes, with or without edges, that were significantly outside the direct or indirect loneliness causal model were excluded from our graph to enhance clarity.

The resulting graph shows an ambiguous edge, signified by a o-> edge, from baseline loneliness (LN) to LN at three-months (std.ES = 0.44); this edge-type specifies that baseline LN is a causal influence of LN at three-months, or a latent variable has a causal influence on LN at baseline and three-months, or both. If the relationship between LN at baseline and three-months is not confounded, the standardized effect size is 0.44, meaning that increasing baseline LN by one standard deviation results in a 0.44 change in LN at three-months while holding the other variables constant. Internalized stigma is also shown to have an ambiguous edge (o->) with LN at three-months (std.ES = 0.32).

At six-months, LN is shown to be causally influenced by both LN at three-months (std.ES = 0.4) and IS at six-months (std.ES = 0.36). At six-months, LN is shown to have a causal influence on rater-rated social functioning (SF) (std.ES = -0.19) and self-reported mental health recovery (MHR) (std.ES = -0.25). Several other variables converged with LN at six-months as

causal influences on both SF and MHR at six-months. Baseline SF was shown to causally influence SF at six-months (std.ES = 0.34), while rater-rated MOT at six-months was shown to have ambiguous causal edges (o->) with both SF (std.ES = 0.27) and MHR (0.24) at six-months, which was also causally influenced by MHR at three-months (std.ES = 0.64).

At the one-year timepoint, LN was solely causally influenced by LN at six-months (std.ES = 0.56). At 12-months, LN was shown as one of several causal influences of SF at 12-months (std.ES = -0.23). Baseline SF (std.ES = 0.31) and SF at six-months (std.ES = 0.37) were also shown to causally influence SF at 12-months.

With the possible exception of the ambiguous edge (o->) between LN at baseline and three-months, our causal model indicated that LN is only causally influenced by IS and LN. The causal model also indicated that, apart from an ambiguous edge (o-o) between anxiety (ANX) and IS at baseline, IS may be the only causal influence of later IS. Baseline IS was shown as the sole causal influence of IS at three-months (std.ES = 0.5). IS at six-months is solely causally influenced by IS at three-months (std.ES = 0.67), while IS at 12-months is solely causally influenced by IS at six-months (std.ES = 0.66). The ambiguous edge (o-o) between baseline ANX and IS means that confounding variables could be influencing this relationship; if there was no confounding, the standardized causal effect size is 0.28.

Our exploratory causal model showed no direct causal relationships between LN and depression (CDSS), anxiety (ANX), positive (POS) or negative (NEG) psychosis symptoms, socio-affective capacity (SAC), or general cognition (GCog) at any timepoint. There were also no causal relationships (direct or indirect) detected between LN and demographic variables (log-age, age at first illness, log-DUP, race, ethnicity, sex) or between LN and treatment condition (CSC or TAU) variables.

Graph Stability

The results from the bootstrap resampling procedure showed varying levels of stability among the edges in the original PAG. The ambiguous edge (o->) from LN at baseline to three-months was corroborated approximately 54% of the time. The causal edges between loneliness at three- and six-months (77%) and six- and 12-months (84%) increased in stability. The ambiguous causal edge (o->) from IS at three-months to LN at three-months was replicated in about 26% of the resamples; however, a direct causal edge (-->) from IS at three-months to LN at three-months was found in almost 34% of the bootstrap resamples. The direct causal edge from IS at six-months to LN at six-months was more stable (64%).

The direct causal edge between IS at baseline and three-months was replicated in about 35% of the resamples. The causal edge between IS at three- and six-months was more stable (57%). Regarding IS, the most stable causal edge was between six- and 12-months (83%).

Several of the original PAG edges were not replicated during the bootstrap procedure, which likely indicates weak relationships. The causal edges from LN to MHR at six-months, and from LN to SF at both six- and 12-months were dropped in the bootstrap analysis. Additional dropped edges included: 1) MOT at six-months to MHR at six-months, 2) MOT six-months to MOT at 12-months, 3) IS at three-months to MHR at three-months, 4) baseline SF to baseline NEG, 5) baseline NEG to SAC at six-months, 5) SAC at six-months to NA at 12-months, 6) SAC at baseline to SAC at 12-months, 7) baseline CDSS to baseline MHR, 8) baseline ANX to baseline IS, 9) baseline ANX to baseline POS, and 10) baseline MOT to baseline POS. A complete table of bootstrap findings can be found in Appendix H.

Post-hoc Analysis

The statistically significant results for the post-hoc pairwise paired t-tests with a Benjamini-Hochberg correction were as follows. LN mean scores improved between baseline ($m = 7.96$, $sd = 2.89$) and three-months, ($m = 7.29$, $sd = 2.84$) ($p < 0.01$), baseline and six-months ($m = 6.94$, $sd = 2.84$) ($p < 0.001$), and baseline and 12-months ($m = 6.95$, $sd = 2.74$) ($p < 0.001$). IS mean scores improved between baseline ($m = 28.5$, $sd = 7.89$) and three-months ($m = 25.8$, $sd = 8.84$) ($p < 0.001$), baseline and six-months ($m = 25.4$, $sd = 9$) ($p < 0.001$), and baseline and 12-months ($m = 26.2$, $sd = 9.37$) ($p < 0.01$). MHR mean scores improved from baseline ($m = 74.7$, $sd = 17.6$) to three-months ($m = 77.7$, $sd = 16.5$) ($p < 0.05$), baseline to six-months ($m = 78.9$, $sd = 15.7$) ($p < 0.01$), baseline to 12-months ($m = 80.4$, $sd = 15.8$) ($p < 0.001$), and three- to 12-months ($p < 0.05$).

MOT mean scores improved between baseline ($m = 7.86$, $sd = 3.46$) and six-months ($m = 8.89$, $sd = 3.54$) ($p = 0.003$). Mean scores for SF improved from baseline ($m = 14.4$, $sd = 6.83$) to six-months ($m = 17$, $sd = 7.92$) ($p < 0.0001$) and baseline to 12-months ($m = 17.6$, $sd = 8.05$) ($p < 0.0001$). Mean scores for NEG showed improvement from baseline ($m = 20.2$, $sd = 5.48$) to six-months ($m = 18.5$, $sd = 5.75$) ($p < 0.001$) and baseline to 12-months ($m = 18.4$, $sd = 5.71$) ($p < 0.001$). CDSS mean scores showed improvement between baseline ($m = 12.7$, $sd = 3.72$) and 12-months ($m = 11.4$, $sd = 3.38$) ($p < 0.001$) and between six- ($m = 12.3$, $sd = 4.06$) and 12-months ($p < 0.01$). Mean scores for ANX improved from baseline ($m = 4.55$, $sd = 2.35$) to 12-months ($m = 3.73$, $sd = 2.26$) ($p = 0.001$) and from six- ($m = 4.24$, $sd = 2.26$) to 12-months ($p < 0.05$). Please see Table 4.3 for post-hoc results for all variables included in the causal model.

Discussion

We conducted an exploratory causal discovery analysis (CDA) of loneliness using data over the first year of treatment for participants in both arms of the RAISE-ETP study. The aim of

this analysis was to identify preliminary causal relationships of loneliness among a clinical sample of people enrolled in treatment for first-episode psychosis (FEP) across the United States. All participants in the RAISE-ETP study met strict inclusion criteria for FEP. Because CDA with the GFCI algorithm requires complete data, incompleteness was addressed in the data by removing participants with missing data over their first year of treatment. We did not find any causal relationships between treatment group assignment and loneliness, which affirmed the choice to treat the analysis as uncontrolled.

There were some ambiguous edges (o->, o-o) in terms of the causal relationships observed among the variables of the interest. The ambiguity observed in some of the causal edges represented the qualitative possibilities between two nodes. The MAG provided a quantitative result for the chosen edge orientation among the given array of possibilities.

The causal model indicated the possibility of a latent variable (o->) influencing the relations between loneliness (LN) at baseline and three-months, and between internalized stigma (IS) and LN at three-months, respectively. Regarding possible latent variables that could be influencing these relationships, self-esteem may be of interest. Research has shown that self-esteem has a strong positive correlation with LN (Ludwig et al., 2020; Switaj et al., 2015), as well as a strong negative correlation with IS (Sarraf et al., 2022).

The causal model showed that there may be an early relationship between internalized stigma (IS) and loneliness (LN). IS was shown as a possible causal influence of LN at three-months and a relatively stable cause of LN at six-months. The associated standardized effect of the causal influence of IS on LN at both timepoints was similar, but not large (0.32 and 0.36).

There was not a causal relationship detected between LN and IS after the first six-months of treatment in the given sample. At one-year, each respective variable was solely caused by their respective six-month counterpart.

Both LN and IS showed similar behavior in the context of the broader treatment environment. For example, our post-hoc analyses indicated both variables exhibited significant improvement in average mean scores during the first three-months of treatment, with no statistically significant differences detected between average mean scores at the three-, six-, and 12-month timepoints. Neither variable appeared to be the direct consequence of clinical psychosis symptoms/common FEP treatment targets (except for *possibly* baseline IS), but both variables *may* causally influence common FEP treatment targets (recovery attitudes in the case of both, social functioning in the case of LN specifically). Lastly, both LN and IS were shown in the causal model to be the primary causal influences of later same-variable experiences during the first year of treatment. Each same-variable cascade appeared to have relatively stable edges and moderate-to-large effects on later same-variable measurement timepoints.

Two unstable edges indicating LN as a causal influence of social functioning (SF) at six- and 12-months were observed in the model. The standardized effect sizes for LN on SF were small for both edges. While this result should be interpreted cautiously, it does warrant some attention because 1) SF is a critical aspect of overall human health, and 2) socializing with peers is a critical aspect of development for adolescents and young adults (Green et al., 2018; Larsen & Luna, 2018; Luciana & Collins, 2021). Previous studies in the general population have shown that LN may impact social functioning among adolescents and adults (Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010; Vanhalst et al., 2017), while previous studies among

psychosis specific populations have shown that SF is strongly correlated with ongoing disability (Addington et al., 2008; Alvarez-Jimenez, et al., 2012; Burton et al., 2019).

In the context of intervention, one cannot expect to change an outcome if the cause(s) of that outcome are not direct treatment targets (Saxe et al., 2022; Saxe et al., 2016). Although we cannot be sure that LN had a meaningful causal influence on SF for participants included in this analysis, research has shown that SF outcomes among psychosis populations have been modest (Fowler et al., 2019; Hodgekins et al., 2015; Lysaker et al., 2021). There is a significant need to better understand the causes of SF difficulties across the psychosis spectrum.

Interestingly, the causal model showed that LN did not have causal relations with several key psychosis treatment targets. For example, LN was not a cause or consequence of rater-rated positive (POS) or negative (NEG) symptoms, motivation (MOT), depression, anxiety, socio-affective capacity (SAC), or general cognition. Previous correlational research among psychosis populations has been mixed regarding the relationship between LN and POS (Angell & Test, 2002; Badcock et al., 2015; Culbreth et al., 2021; Ludwig et al., 2020; Steenkamp et al., 2022; Switaj et al., 2014), NEG/MOT (Badcock et al., 2015; Culbreth et al., 2021; Lim et al., 2018; Ludwig et al., 2020), and social cognition (Tremeau et al., 2016; Ludwig et al., 2020). What we did observe in the exploratory causal model was that LN converged with both NEG and MOT as an additional causal influence of SF and mental health recovery (MHR) at six-months.

Few studies have examined LN and anxiety within the psychosis spectrum, but they have generally reported strong correlations (Leathem et al., 2021; Lim et al., 2018; Steenkamp et al., 2022; Sunderman et al., 2014). However, depression and LN have been consistently shown to have a strong positive association on self-report or rater-rated measures of depression (Culbreth et al., 2021; Lim et al., 2020; Ludwig et al., 2020; Sundermann et al., 2014; Switaj et al., 2018;

Switaj et al., 2014). The complete lack of causal relation between LN and CDSS in this analysis was unexpected. The people included in our analysis were, on average, less depressed than those who were excluded. Most of the studies of LN within the psychosis spectrum have recruited general or prolonged psychosis populations, which means those participants, on average, were older than the average age of RAISE-ETP participants. Many studies of loneliness within the psychosis spectrum have used self-report measures of depression. It is unclear if the absence of a causal relationship between LN and CDSS in this study was due to our inclusion/exclusion criteria (e.g., complete cases), possible differences in developmental stages, possible differences in self-report and rater-rated measures, or simply because there was no causal relation.

Overall, the findings from our exploratory causal model are somewhat consistent with theories of loneliness. We found probable causal links between internalized stigma and loneliness, particularly in the first six-months of treatment, which is consistent with aspects of the conceptual models proposed by Lim et al. (2018) and Badcock et al. (2020). We also found some evidence for the negative influence of both loneliness and internalized stigma on attitudes of mental health recovery, which is congruent with the broader model prosed by Capaccio and Hawkley (2009).

Limitations

There are several notable limitations of this study. Due to the absence of a validated measure, LN was measured using a composite score of two Psychological Well-Being Scale (PWB) items. Both PWB items ask participants to rate their perceived levels of companionship and social support; however, a psychometrically sound measure of loneliness would increase some confidence in our preliminary findings. The items selected for inclusion in this study were

consistent with items included on the UCLA 3-Item Loneliness scale, which has been shown to be a valid short-form assessment of loneliness among clinical populations (Hughes et al., 2004).

While the sample size of included participants and number of timepoints was adequate to perform the GFCI analysis, a larger sample would increase confidence in the overall causal model. For example, a larger sample with a minimum of three timepoints may have allowed us to discern a greater number of causal relations at baseline. Our current model showed ambiguous findings at baseline (o-o, o->) that could have implications on the final causal model. Additionally, a larger sample would increase confidence that the causal edges shown in our model are oriented in the proper causal direction.

Similarly, a more representative sample would improve confidence in the overall causal model. Regarding the sample characteristics, we are limited by our own inclusion criteria (e.g., complete cases), as well as the strict inclusion criteria used for the RAISE-ETP study. Those included in our analysis had, on average, less depression and anxiety with higher socio-affective capacity and general cognition than those excluded from the analysis due to missing data. Moreover, the RAISE-ETP criteria was strictly adhered to regarding how researchers defined FEP, which is likely not representative of the people generally served in community-based early psychosis treatment programs.

Overall, these limitations limit our ability to interpret the causal model more broadly. For example, we may have a causal model of LN for people with schizophrenia spectrum diagnoses who are likely *engaged* in the first year of their treatment experience, which could reasonably result from being less symptomatic and higher functioning at baseline in several important domains. While the preliminary findings make important contributions to the existing literature,

more research is needed to understand the causal relationships of loneliness in early or FEP populations.

Future Directions

Longitudinal causal research is needed to provide clarity regarding the causal relationships of LN and related factors among people experiencing early psychosis/FEP. Studies of this type are needed to determine the causal cascade(s) pertaining to under-researched phenomena such as loneliness, internalized stigma, and recovery attitudes along with clinical factors such as psychosis symptoms and functional outcomes. A limitation of much of the clinical literature is the predominance of correlational studies. Unlike correlational work, causal methods (either through CDA or RCTs when feasible) are better able to discern causal from non-causal correlates (which includes determining causes from consequences) (Saxe et al., 2022), which may in turn have a significant impact on the development of efficacious interventions (Saxe et al., 2022; Saxe et al., 2016). Additional longitudinal work in this domain would also help determine whether overall treatment trajectories are influenced by the presence or severity of LN or internalized stigma.

It is unclear whether there are differences that impact LN and overall causal relations based on developmental stage. For example, we do not know if populations with early (or first-episode) psychosis rate or report their experiences of LN (and related factors) differently than people with prolonged psychosis. Further, we do not know whether people who experience psychosis make meaning of their subjective and/or clinical experiences differently based on their developmental stage and/or life experiences. Additional research using qualitative or mixed methods would help determine whether there are potential developmental differences pertaining to perceived causes and consequences of loneliness.

Clinically, our preliminary findings suggest that loneliness is not a direct consequence of primary psychosis symptoms but may be a causal contributor to important outcomes. Therefore, we may want to avoid assumptions about loneliness based on the presence/absence of common clinical symptoms. While ongoing assessment of loneliness or internalized stigma is not a unified practice among CSC programs, our preliminary findings suggest that clinicians and researchers may want to assess the presence and severity of LN and IS throughout treatment. The goal of CSC programs is to enhance functional outcomes and the quality-of-life (QOL) for participants (Kane et al., 2016; Kane et al., 2015), but uninterrupted experiences of LN or IS could reasonably reduce QOL and potentially inhibit functional recovery. Brief scales, such as the UCLA 3-Item Loneliness scale and the Internalized Stigma of Mental Illness Scale - Abbreviated (ISMI-10) could be incorporated into clinical care and research paradigms with relative ease. If using a standardized measure is not an option for clinical care, our preliminary findings suggest that clinicians may want to consider asking participants about their experiences with LN and IS. Regarding LN, clinicians could simply ask if someone has companionship when wanted, feels left out, or ever feels lonely.

Conclusion

To our knowledge, this is the first study to explore loneliness in a FEP population using causal discovery methods. Findings should be interpreted with caution due to the preliminary nature of this study, as well as potential issues with representativeness related to the sample used for the analysis. The primary outcomes of this analysis showed possible causal relationships between loneliness, internalized stigma, social functioning, and mental health recovery ratings. We found no direct causal relationships between loneliness and rater-rated depression, anxiety, or

psychosis symptoms. Additionally, we found that loneliness was the strongest causal influence on later experiences of loneliness during the first year of treatment.

Table 4.1

Partial Ancestral Graph (PAG) Edge Types

Edge Type	Present Relationships	Absent Relationships
A --> B	A is a cause of B. It may be a direct or indirect cause that could include other measured variables. There could also be an unmeasured confounder of A and B.	B is not a cause of A.
A <-> B	There is an unmeasured variable (L) that is a cause of A and B. There may be measured variables along the causal pathway from L to A or from L to B.	A is not a cause of B. B is not a cause of A.
A o-> B	Either A is a cause of B (-->), or there is an unmeasured confounder of A and B (<->), or both.	B is not a cause of A.
A o-o B	One of the following is true: 1) A is a cause of B, 2) B is a cause of A, 3) there is an unmeasured confounder of A and B, 4) both 1 and 3, 5) both 2 and 3.	

Note: Adapted from *Tetrad Manual* (2023), Center for Causal Discovery, Retrieved from:

https://cmu-phil.github.io/tetrad/manual/.

Table 4.2

RAISE-ETP Demographic and Clinical Characteristics

	(n=161)	
	Mean or %	(SD)
Demographics		
Age (years)	23.8	(4.9)
Sex (male)	78%	
Racial background		
American Indian/ Alaska Native	5.0%	
Asian	2.5%	
Native Hawaiian or Other Pacific Islander	0.6%	
Black or African American	29.8%	
White	62.1%	
Ethnicity: Hispanic or Latino	16%	
Baseline Variables		
Age of first illness	16.4	(6.4)
Duration of untreated psychosis (DUP) (weeks)	169.4	(213.6)
Treatment group assignment (CSC)	58%	
Loneliness	8	(2.9)
Self Rating Stigma Scale	28.5	(7.9)
Calgary Depression Scale for Schizophrenia	12.7	(3.7)
PANSS negative symptoms	20.2	(5.5)
PANSS positive symptoms	18.7	(5.1)
Anxiety (PANSS)	4.5	(2.3)
Mental Health Recovery Measure	74.7	(17.6)
QLS motivation	7.9	(3.5)
QLS socio-affective capacity	8.1	(2.2)
QLS social functioning	14.4	(6.8)
QLS role functioning	5.4	(6.7)
General Cognition Z-score	0.13	(0.9)

Note: PANSS = Positive and Negative Syndrome Scale, QLS = Heinrichs-Carpenter Quality of Life Scale.

Figure 4.1

Preliminary Causal Model of Loneliness in a First-Episode Psychosis Sample

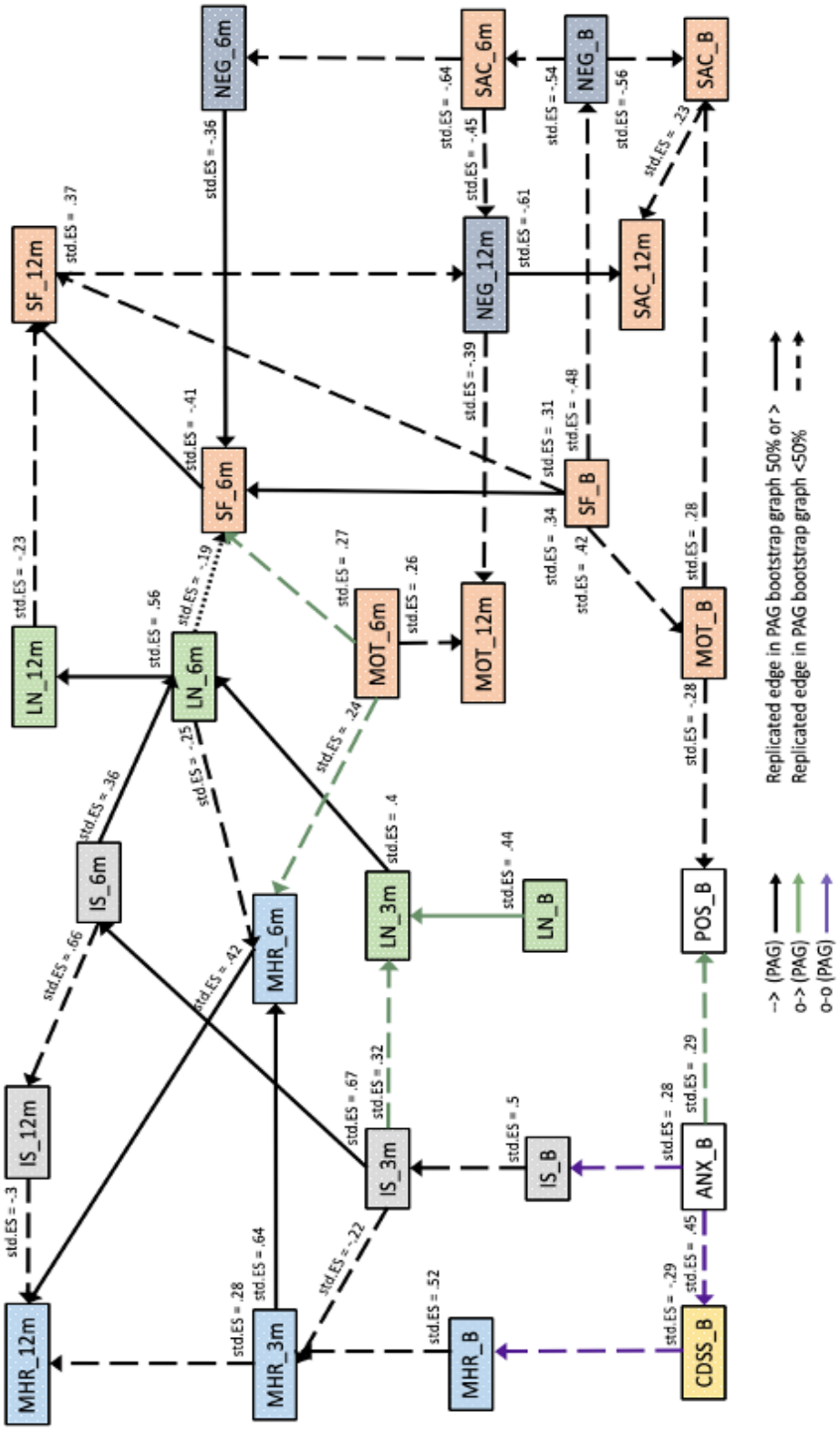

Table 4.3

Pairwise Paired T-test Results for RAISE-ETP Participants Over the First Year of Treatment for Variables Included in the Causal Model

	Mean Score Difference Between Timepoints					
Measure	B – 3m	B – 6m	B – 12m	3m – 6m	3m –12m	6m – 12m
LN	0.67**	1.02***	1.01***	0.35	0.34	-0.01
IS	2.7***	3.1***	2.3**	0.4	-0.4	-0.8
MHR	-3*	-4.2**	-5.7***	-1.2	-2.7	-1.5
MOT		-1.03**	-0.59			0.44
SAC		0.06	-0.09			-0.15
SF		-2.6****	-3.2****			-0.6
NEG		1.7***	1.8***			0.1
POS		2.7****	3.7****			1*
CDSS		0.4	1.3***			0.9
ANX		0.31	0.82**			0.51*

Note: Mean score differences were calculated by subtracting the second listed timepoint from the first listed timepoint. All p-values were adjusted for multiple tests with Benjamini-Hochberg; p-values **** < .0001, *** < .001, ** < .01, * < .05.

CHAPTER 5: GENERAL DISCUSSION

The three studies presented here explored the causal relationships of loneliness (LN) among persons affected by psychosis using causal discovery analysis (CDA) methods. Each of the three studies explored LN in the context of three distinct psychosis populations. The first study, ***Predictors and Possible Causes of Loneliness Within a General Psychosis Spectrum Sample***, included a general psychosis (GP) sample. The second study, ***An Initial Causal Structure of Loneliness Among People with Early Psychosis Enrolled in Coordinated Specialty Care***, included a broadly defined early psychosis (EP) sample. The third study, ***Uncovering a Preliminary Causal Model of Loneliness within a First-Episode Psychosis Sample Over the First Year of Treatment***, included a specifically defined first-episode psychosis (FEP) sample. The average ages of people included in each of three studies were as follows: 33.4 years (SD = 10.8) in the GP sample, 22.6 years (SD = 5.9) in the EP sample, and 23.8 years (SD = 4.9) in the FEP sample. The GP and FEP samples were geographically diverse, while the EP sample was comprised of people receiving CSC services in Minnesota. The GP and EP samples had confirmed psychosis spectrum diagnoses, while the FEP sample consisted of people with diagnoses from within the schizophrenia spectrum only.

All three study samples were receiving some form of treatment or intervention. The GP sample differentially received cognitive training based on their randomization to either the TCT or CG group; however, the entire sample had access to the PRIME application, which provided both motivational support and a supportive online community of peers (Fisher et al., 2023). Participants included in the EP sample were all enrolled in community-based CSC programs for early psychosis. The RAISE-ETP participants were also enrolled in community-based mental healthcare; however, participants received either NAV or TAU based on site randomization.

Treatment group was not part of the causal network for either the GP or FEP sample, nor was it correlated with loneliness in the linear mixed model for the GP sample.

Each of the three samples were constrained, either by initial recruitment criteria and/or the data processing procedures required for each of the analyses. The results of each of the three studies, individually and taken together, are preliminary and should therefore be interpreted with some caution. While the individual and overall findings are preliminary, these studies have provided several important contributions to the overall literature focused on LN in psychosis.

Summary of Findings & Contributions

Loneliness

Loneliness (LN) was shown as a primary causal influence of later LN for the GP and FEP samples, while the causal relationship between LN at baseline and six-months was mediated by self-reported depression at six-months in the EP sample. In the GP sample, baseline LN was the only direct causal influence of LN at four-months (std.ES = 0.74), which was the only direct causal influence on LN at six-months (std.ES = 0.82). The magnitude of the causal effect of LN was relatively large for each timepoint for the GP sample. In the FEP sample, baseline LN was shown as a possible causal influence (o->) of LN at three-months (0.44). At three-months, LN was shown as a direct causal influence of LN at six-months (std.ES = 0.4), which was the only causal influence of LN at 12-months (std.ES = 0.56). The magnitude of the causal effect of LN on later LN within the FEP sample was moderate and less robust when compared to the GP sample. The magnitude of the causal effect of LN on later LN increased as time progressed for both the GP and FEP samples.

Regarding average mean score changes in LN over time, the three studies showed similar results. There was no reported statistically significant improvement in average LN mean scores

for the GP sample (Fischer et a., 2023). Post-hoc analyses revealed statistically significant improvement in average LN mean scores over the first six-months (approximately) of treatment for the EP sample, and over the first three-months of treatment for the FEP sample. While we were unable to assess LN for time periods exceeding six-months within the GP or EP samples, no statistically significant improvements in average LN mean scores were observed between the three-, six-, and 12-month treatment timepoints for the FEP sample.

Several preliminary patterns were observed that contribute to the existing LN and psychosis literature. The causal influence of LN on later LN appeared to have a larger causal effect among the generally older GP sample when compared to the generally younger FEP sample. LN appeared to be mostly self-sustaining within both the GP and EP samples; however, self-reported depression appeared to be both a causal influence and consequence of LN in the EP sample. For both the GP and FEP samples, LN did not appear to be a primary consequence of common psychosis treatment targets (e.g., clinical, functional, cognitive variables); while the EP sample was shown as a *possible* consequence of self-reported depression and behavioral inhibition (BIS). Across all three samples, LN was observed to have a causal relationship with internalized stigma (IS) or perceived discrimination (InDI-D). These preliminary patterns are consistent with some propositions of the social cognitive model of loneliness (Cacioppo et al., 2006; Cacioppo & Hawkley, 2009; Hawkley & Cacioppo, 2010) (Appendix A), which suggests that LN may be a self-sustaining process that can influence mood and social perception.

Internalized Stigma and Perceived Discrimination

Across all three causal models, LN was shown to have a causal (or possibly causal) relationship with internalized stigma (IS) or day-to-day discrimination experiences (InDI-D). In the GP sample, LN at four-months was shown as a direct causal influence of IS, as measured by

the ISMI, at four-months (std.ES = 0.51). In the EP sample, baseline LN was shown as a possible causal influence of baseline InDI-D (std.ES range = 0.32, 0.46). The edge from LN to InDI-D in the EP sample was ambiguous, signified by an o-> edge, which denotes that baseline LN may causally influence InDI-D, or a latent variable may be causally influencing both LN and InDI-D, or both. In the FEP sample, IS at three-months, as measured by the SRSS, was shown to have an ambiguous (o->) relationship with LN at three-months (std.ES = 0.32). At six-months, we saw that IS was a direct causal influence of LN (std.ES = 0.36). The orientation of the causal edge was reversed for the FEP sample when compared to the GP and EP samples. The magnitude of the causal effect of LN on IS/InDI-D was largest for the GP population; however, the upper and lower values in the EP sample causal effect range were similar with the causal effect estimates observed for the GP and FEP samples, respectively.

Several preliminary patterns were observed that may add to the existing literature. The largest effect size estimate between LN and IS/InDI-D was observed in the GP sample. Across all three studies, IS/InDI-D were the primary causal influences of later IS/InDI-D. There were no reported statistically significant improvements in average IS mean scores in the GP sample (Fisher et al., 2023). Post-hoc analyses revealed 1) no statistically significant change in average mean scores for InDI-D in the EP sample, and 2) a statistically significant improvement in average IS mean scores from baseline to three-months only among the FEP sample. The above findings are comparable to what was observed for LN.

Collectively, our preliminary findings showing causal (or possibly causal) relations between LN and IS/InDI-D are somewhat consistent with proposed conceptual models of LN and psychosis. The conceptual model proposed by Lim et al. (2018) (Appendix B) suggests that LN may have reciprocal relationships with clinical and social factors across several domains, one

being societal perception (internalized stigma, perceived discrimination). While we do not have preliminary evidence supporting reciprocal relations, the preliminary findings across each study provide some support for a causal relationship between LN and the societal perception domain.

The conceptual model proposed by Badcock et al. (2020) (Appendix C), suggests a feedback loop exists between psychosis, IS, social withdrawal, and LN. Again, the preliminary findings across all three studies lend some support for causal relationships between LN and IS/InDI-D experiences; however, the findings presented here appear to show a more direct causal relationship between LN and IS/InDI-D. There were no causal relationships observed between psychosis symptoms (POS/NEG) and IS/InDI-D across the three preliminary models. Notably, GFCI is an acyclical algorithm, meaning these preliminary findings cannot rule out the possibility of reciprocal or cyclical relationships.

Clinical Mental Health Outcomes

The three preliminary causal models displayed mixed findings regarding causal relations between LN and depression. The GP and EP studies both assessed self-reported depression (DEP), which produced different edge-types and orientations. For the GP sample, there was no direct causal relationship depicted between baseline LN and DEP (BDI-II); there was an ambiguous (o-o) edge observed between baseline DEP and baseline self-reported motivation to engage in activities (MEA), which was shown as a *possible* causal influence of baseline LN. At four-months, LN was shown as a direct causal influence on DEP. For the EP sample, using the pooled causal model, baseline DEP (MSSC) was shown to have an ambiguous (o-o) relationship with baseline LN, but this relationship may be confounded. Baseline LN was shown as causal influence of DEP at six-months, which was then shown to causally influence LN at six-months.

The same rater-rated assessment of depression (CDSS) was used among the EP and FEP samples. In the pooled EP causal model, LN at six-months was shown as a possible direct causal influence on CDSS at six-months (std.ES range .53, .63). This edge was dropped during the bootstrap procedures, which indicates the edge was unstable across the 10 imputed datasets. The causal model for the FEP sample showed no causal relationship between LN and CDSS at any timepoint over the first year of treatment.

There were also mixed findings across all three studies for motivation. The studies with GP and EP samples incorporated self-rated measures of motivation. For the GP sample, an ambiguous relationship (o-o) was observed between baseline motivation to engage in activities (MEA), as assessed by the MAPS-SR, and baseline LN (possible std.ES = -0.56). Baseline MEA also shared ambiguous edges (o-o) with the following variables at baseline: motivation for close relationships (MCR), DEP (BDI-II), and IS (ISMI). At four-months, a different ambiguous edge type (o->) showed LN as a possible causal influence of MEA.

For the EP pooled causal model, self-rated motivation was assessed using the BIS/BAS and MSSC. We saw that behavioral inhibition (BIS) at six-months was shown to causally influence LN at six-months (this edge was dropped during the bootstrap resamples). There were no causal relations observed between LN and any of the behavioral activation (BAS) subscales (drive, reward, fun). At six-months, the self-rated MSSC motivation item was shown to have a possible indirect (mediated) causal influence on LN (through the causal influence on DEP at six-months).

The QLS, which is rater-rated, was used to assess motivation (MOT) in the GP and FEP samples. In the GP sample, baseline LN was shown as a causal influence of MOT at four-months. In the FEP sample, there was no direct edge between LN and MOT at any timepoint

over the first year of treatment; LN was observed to converge with MOT to causally influence self-rated mental health recovery attitudes (MHR) and rater-rated social functioning (SF) at six-months (MOT was shown to have a o-> edge for both variables).

Negative symptoms of psychosis (NEG), for which impaired motivation is a key feature, were also assessed among the GP and FEP samples using standardized rater-rated interviews. In the GP sample, NEG (QSANS) were included as one of three significant predictors of LN in the reduced linear mixed model ($\beta = 0.11$, SE = 0.04, CI [0.04, 0.19], $p = 0.003$). However, the preliminary causal model for the GP sample showed no direct causal relations between LN and NEG. Both variables converged on MOT at four-months; baseline LN was shown as a causal influence of MOT at four-months, while QSANS at four-months was shown to have an ambiguous (o->) causal relationship with MOT at four-months. In the FEP sample, there were no direct causal relations observed between LN and NEG (PANSS) over the first year of treatment. Both LN and NEG variables converged at six-months as causal influences of SF.

There were no direct causal relations observed between LN and the following clinical mental health variables at any timepoint across all three studies: rater-rated positive symptoms (POS) in GP or FEP sample (measured by QSAPS, PANSS), anxiety (ANX) in the EP (self-rated MSSC) or FEP (rater-rated PANSS) samples, self-rated symptom distress (IMR-SD) in the EP sample, self-rated trauma exposure (LEC-5) in the EP sample, defeatist beliefs (DB) in the GP sample, and SI in the EP and FEP samples.

These preliminary findings contribute to the broader literature in the following ways. The causal relationships observed between LN and DEP (and *possibly* CDSS in the case of the EP sample) provides some support for the conceptual model proposed by Lim et al. (2018); however, LN was shown as a both a cause and consequence of DEP among the GP and EP

samples. While our findings cannot provide support for a reciprocal causal relationship, it is possible that LN and DEP may interact differently across different psychosis populations. The initial findings regarding LN and DEP may indicate that self-rated depression could be more causally related to LN than rater-rated depression in EP/FEP samples.

Motivation, which is a significant issue in psychosis, was not shown to have consistent causal relationships with LN across the three studies. The conceptual models of LN and psychosis proposed by Lim et al. (2018) and Badcock et al. (2020) both suggest that psychosis symptoms have a causal influence on LN. There were only two timepoints across all three studies where motivation *may* have had a direct causal influence on LN; there was an ambiguous edge (o-o) between baseline MEA and LN in the GP sample, and an unstable causal edge between BIS and LN at six-months in the EP sample. Self-rated motivation was shown as a possible indirect causal influence on LN at six-months (mediated by DEP at six-months) in the EP sample. Regarding the GP and EP sample findings, there was some weak support that MEA or BIS, which could both be indicators of social withdrawal (as depicted in the Badcock et al., 2020 conceptual model), may have a direct causal influence on LN.

More broadly, across the preliminary models, there were no direct causal relationships detected between LN and psychosis symptoms (POS/NEG). LN and NEG were shown to converge on MOT at four-months in the GP sample and both MHR and SF in the FEP sample. Outside of self-reported depression, and possibly motivation, clinical mental health symptoms appeared to have a minimal causal impact on LN across all three preliminary models. Loneliness was observed as a possible, but generally weak causal influence (based on associated causal effect size, bootstrap edge replication, or both) on clinical variables in our three preliminary models. Taken together, the preliminary models were not able to provide support for the

proposed role of clinical symptoms in the conceptual frameworks proposed by Lim et al. (2018) or Badcock et al. (2020). Notably, our inability to provide support for the proposed role of clinical symptoms in the development or maintenance of LN could be due to limitations associated with our preliminary causal models, limitations associated with correlational research (which both frameworks are largely based), or both.

Functional Outcomes

All three studies included assessments of functional outcomes. The rater-rated QLS was used to assess social functioning (SF) and occupational (OF) or role (RF) functioning for the GP and FEP samples; functioning in the EP sample was assessed using self-rated IMR items, which asked participants to rate their functional impairment (IMR-FI), time spent in structured roles (IMR-TSR), and degree of contact with people outside of family (IMR-OC). The participants in the EP sample were also asked to indicate whether friends were a part of their natural support system (yes/no) (FRNS). Recovery attitudes were also assessed in the FEP sample using the MHR.

Direct causal edges were observed between LN and SF in the FEP group only. At both six- and 12-months, LN was shown as a possible causal influence on SF at six- and 12-months; however, the magnitude of the causal effect for each edge was small, and both edges appeared unstable due to being dropped during the bootstrap procedure. There were no direct or indirect edges observed in the pooled findings between LN and IMR-OC or LN and FRNS in the EP sample. One indirect edge was observed in the pooled findings from the EP sample; at six-months, IMR-FI causally influenced DEP at six-months, which was a causal influence of LN at six-months. There were no direct or indirect causal influences observed between LN and measures of OF/RF in the GP and FEP samples, or between LN and IMR-TSR in the EP sample.

We observed a potential relationship showing LN as a causal influence of recovery attitudes (MHR) at six-months in the FEP sample; however, this relationship was dropped from the bootstrap resampling procedure indicating that the edge was unstable. There were no direct relationships observed between LN and MHR at any other timepoint over the first year of treatment in the FEP group. Recovery attitudes were not assessed within the GP or EP samples.

The preliminary functional findings provide some evidence that LN may be a causal influence of rater-rated SF in the FEP sample; however no direct edges between LN and rater-rated SF were found in the GP sample or between LN and IMR-OC or FRNS in the EP sample. An indirect causal influence was detected for IMR-FI in the pooled EP causal model, where IMR-FI causally influenced DEP, which was a direct causal influence of LN. Based on the preliminary models, it is unclear whether social functioning is causally influenced by LN or whether the causal influence of LN on SF could differ based on development.

These preliminary findings provide limited support for the conceptual model suggested by Lim et al. (2018). Lim's model proposes reciprocal relationships between LN and domains of social support (structural, functional) and well-being (quality of life, recovery). In the FEP sample, we found relatively weak and unstable relationships between LN and SF at the six- and 12-month timepoints, while no direct causal relations were observed between LN and SF, IMR-OC, or FRNS in the respective GP and EP samples. Across the three studies, there were no causal relations detected between LN and occupational/role functioning variables (OF, RF, IMR-TSR). In the FEP sample, we did find a weak causal edge showing LN at six-months was a causal influence on MHR at six-months for the FEP sample. This relationship was only observed at one of four timepoints over the first year of treatment, whereas IS was shown to have a possible causal influence on MHR at three- and 12-month timepoints. Overall, these results may suggest

that the presence of non-familial others, role functioning (work, school, etc.) may not have a causal influence on LN among people with psychosis. Importantly, scores obtained from the QLS and IMR scales are more likely to reflect the objective experience of isolation versus the subjective experience of LN.

Cognitive Outcomes

Aspects of social cognition were assessed in our GP and FEP samples. Emotion recognition was assessed in the GP sample using the ER-40 task. There were no causal edges observed between LN and ER-40 measures at any timepoint. Socio-affective capacity (SAC), which was a composite score using items from the rater-rated QLS, was assessed in the FEP group. There were no causal edges observed between LN and SAC at any timepoint over the first year of treatment. General cognition (GCog) was assessed in the FEP sample using a composite z-score. There was no causal edge between LN and GCog detected over the first year of treatment for the FEP group.

The current literature regarding LN, cognition, and psychosis is limited. We found no causal relationship between LN and aspects of social functioning (ER-40, SAC) in either the GP or FEP sample. These preliminary findings were congruent with a correlational study showing no relationship between social cognition and LN (Ludwig et al., 2020); however, they did not provide support for the social cognitive model of loneliness proposed by Cacioppo & Hawkley (2009). There is also limited research examining the relationships between general cognition and LN in the context of psychosis. A study by Badcock et al. (2015) found that more severe LN was correlated with lower scores on a digit-symbol coding (DSC) task in a general psychosis sample. While we did not assess GCog in the GP sample, there were no causal relations detected between LN and GCog in the FEP sample.

Limitations

There were several notable limitations associated with this collection of studies. The first set of limitations pertains to measurement. Loneliness was only measured using a standardized and psychometrically validated scale in the GP sample; composite scores using items from two different measures were used to measure LN among the EP and FEP samples. Each of the composite measures assessed participant perception of their loneliness experiences (explicitly), as well as aspects of social loneliness (perceived social belonginess and support, respectively). However, we cannot be sure that the causal models would remain the same if LN was measured uniformly across all three populations.

There were also different measures used for many of the primary variables of interest. For example, internalized stigma was measured in the GP and FEP samples using two different self-report scales. Internalized stigma was not measured at all in the EP sample, which instead used a validated assessment of self-reported discrimination experiences. Self-rated depression was captured in the GP sample using the BDI-II and with the MSSC in the EP sample; self-rated depression was not captured in the FEP sample. Rater-rated depression was captured using the CDSS in both the EP and FEP samples; rater-rated depression was not captured in the GP sample.

Similarly, self-rated motivation was assessed in the GP sample using the MAPS-SR, while the MSSC and the BIS/BAS were used in the EP sample; there was no self-report measure of motivation in the FEP sample. Rater-rated motivation was assessed using somewhat different items from the Intrapsychic Foundations subscale of the QLS in both the GP and FEP samples; there were no rater-rated assessments of motivation included in the EP sample. Anxiety was not assessed in the GP sample; however, it was assessed as a self-report in the EP sample and as a

rater-rated composite score using PANSS items in the FEP sample. Positive and negative symptom severity was assessed using the QSANS in the GP sample and the PANSS in the FEP sample. Positive/negative symptom severity was not explicitly assessed in the EP sample. Scores from the SANS/SAPS and PANSS scales have been shown to be highly correlated with convergent validity (van Erp et al., 2014; Peralta & Cuesta, 1994).

To address the issue of multiple different measures, standardized effect size estimates were obtained from the linear SEM models. Raw effect size estimates are difficult to compare across scales that use different units of measurement. Standardized effect size estimates do not use specific units and instead report the magnitude and direction of an effect in the context of standard deviations. While it may not be a perfect solution, standardized effect size estimates allowed us to compare the causal (or possibly causal) effects between variables assessed on different scales across all three studies.

A second significant limitation is associated with the ambiguous edges observed in the PAGs across all three studies. There were two types of ambiguous edges observed in the PAGs (o-o and o->). Both ambiguous edge types indicate qualitative differences regarding possible relations between two nodes (variables), with o-o edge types indicating the greatest array of possibilities. A choice was made to overlay a MAG onto the PAG to show one possible set of quantitative outcomes for graphs with ambiguous edges. The use of MAGs allowed us to show standardized effect size estimates *if* ambiguous edges were directly causal. A MAG does not change the orientation for non-ambiguous edges (e.g., -->, <->). Notably, we saw less ambiguous edge orientations in the causal model representing the FEP sample, which is likely due to both the sample size and number of timepoints.

The third set of limitations is specific to the samples. The sample sizes for the GP and EP studies were small; the sample size for the FEP study was adequate. It is well recognized that small samples may increase the possibility of Type I (false positive) or Type II (false negative) errors. Small samples in CDA reduce confidence in the accuracy of edge detection and orientation. For example, a causal edge was found between LN and IS/InDI-D in all three studies, but we cannot be sure the edges showing LN as a cause of IS, or LN as a possible cause of InDI-D, in the GP and EP samples are oriented correctly. In other words, we cannot be sure that IS/InDI-D are not causally influencing LN in the GP or EP samples. The overall pattern observed between LN and IS/InDI-D across the three studies does increase confidence that a causal relationship may be present. An additional issue of too few timepoints is present for the EP sample (baseline, six-months); studies of adequate sample size with three or more timepoints are better equipped to assess longitudinal causal relationships.

There are limitations associated with representativeness due to each study sample being constrained. The GP sample was initially constrained by research inclusion/exclusion criteria (such as minimum outpatient status, clinical stability, substance use history, English fluency, and access to necessary technology). The GP sample was further constrained by excluding participants without complete measures at all three timepoints (for the variables of interest) from the GFCI analysis. The analysis of baseline differences confirmed that the GP participants with complete measures at all timepoints (which included six people with one imputed timepoint) had statistically significant lower mean scores of depression at baseline when compared to those with incomplete measures. Therefore, the sample used for the causal analysis was not truly representative of the broader study sample, which was already very likely constrained.

For the EP sample, we initially started with a naturalistic sample of participants in CSC programs in Minnesota (predominantly located in the Twin Cities metropolitan area). Inclusion criteria for the MBC protocol is minimal (enrolled in CSC, psychosis spectrum diagnoses, age between 15-40 years) and there are no exclusion criteria. It is possible that important differences exist between the people who authorized their clinical information for research purposes and those who did not. However, the sample and measures that were included in the CDA became quite constrained due to exceptional amounts of missing data. The EP participants included in the GFCI analysis had greater than 60% of data present across all measures included in the analysis. Of the 266 people who had some baseline data, only 80 participants met the 60% or greater cutoff criteria for inclusion. The remaining dataset was 87% complete for those 80 participants enrolled in CSC. The remaining missing data was imputed using MICE, which has been shown to be a less biased method to deal with missing data than complete cases (Allison, 2015; Azur et al., 2011; Madley-Dowd et al., 2019; van Buuren, 2018; van Buuren & Groothuis-Oudshoorn, 2011). The population was significantly constrained prior to performing MICE, which could have introduced bias into the MICE procedure. Overall, the included EP sample was likely not representative of the broader population of people receiving CSC for EP in Minnesota.

The FEP sample, although larger, was also significantly constrained. The data used for the analysis was originally collected as part of the RAISE-ETP study. The sample characteristics for RAISE-ETP have been well documented (Kane et al., 2015; Kane et al., 2016); notably, participants were excluded if they did not meet strict criteria for diagnoses (schizophrenia spectrum only), previous episodes of psychosis (one only), and antipsychotic medication (no more than six-months of previous cumulative use). While the strict inclusion/exclusion criteria were likely necessary for the original RCT, there is a strong likelihood that the RAISE-ETP

sample is not representative of the population encountered by community-based CSC services. The FEP sample was further constrained by the choice to remove participants with incomplete data (for the variables of interest) over the first year of treatment. The analysis of baseline differences confirmed that people included in the CDA had, on average, less depression and anxiety with higher general cognition and socio-affective capacity, than excluded RAISE-ETP participants.

The result of having constrained populations is that we may have causal models of LN for participants with less severe baseline presentations in important domains such as depression. The preliminary causal models may also reflect causal relationships for people who are more likely to *engage* in treatment or research experiences (evident by having complete cases or meeting higher measurement completion cutoffs). The EP and FEP participants were enrolled in some form of community-based mental healthcare (CSC for the EP sample, CSC or TAU for the FEP sample), and we know that the participants included in the GFCI analyses participated in most/all of the data collection procedures, which could reasonably indicate that those participants may have been more engaged in their treatment experiences than those with incomplete or significantly missing data. People with psychosis experiences who consistently engage in data collection and/or treatment appointments could be categorically different than those who enroll in research or community-based services but do not regularly attend appointments or complete assessments as requested.

Implications and Future Directions

Research Implications

Most of the current research in this domain is correlational. While correlational studies provide useful information about the presence, strength, or apparent interactions between

variables, studies of this type give us no real information about causation. One major critique of the abundance of correlational work in social sciences, and particularly mental health research, is that the development and implementation of interventions to improve meaningful outcomes is severely limited by an overreliance on correlational methods (Saxe et al., 2022; Saxe et al., 2016). Causal research methods, such as RCTs or CDA, are needed to enhance our collective knowledge of complex clinical issues and improve the efficacy of clinical interventions. To our knowledge, the studies presented here are the first preliminary explorations of LN in psychosis specific populations using CDA methods. Additional longitudinal research is needed to better understand the causal relationships of loneliness among persons with psychosis using RCTs if/when they are appropriate or CDA methods when RCTs are not feasible or ethical.

Additional studies using causal methods (RCT, CDA) among the general population are also needed. Specifically, more research is needed among large, representative non-clinical samples to further our understanding of the causal relations of LN more broadly. Causal discovery methods may be best suited for this type of research. Additional CDA research of this type could provide clarity to current theoretical or conceptual models of LN in the broader population, as well as create a foundation for meaningful comparisons between clinical and non-clinical samples, as well as developmentally different samples.

More research is needed to understand whether there are developmental or experiential differences that may impact the cascade of LN in different psychosis populations. For example, while age was not associated with LN in any of our causal models, we could not determine whether potential differences in stages of development (adolescents/young adults versus adults aged 30+) impacted ratings of LN or other variables such as depression or IS/InDI in the context of LN. We were also unable to determine whether experiential differences with psychosis could

account for different causal cascades of LN. For example, do people who experience psychosis for longer/shorter periods of time experience or rate LN differently? Research using qualitative or mixed method approaches could provide us with some insight into possible developmental or experiential differences regarding self-ratings and meaning making of LN in the presence of psychosis.

Another important area of future clarification would be the relationship between LN and self-rated versus rater-rated clinical experiences (e.g., symptoms, functioning, attitudes). A preliminary pattern was detected in our exploratory models that showed LN *may* have more of a causal relationship with self-reported measures of depression or motivation. Regarding depression, two of the preliminary causal models showed a causal relationship between LN and self-reported depression in different psychosis populations (GP, EP). The relationship between LN and rater-rated depression appeared more questionable among the EP sample than self-rated depression scores; moreover, there was no relationship found in the FEP population between LN and rater-rated depression.

While rater-rated assessments may be preferred in some research or clinical paradigms, LN is not well suited for such approaches because the experience is subjective. Additional research is needed to compare causal relations between LN and self- or rater-rated scores for both depression and motivation. Another avenue of assessment clarification could include the use of ecological momentary assessment (EMA) data collection practices for causal research. Incorporating EMA data collection practices would allow for the collection of real-time ratings for LN and associated factors in a variety of contextually different situations without relying heavily on recall for self-reports.

Participatory research methods are much needed. Just as an over-reliance on correlational research may impact our ability to develop and implement effective interventions, an over-reliance on people without contextual experience may be just as limiting to our ability to solve complex problems. Expertise is needed across academic, clinical, methodological, and experiential perspectives. Moreover, to actively exclude people with lived experience of psychosis from research (or clinical) development processes strongly suggests the presence of explicit or implicit biases about the capabilities of individuals based on their affiliation with a large, heterogeneous population of people. Of course, not all people with lived experience will want to participate in research (or clinical) development/implementation processes, but this should not dissuade us from attempting to use inclusive research methods. The beauty of large, heterogeneous groups is that all kinds of people have affiliation; this is no different than the reality between those of us that actively participate and consume research and those in the broader community with limited or no interest in such endeavors.

Participatory Research Example

The following is an example of the feasibility and practicality of collaborating with people who have lived experience. This writer collaborated with an Advisory Research Council (ARC) to develop a semi-structured interview focused on LN for use in a later study. The ARC was composed of five people with diverse identities and experiences, but they shared experiences of early psychosis and engagement in CSC treatment services. This writer met with each ARC member prior to the start of group activities to explain the project and discuss any questions that arose. All members of the ARC were paid for their time and subsequent contributions, as would be expected in most professional endeavors.

Prior to starting formal work with the ARC, and as agreed upon in the initial discussions, this writer drafted an initial semi-structured interview focused on LN and early psychosis. The ARC members were provided with this original question-set and were asked to provide feedback about the questions themselves, as well as to provide feedback about areas for exploration that were not included in the original interview (e.g., areas missed by this writer). All members of the ARC provided feedback and actively engaged in discussions about how the interview questions could be improved, as well as identified areas that this writer may have missed that would improve the semi-structured interview.

Feedback from all members was incorporated, and after several iterations, a final version of the semi-structured interview was agreed upon by all six participations (ARC, this writer). The semi-structured interview can be viewed in Appendix I. The final version of this interview was 10 questions. Each question incorporated additional probing questions to be used if needed. The final interview included questions that gathered participant insight on definitional, developmental, clinical, and social aspects of LN experiences; the final interview also included participant insight on the whether their experience of LN was impacted by their CSC treatment program.

The final version of this semi-structured interview was categorically better than the original draft, or any draft this writer would have created without the perspectives of those with lived experience. From a participant perspective, the language and structure of the questions was simplified and specific, making each question (and related probes) much easier to understand and answer. From a data collection perspective, the final version of this questionnaire will allow researchers to capture a more robust picture of LN in the context of early psychosis (or psychosis more generally if used with a more general population).

Clinical Implications

The overall outcomes across the three preliminary models showed some compelling patterns. First, LN appeared to be (mostly) self-sustaining and did not appear to change based on its known correlates in any of the preliminary causal models. These initial findings suggest that LN may not remit if it is uninterrupted, and that we likely cannot rely on LN to improve along with our typical treatment targets. Preliminary findings also suggest that LN may not be a consequence of specific clinical symptoms of psychosis, which was particularly evident in our EP and FEP models. Regarding EP populations specifically (which by virtue of its inclusive definition includes FEP populations), the broader CSC treatment paradigm does not typically incorporate the direct assessment of LN or LN-specific monitoring or intervention practices. A primary treatment goal for most clinical interventions, including CSC, is improving quality of life (Kane et al., 2016; Kane et al., 2015). Loneliness has been shown to have a negative impact on quality of life among the general population (Park et al., 2020) and psychosis populations (Lim et al., 2018; Roe et al., 2011). Future treatment approaches should begin to incorporate ongoing assessment and treatment of LN for participants endorsing LN. There are psychometrically valid and short assessments available for research and clinical use, such as the UCLA 3-Item Loneliness Scale (Hughes et al., 2004).

A similar pattern was observed with internalized stigma (IS) and discrimination experiences (InDI-D). Like LN, IS/InDI-D appeared to be a primary cause of later same variable experiences and neither variable appeared to change as a direct result of clinical or functional improvement. The IS variable for the FEP sample showed some statistically significant improvement in the first three-months of treatment (also similar to LN), while the InDI-D variable (as well as anticipated discrimination, InDI-A) showed no improvement over the first

six-months of treatment in the EP sample. The initial findings suggest that without interruption IS/InDI-D may not improve on their own or along with clinical symptoms of psychosis. Importantly, across all three studies, there were observed causal (or possibly causal) relations between LN and IS/InDI-D, and, as previously identified, LN is not a typical treatment target in interventions for psychosis or early psychosis. Future treatment approaches would ideally include ongoing measures and intervention for internalized stigma for affected participants. Similar to LN, there are short-item scales accessible for use; both the GP and FEP studies used short assessments to measure IS (ISMI-10 and SRSS).

Researchers and clinicians may also want to consider incorporating broad measures of discrimination experiences, such as the InDI, into their research and clinical practices. People with psychosis have many identities outside that of their specific diagnoses, and it may be beneficial for participants and researchers/clinicians to enhance their understanding of how participants are impacted by the world and in what ways. We may also learn about limitations within our own research or clinical environments from the participant perspective. Additionally, incorporating measures of this type may help us uncover individual or community-based protective factors. Overall, taking some time to assess experiences such as loneliness, internalized stigma, and intersectional discrimination experiences may help us to improve clinical care, as well as offer opportunities for research or clinical teams to promote belongingness in clinical and broader social environments.

Social Implications

It is certainly possible, and probably likely, that clinical interventions alone may not be enough to address an experience such as LN among psychosis populations. In the context of clinical environments, social opportunities may already be present in the form of treatment

groups. However, additional opportunities may be feasible. For example, a team of clinicians and people with lived experience could collaborate to create social opportunities for participants within that specific program or organization. Another strategy to create social opportunities could include collaboration between a team of clinicians, people with lived experience, and non-clinical community-based programs or organizations.

The experience of LN is subjective and not confined to clinical spaces; therefore, opportunities for social engagement may be best if they were not confined to clinical spaces, particularly in the context of the patterns observed between LN and internalized stigma/perceived discrimination in these three studies. While this could be a significant challenge, policy development could create funding opportunities, or other incentives, to enhance the ability for feasible collaboration between academic, clinical, and community-based organizations. If community-collaboration is not feasible, clinical programs could explore the potential social advantages of creating group-based opportunities with diagnostically diverse inclusion criteria, versus limiting participation based on diagnostic category alone. Groups with greater representation, even in clinical contexts, could potentially help to reduce both loneliness and internalized stigma for participants.

Engaging socially with others can be a challenging situation for some people within the psychosis spectrum. A recent systematic review of EMA literature found that people diagnosed with schizophrenia reported much higher levels of stress in social situations, along with a greater desire for solitude while among people, when compared to their counterparts without psychosis spectrum diagnoses (Mote & Fulford, 2020). Importantly, this systematic review also examined positive affect and found that 1) people with schizophrenia diagnoses reported the same levels of positive affect during social encounters as controls, and 2) people with schizophrenia reported

greater levels of positive affect when they were with people compared to their ratings while alone (Mote & Fulford, 2020). It appears that while people within the psychosis spectrum may experience just as much pleasure in social situations as those without psychosis, being with people can also be especially stressful for people within the psychosis spectrum. Interventions aimed at reducing stress and increasing motivation may be helpful and necessary approaches to adequately support those within the psychosis spectrum with accepting social invitations and attending those engagements.

Community Implications

Broader initiatives such as targeted educational campaigns and community outreach may be needed to address the broader social issues of LN, social exclusion, and stigma. There are different levels of the social sphere that may benefit from targeted education and outreach. One example could include mental health providers. A systematic review of literature focused on stigma in mental healthcare found that mental health professionals had more stigmatizing views of schizophrenia spectrum disorders than they did toward most other psychiatric diagnoses (Valery & Prouteau, 2020). Factors that contributed to greater stigma among mental health professionals were reported to be biological-based beliefs about schizophrenia spectrum disorders, amount of interaction with people diagnosed in the schizophrenia spectrum, and categorical versus continuum beliefs about the diagnoses (Valery & Prouteau, 2020). Perhaps targeted education and training could be provided for future or current mental health providers (or their organizations) that do not specifically work with populations impacted by psychosis.

Psychosis related stigma may be more prominent than we would like to admit across the clinical mental health landscape. It is likely that, without proper training or exposure, clinicians (or administrators) may inadvertently perpetuate stigma in their clinical practice through their

language or their actions. Partnerships between academic institutions, clinical providers, and persons with lived experience are needed to provide additional training and clinical education to mental health providers (and organizations) that do not routinely work with people with psychosis experiences but may still encounter people with psychosis experiences.

Mental health professionals have been shown to report fewer stigmatizing beliefs regarding psychosis spectrum disorders when compared to the general population (Valery & Prouteau, 2020). In the broader social sphere, social stigma of mental illness and related discrimination/exclusion have been prevalent and well-documented issues. While many gains have been made in improving our understanding of psychosis in academic and clinical environments, much about psychosis does not appear well-understood among the public. For example, many people may believe that persons with psychosis are more violent than others or that psychosis is an untreatable issue with negative prognoses (Valery & Prouteau, 2020). Importantly, while psychosis spectrum disorders can be debilitating for some, they can also be a highly treatable issue with positive outcomes and prognoses (Birchwood et al., 1998; McGorry et al., 2008).

Loneliness, social exclusion, internalized stigma, and discrimination are all associated with social acceptance, belongingness, and inclusion. Targeted education and community outreach to the broader public is necessary to address loneliness and stigma in the broader social environment. A meta-analysis found that education campaigns and direct community outreach were both effective in reducing stigmatizing beliefs toward people with mental illness (Corrigan et al., 2012). Interestingly, researchers found that direct community outreach (e.g., in person) was most effective in reducing stigmatizing beliefs among adults when compared to educational campaigns; these researchers also reported their “most important” finding was that direct, in

person contact with someone with lived experience had the biggest effect on reducing stigma among adults in the general public (Corrigan et al., 2012). For adolescents, researchers reported that educational campaigns, which may include people with lived experience, were the most effective at reducing stigmatizing beliefs and behavioral intentions (Corrigan et al., 2012). It is incumbent upon those with knowledge and understanding of psychosis, as well as policy makers and administrators, to create avenues and opportunities to provide accurate and actionable information to the public in a manner that supports social inclusion, belongingness, and the recognition of agency and abilities.

Conceptual Implications

The experience of LN has been an overlooked issue in the clinical psychosis literature, despite long-standing goals to improve social functioning and quality of life within this population. It stands to reason that LN may have been thought of as a consequence, or byproduct, of psychosis symptoms and related functional impairments, whereby improvement in symptom manageability and social functioning/engagement would naturally reduce the experience of LN. This would provide some explanation as to why LN has not been typically assessed in research or treatment paradigms. However, symptom severity and objective measures of social engagement or isolation (e.g., time spent in structured roles, time spent with people who are not family or service providers, etc.) are both typically assessed. Much of the emerging research on LN in psychosis has also centered around clinical and functional issues, and, as has been previously noted, much of that research has produced correlations between LN and the clinical and functional outcomes of psychosis. The two conceptual models of LN and psychosis presented herein were based on this correlational literature, and both include LN as a consequence of psychosis and aspects of social functioning.

However, the preliminary findings across the three causal models suggest that a different conceptualization of LN in the context of psychosis may be necessary. Loneliness did not appear to be simply a consequence of the clinical or functional issues associated with psychosis. While this finding has been noted at different points throughout this discussion, it bears repeating. Though we did observe some mixed findings regarding the role of self-reported MEA, BIS, or DEP as causal influences of LN, we found no support for the role of POS or NEG symptom clusters as causes of LN. Alternatively, we observed that LN was a causal influence, or possible causal influence, of important clinical variables (self-reported motivation, depression, social functioning, etc.). Loneliness appeared to be much more independent in our three causal models than what may have been predicted by either of the two conceptual models of LN and psychosis. While loneliness appeared to have stronger causal relations with self-reported measures across the three studies, it still appeared largely independent in the context of change over time when compared to its known correlates. Taken together, these findings indicate that *LN may not be a passive consequence of psychosis, but it may be a separate and active process.*

Loneliness, or *perceived* social isolation, is not the same as *objective* social isolation (Hawkley & Cacioppo, 2010). More specifically, someone can experience LN while also having access to social supports, whereas others can experience objective social isolation and not be lonely. Importantly, this distinction was also acknowledged in the broad majority of literature on LN and psychosis referenced in this dissertation. However, despite this distinction, LN is not typically measured in clinical or research paradigms focused on psychosis (while objective social isolation is a frequent measurement and treatment target). Moreover, both conceptual models of LN and psychosis show LN as a consequence of variables that have been traditionally assessed

using objective measures of social isolation (structural/functional social support, social withdrawal).

Importantly, at no point in any of the three studies was LN caused by an objective measure of social isolation (which included role functioning measures). Loneliness appeared to be an active process that was also separate from objective social isolation. This finding is also consistent with what has been reported in the general LN literature (Hawkley & Cacioppo, 2010). In other words, not only should we avoid assumptions of LN based on the presence/absence of psychosis symptoms, but we should also not assume people with psychosis are lonely (or not) based on measures of objective isolation. *Objective social isolation and LN are separate, yet important measurement and treatment targets in psychosis populations*.

Another finding with conceptual implications that bears repeating was the pattern observed between LN and IS/InDI-D (perceived discrimination, PD) across all three preliminary causal models. The conceptual models of LN and psychosis each included IS/PD as causes of LN. Lim et al. (2018) proposed that IS/PD were direct causes and/or consequences of LN, while Badcock et al. (2020a) proposed that IS caused social withdrawal, which then caused LN. Importantly, both of these models included psychosis symptoms as causes of LN or IS. The relationship between psychosis symptoms and IS was shown much more directly in the process-oriented model proposed by Badcock et al. (2020a).

While LN and IS/PD were shown to have causal relations across all three studies, they both appeared to operate independently from most of the clinical, functional, and cognitive variables included in each model. The model proposed by Lim et al. (2018) did not identify any links between variables thought to cause LN; however, our findings are inconsistent with the process of LN in the context of psychosis proposed by Badcock et al. (2020a). Across the three

causal models, IS/PD was not shown to be a consequence of psychosis symptoms at any point. *Like LN, IS/PD may be an active process separate from psychosis symptoms*.

However, there remains a question about whether IS/PD is separate from psychosis spectrum diagnoses. Diagnostic category was an included variable in causal models for studies one and two, and it was not shown to have a causal relationship with either LN or IS/PD (diagnostic category was not examined in study three because there was no variation). There was no measure indicating participants were asked how they felt about their diagnoses. Each measure of IS explicitly examined IS in the context of mental illness (i.e., assigned diagnostic label), while the InDI-D explicitly recognizes mental illness as an aspect of intersectional identity (but may not explicitly measure it). This suggests that IS/PD may be a consequence of what it means to labeled (diagnosed) with a psychosis or schizophrenia spectrum disorder in a given social context, versus a consequence of the literal symptoms of psychosis. *Although LN and IS/PD were not caused by psychosis symptoms, they could both be causally related to the aftermath of being assigned a psychosis spectrum diagnosis.*

There were differences observed for both LN and IS/InDI-D when comparing the GP group to the EP and FEP groups. Importantly, the GP group was, on average, approximately 10 years older than the EP and FEP groups. When looking at LN as a primary cause of later LN, the causal effect was larger for the GP group when compared to the FEP group. Regarding the causal relationship between LN and IS/InDI-D in each of the three studies, the largest causal effect was also observed in the older, on average, GP sample. These findings were consistent with aspects of the theory of LN proposed by Cacioppo and Hawkley (2009), which proposed that LN worsens as it become more chronic, and social perceptions are altered as a result of worsening LN. *Developmental differences, time, or both may lead to a disparate causal effects between LN*

and later LN (e.g., self-maintaining relationship) and between LN and IS/PD in different psychosis populations.

When looking at changes in LN or IS/InDI-D over time, no changes were observed for either variable in the GP sample across the six-month study period. However, LN improved significantly across the first six-months of treatment for the EP sample, and within the first three-months of treatment for the FEP sample. In the FEP sample, IS was shown to improve in the first three-months. Notably, there was no three-month measure of LN or InDI-D in the EP sample, so we cannot be sure if significant improvement in LN leveled off after the first few months of treatment (as was observed in the FEP sample). *Both LN and IS/PD should be conceptualized as important treatment targets in psychosis populations that will each likely require targeted intervention.*

Studies have shown that treatment approaches designed to target maladaptive beliefs and social perceptions, such as cognitive behavior therapy (CBT), have been effective at reducing LN (Masi et al., 2010) and IS/PD (Jagan et al., 2023). In the context of psychosis treatment approaches, CBT is a frequently used clinical modality. If LN and IS/PD are assessed in an ongoing manner during the course of treatment, many clinicians may already have the skills in place to provide meaningful interventions to address both LN and IS/PD. *Both LN and IS/PD may be feasible treatment targets in programs providing specific services for psychosis spectrum disorders.*

Based on the findings across the three preliminary causal models, targeted intervention for LN and IS/PD may be especially important for EP/FEP populations. As previously mentioned, the standardized causal effect estimates for LN as a cause of LN, and for the relationships between LN and IS/PD, were weaker in the EP/FEP samples than the GP sample.

There was also evidence of significant improvement in LN early in the treatment experience for both the EP and FEP samples, while IS was shown to improve early in the treatment experience for the FEP sample. Taken all together, both LN and IS/PD showed signs of increased malleability in the EP and FEP samples compared to the GP sample. This is an important finding because the first five-years after an initial psychosis episode are thought to have a high degree of plasticity, making this time a critical period for intervention (Birchwood et al., 1998; McGorry et al., 2008). *Targeted interventions for LN and IS/PD may be more feasible and more effective if they are implemented during the early phase of psychosis.*

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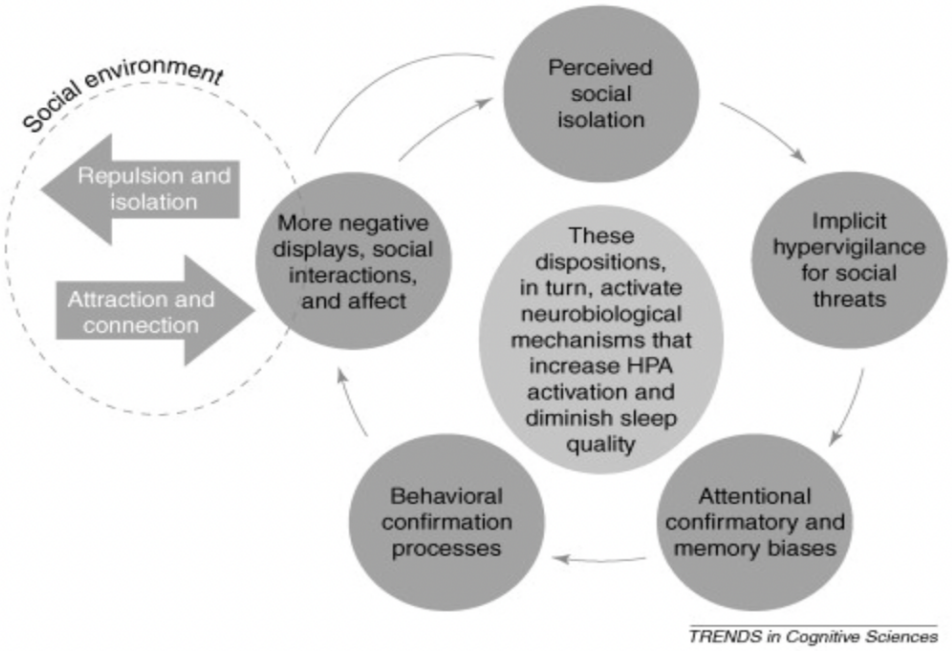
Appendix A

Social Cognitive Model of Loneliness



(Cacioppo & Hawkley, 2009)

Appendix B

Theoretical Framework of Loneliness for Persons with Psychosis

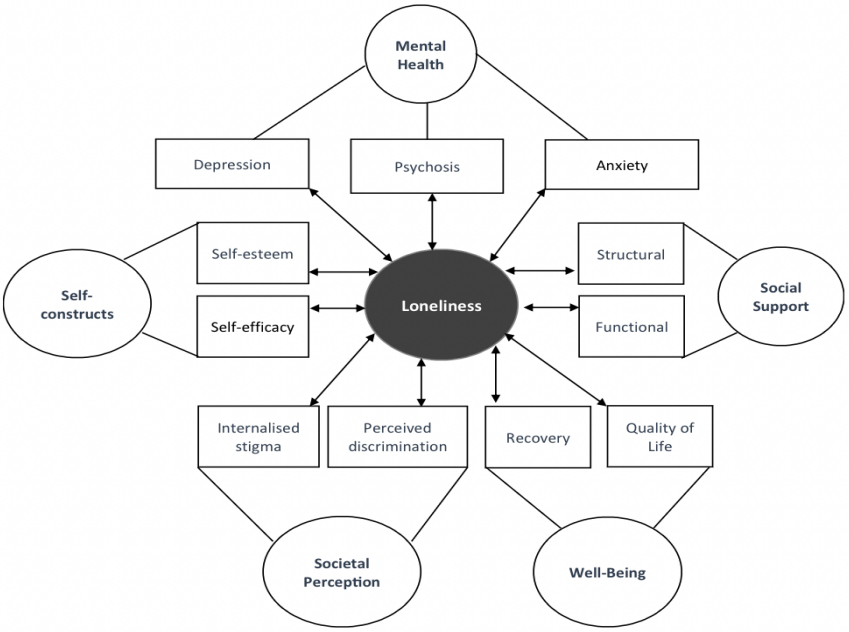
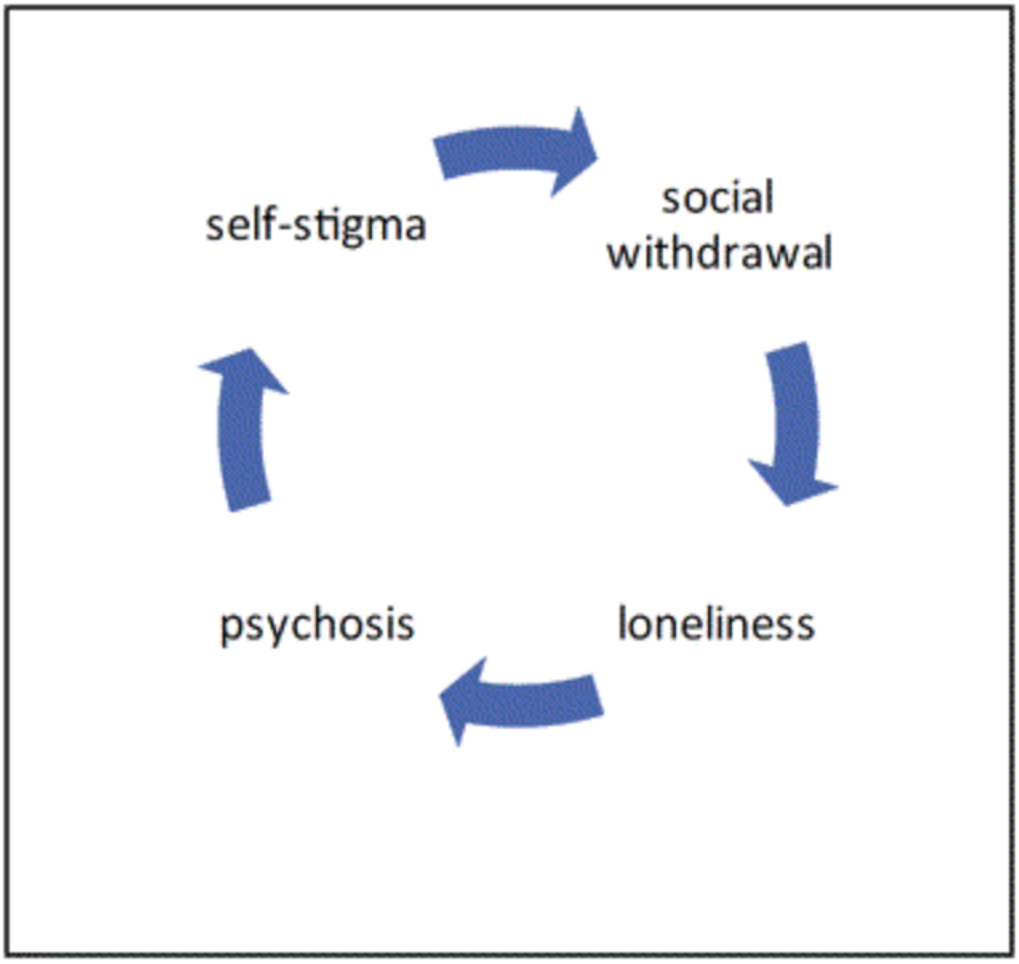


Fig. 2 Theoretical model of loneliness in individuals with psychosis: a focus on psychological and social factors. *Note* Bidirectional arrows are used to indicate possible reciprocal relationships over time that need to be examined. For clarity, we only indicated arrows between loneliness and each specific factor, rather than between specific factors. Additional factors that warranted further investigation, trait anxiety, social anxiety, and social self-efficacy should also be considered

(Lim et al., 2018)

Appendix C

Proposed Negative Feedback Loop for Persons with Psychosis



(Badcock et al., 2020)

Appendix D

Full Table for Proportion of 1,000 Bootstrap Resampling Procedure

Edge Type (PAG)	Nodes		Proportion of 1000 bootstrap resamples with edge type						
	Node 1	Node 2	-->	<--	o->	<-o	o-o	<-->	No Edge
-->	ULS_4m	ULS_6m	**0.9061**	-	0.047	-	0.035	0.003	0.009
-->	ISMI_4m	ISMI_6m	**0.9031**	-	0.0619	0.001	0.01	0.02	0.004
-->	QSANS_6m	MOT_6m	**0.8232**	0.035	0.024	0.008	0.009	0.025	0.0759
-->	BDI-II_4m	BDI-II_6m	**0.8182**	-	0.1269	0.002	0.037	0.016	-
-->	MCR_4m	MCR_6m	**0.8112**	-	0.1019	0.001	0.015	0.007	0.0639
-->	QSAPS_4m	QSAPS_6m	**0.7682**	-	0.021	0.013	0.1898	0.004	0.004
-->	RWP_4m	RWP_6m	**0.6294**	-	0.1528	0.001	0.021	0.005	0.1908
-->	MEA_6m	SP_6m	**0.6044**	0.1149	0.025	0.008	0.006	0.003	0.2388
-->	ULS_B	ULS_4m	**0.5485**	-	0.2797	0.002	0.1029	0.02	0.047
o-o	OF_4m	OF_B	-	0.2617	0.016	0.1778	**0.5265**	0.013	0.005
-->	RWP_6m	MEA_6m	**0.5245**	0.1449	0.013	0.015	0.003	0.008	0.2917
o->	QSAPS_B	QSAPS_4m	0.2408	-	**0.5005**	0.011	0.1958	0.033	0.019
-->	QSANS_4m	SF_4m	**0.4835**	0.1279	0.0619	0.033	0.1049	0.007	0.1818
-->	QSANS_4m	MOT_4m	**0.4775**	0.2368	0.1668	0.04	0.024	0.046	0.009
-->	SP_B	SP_4m	**0.4635**	-	0.2198	0.013	0.1079	0.0649	0.1309
-->	SF_B	SF_6m	**0.4505**	-	0.2607	0.021	0.1618	0.0549	0.0509
o->	er40_rtcr_B	er40_rtcr_6m	0.1259	-	**0.4486**	-	0.016	0.2348	0.1748
o->	er40_rtcr_4m	er40_rtcr_6m	0.3856	-	**0.4406**	0.001	0.032	0.026	0.1149
o-o	er40_rtcr_B	er40_rtcr_4m	0.0829	0.001	0.1598	0.001	**0.4216**	0.2398	0.0939
o-o	MEA_B	RWP_B	0.3666	0.046	0.034	0.1249	**0.4106**	0.003	0.015
o-o	age1sx	age	0.011	0.025	0.009	0.2158	**0.4026**	-	0.3367
o-o	DBS_B	DBS_4m	0.3616	-	0.1469	0.002	**0.3866**	0.0689	0.034

-->	RWP_4m	MEA_4m	0.3866	0.2587	0.1778	0.034	**0.0659**	0.001	0.0759
o-o	MOT_B	QSANS_B	0.1359	0.2627	0.1089	0.0649	**0.3766**	-	0.0509
o->	er40_cr_B	er40_cr_6m	0.1898	-	**0.3477**	0.002	0.0969	0.0889	0.2747
o->	er40_cr_B	er40_cr_4m	0.2228	-	**0.3067**	0.003	0.2687	0.0789	0.1199
o-o	QSANS_B	SF_B	0.2208	0.0969	0.041	0.0859	**0.2857**	0.009	0.2607

Appendix E

Bootstrap Resampling Outcomes for Individual Causal Graph

Edge Type in PAG	Nodes		Proportion of 1000 pooled bootstrap resamples with edge type						
	Node 1	**Node 2**	**-->**	**<--**	**o->**	**<-o**	**o-o**	**<-->**	**No Edge**
-->	DEP_6m	LN_6m	**0.7093**	0.1698	0.043	0.007	0.019	0.001	0.0509
-->	InDI_D_B	InDI_D_6m	**0.6394**	0.003	0.0869	0.005	0.037	0.0509	0.1778
-->	BIS_B	BIS_6m	**0.6324**	-	0.1538	0.001	0.033	0.008	0.1718
-->	InDI_A_B	InDI_A_6m	**0.6254**	0.001	0.1129	0.011	0.0899	0.0619	0.0979
-->	IMR-SD_6m	IMR-FI_6m	**0.6064**	0.2727	0.028	0.043	0.036	0.014	-
o-o	MOT_B	DEP_B	0.021	0.3367	0.0549	0.048	**0.5315**	0.004	0.004
-->	CDSS_6m	InDI_D_6m	**0.5105**	0.2687	0.0799	0.024	0.011	0.036	0.0699
o-o	IMR-SD_B	imrFI_B	0.0719	0.3726	0.021	0.044	**0.4895**	0.001	-
-->	InDI_D_B	InDI_A_B	**0.4845**	0.0699	0.0659	0.0699	0.2777	0.012	0.02
-->	MOT_6m	DEP_6m	**0.4845**	0.3317	0.0769	0.024	0.0699	0.008	0.005
-->	MOT_6m	IMR-SD_6m	**0.3946**	0.1668	0.0649	0.014	0.021	0.005	0.3337
o->	race	ANX_B	0.03	-	**0.3916**	0.002	0.1898	0.002	0.3846
-->	ANX_B	BIS_B	**0.3437**	0.047	0.0609	0.037	0.1778	0.001	0.3327
-->	SI_B	SI_6m	**0.3057**	-	0.2478	0.003	0.1698	0.009	0.2647
o->	LEC_B	InDI_D_B	0.1149	0.1538	**0.2997**	0.0569	0.2078	0.003	0.1638
o-o	DEP_B	ANX_B	0.2138	0.1419	0.1928	0.023	**0.2997**	0.001	0.1279

Appendix F

Full PAG and MAG Edge Counts

PAG Edges	PAG Edge Count	MAG Edges	MAG Edge Count
BIS_B --> BIS_6m	5	BIS_B --> BIS_6m	10
BIS_6m --> IMR-SD_6m	3	BIS_6m --> IMR-SD_6m	4
BIS_6m --> LN_6m	3	BIS_6m --> LN_6m	4
CDSS_B o-o SI_B	7	NA	-
NA	-	CDSS_B --> SI_B	7
CDSS_6m --> SI_6m	3	CDSS_6m --> SI_6m	3
CDSS_6m --> ANX_6m	3	CDSS_6m --> ANX_6m	3
IMR-FI_B --> IMR-SD_B	7	IMR-FI_B --> IMR-SD_B	10
IMR-FI_B --> IMR-SD_6m	3	IMR-FI_B --> IMR-SD_6m	3
NA	-	IMR-FI_6m --> IMR-SD_6m	4
IMR-FI_6m --> ANX_6m	3	IMR-FI_6m --> ANX_6m	3
IMR-FI_6m --> DEP_6m	3	IMR-FI_6m --> DEP_6m	4
NA	-	IMR-SD_B --> IMR-SD_6m	4
IMR-SD_6m --> IMR-FI_6m	4	IMR-SD_6m --> IMR-FI_6m	6
NA	-	IMR-SD_6m --> ANX_6m	3
InDI-A_B --> InDI-A_6m	8	InDI_A_B --> InDI_A_6m	10
InDI_A_6m --> IMR-FI_6m	3	InDI-A_6m --> IMR-FI_6m	4
InDI-A_6m --> InDI-D_6m	5	InDI-A_6m --> InDI-D_6m	6
InDI-D_B --> InDI-A_B	8	InDI-D _B --> InDI-A_B	10
InDI-D_B --> InDI-D _6m	3	InDI-D_B --> InDI-D_6m	3
InDI-D_6m --> InDI-A _6m	3	InDI-D_6m --> InDI-A_6m	3
LEC_B o-> InDI-D_B	8	NA	-
NA	-	LEC_B --> InDI-D_B	8
LN_B --> DEP_6m	3	LN_B--> DEP_6m	4
LN_B o-> InDI-D _B	8	NA	-
NA	-	LN_B --> InDI-D_B	10
LN_6m --> CDSS_6m	3	LN_6m --> CDSS_6m	4
race o-> ANX_B	8	NA	-
NA	-	race --> ANX_B	10
SI_B o-> SI_6m	4	NA	-
SI_B o-o SI_6m	5	NA	-
NA	-	SI_B --> SI_6m	10
ANX_B --> BIS_B	7	ANX_B --> BIS_B	10
ANX _B --> IMR-FI_B	5	ANX_B --> IMR-FI_B	7
ANX _6m --> BIS_6m	3	ANX_6m --> BIS_6m	4
ANX _6m --> MOT_6m	4	ANX_6m --> MOT_6m	4
DEP_B o-> ANX _B	8	NA	-

NA	-	DEP_B --> ANX_B	8
DEP_B o-o CDSS_B	9	NA	-
NA	-	DEP_B --> CDSS_B	9
DEP_B o-o LN_B	9	NA	-
NA	-	DEP_B--> LN_B	10
DEP_B o-o MOT_B	7	NA	-
NA	-	DEP_B --> MOT_B	7
DEP_6m --> LN_6m	6	DEP_6m --> LN_6m	7
DEP_6m --> MOT_6m	3	DEP_6m --> MOT_6m	4
MOT_B o-o DEP_B	3	NA	-
NA	-	MOT_B --> DEP_B	3
MOT_6m --> DEP_6m	5	MOT_6m --> DEP_6m	5

Appendix G

Pooled Average Bootstrap Resampling Outcomes for Pooled Causal Graphs

Edge Type in PAG	Edge Count	Nodes		Proportion of 1000 pooled bootstrap resamples with edge type						
		Node 1	Node 2	-->	<--	o->	<-o	o-o	<-->	No Edge
-->	10	BIS_B	BIS_6m	**0.65075**	-	0.14615	0.0053	0.04895	0.02369	0.13908
-->	10	InDI-A_B	InDI-A_6m	**0.63398**	0.00262	0.11539	0.006	0.10289	0.05234	0.08852
-->	9	SI_B	SI_6m	**0.39073**	0.001	0.24732	0.00286	0.17914	0.00463	0.17637
o-o	9	DEP_B	MOT_B	0.36806	0.02422	0.04197	0.0697	**0.48352**	0.00425	0.00878
-->	7	DEP_6m	LN_6m	**0.5573**	0.20749	0.04439	0.01028	0.015	0.00483	0.1614
-->	7	IMR-SD_6m	IMR-FI_6m	**0.5299**	0.27614	0.03157	0.04353	0.05097	0.012	0.07834
-->	6	InDI-A_6m	InDI-D_6m	**0.58443**	0.22028	0.0408	0.04363	0.03133	0.0691	0.0126
-->	6	InDI-D_B	InDI-A_B	**0.45737**	0.09873	0.06458	0.06025	0.2892	0.0065	0.02333
-->	6	DEP_6m	MOT_6m	**0.60392**	0.2356	0.06743	0.015	0.01767	0.03	0.03658
-->	5	DEP_B	LN_B	**0.35724**	0.05154	0.1227	0.0228	0.3063	0.002	0.13746
o-o	5	IMR-FI_B	IMR-SD_B	0.32508	0.0835	0.09892	0.0308	**0.45976**	0.00267	0.001
-->	5	ANX_B	BIS_B	**0.34926**	0.05036	0.0731	0.05376	0.15344	0.0036	0.3165
o-o	4	IMR-SD_B	IMR-FI_B	0.0859	0.36335	0.03425	0.07043	**0.44453**	0.002	-
o->	4	LEC-5_B	InDI-D_B	0.13438	0.1648	**0.31143**	0.05968	0.22628	0.00375	0.09965
o-o	4	LEC-5_B	InDI-D_B	0.10365	0.21105	0.18158	0.08615	**0.31418**	0.00425	0.09915
o-o	4	ANX_B	DEP_B	0.13985	0.24428	0.02525	0.13915	**0.3242**	0.00225	0.12515
o-o	4	DEP_B	ANX_B	0.24078	0.13638	0.16435	0.02	**0.30745**	0.001	0.13013
-->	4	MOT_6m	DEP_6m	**0.5372**	0.27075	0.0427	0.024	0.05268	0.005	0.09023
-->	3	LN_6m	CDSS_6m	**0.5581**	0.17883	0.0343	0.01933	0.022	0.00567	0.1818
o-o	3	InDI-D_B	InDI-A_B	0.27107	0.14953	0.0779	0.05093	**0.43123**	0.00333	0.016
-->	3	InDI-D_B	InDI-D_6m	**0.5771**	0.004	0.1232	0.005	0.03667	0.03897	0.2181

-->	2	LN_6m	DEP_6m	**0.52395**	0.32065	0.04195	0.036	0.0415	0.0055	0.03045
-->	2	BIS_6m	IMR-SD_6m	**0.42255**	0.28775	0.0355	0.03945	0.016	0.0225	0.17635
-->	2	IMR-FI_6m	DEP_6m	**0.37865**	0.2792	0.04845	0.0295	0.021	0.0205	0.22275
-->	2	InDI-D_6m	InDI-A_6m	**0.4945**	0.29425	0.031	0.0275	0.0115	0.12635	0.015
o->	2	race	ANX_B	0.04	0.01	**0.4166**	0.002	0.16535	0.003	0.3691
-->	2	ANX_6m	BIS_6m	**0.4925**	0.2053	0.04795	0.009	0.0075	0.025	0.21275
-->	2	ANX_6m	MOT_6m	**0.4625**	0.22225	0.05545	0.014	0.025	0.0205	0.2003
-->	2	DEP_B	ANX_B	**0.26675**	0.1279	0.15235	0.0275	0.2123	0.002	0.2113
-->	1	LN_B	DEP_6m	**0.4286**	-	0.0999	0.001	0.0809	0.011	0.3786
o-o	1	DEP_B	LN_B	0.3197	0.0519	0.0779	0.016	**0.3257**	0.002	0.2068
o-o	1	DEP_B	CDSS_B	0.2567	0.0899	0.0709	0.1139	**0.2907**	0.006	0.1718
-->	1	DEP_B	CDSS_B	**0.2717**	0.0719	0.1339	0.044	0.2108	0.008	0.2597
-->	1	IMR-FI_B	IMR-SD_B	**0.4116**	0.0969	0.045	0.0549	0.3906	0.001	-
-->	1	IMR-FI_6m	IMR-SD_6m	**0.5435**	0.2468	0.0919	0.018	0.0639	0.009	0.027
o-o	1	InDI-A_B	InDI-D_B	0.1558	0.3227	0.0569	0.0689	**0.3546**	0.009	0.032
o-o	1	MOT_B	DEP_B	0.021	0.3367	0.0549	0.048	**0.5315**	0.004	0.004

APPENDIX H

FULL BOOTSTRAP TABLE

Edge Type in PAG	Nodes		Proportion of 1000 bootstrap resamples with edge type						
	Node 1	**Node 2**	**-->**	**<--**	**o->**	**<-o**	**o-o**	**<-->**	**No Edge**
-->	MHR_6m	MHR_12m	**0.8641**	-	0.047	-	-	0.009	0.0799
-->	LN_6m	LN_12m	**0.8392**		0.041	0.004	0.001	0.0529	0.0619
-->	IS_6m	IS_12m	**0.8342**	-	0.0739	0.005	0.015	0.046	0.026
-->	MOT_6m	RF_6m	**0.8012**	0.042	0.0559	0.02	0.019	0.005	0.0569
-->	LN_3m	LN_6m	**0.7712**		0.029	-	0.007	0.031	0.1618
-->	MHR_3m	MHR_6m	**0.7373**	-	0.1439	0.001	0.002	0.1119	0.004
-->	RF_6m	RF_12m	**0.7193**	-	0.039	0.002	-	0.006	0.2338
-->	NEG_12m	SAC_12m	**0.7103**	0.2058	0.0549	0.014	0.007	0.006	0.002
-->	SF_6m	SF_12m	**0.6993**	-	0.0609	0.002	0.001	0.0609	0.1758
-->	CDSS_M12	SI_M12	**0.6773**	0.1598	0.008	0.045	0.01	0.04	0.0599
-->	CDSS_12m	ANX_12m	**0.6643**	0.2238	0.01	0.038	0.006	0.0579	-
-->	IS_6m	LN_M06	**0.6424**	0.1099	0.022	0.007	0.003	0.0679	0.1479
-->	SF_B	SF_M06	**0.6184**	-	0.0559	-	0.014	0.0799	0.002
-->	IS_3m	IS_6m	**0.5664**	0.006	0.2967	0.003	0.0879	0.038	0.002
-->	POS_B	POS_12m	**0.5634**		0.1249		0.01	0.0769	0.2248
o->	LN_B	LN_3m	0.3427	0.014	**0.5385**	-	0.0689	0.004	0.032
-->	RF_B	RF_12m	**0.5385**	-	0.043	-	-	0.1129	0.3057
-->	NEG_6m	SF_6m	**0.5245**	0.3147	0.0549	0.019	0.012	0.033	0.001
-->	MOT_12m	RF_12m	**0.5185**	0.1898	0.012	0.002	-	0.007	0.2707
-->	POS_6m	POS_12m	**0.5095**		0.033	-	-	0.003	0.4545
-->	CDSS_6m	SI_6m	**0.5035**	0.2278	0.017	0.1728	0.018	0.012	0.049

-->	MHR_3m	MHR_12m	**0.4785**	-	0.011	-	0.002	0.1089	0.3996
-->	SF_B	SF_12m	**0.4755**	-	0.031	-	-	0.0809	0.4126
-->	GCog_B	GCog_12m	**0.4755**	-	0.1808	0.005	0.3377	0.001	-
-->	CDSS_6m	ANX_6m	**0.4705**	0.3247	0.018	0.0639	0.014	0.025	0.0839
-->	NEG_12m	MOT_12m	**0.4705**	0.0929	0.019	0.004	0.001	0.012	0.4006
-->	SF_6m	MOT_6m	**0.4695**	0.1419	0.015	0.0629	0.003	0.044	0.2637
-->	IS_12m	MHR_12m	**0.4555**	0.3736	0.004	-	-	0.021	0.1459
o-o	CDSS_B	ANX_B	**0.2318**	0.1439	0.0849	0.0689	**0.4386**		0.032
-->	NEG_6m	SAC_6m	**0.4376**	0.3437	0.044	0.1189	0.049	0.007	
-->	SF_12m	NEG_12m	**0.4286**	0.2657	0.001	0.025		0.007	0.2727
-->	MOT_B	SF_B	**0.4006**	0.1538	0.1049	0.016	0.0929	0.007	0.2108
-->	SAC_B	NEG_B	**0.3766**	0.2378	0.038	0.042	0.2887	0.003	
-->	MOT_B	SAC_B	**0.3626**	0.1479	0.038	0.0839	0.1818	0.013	0.1588
-->	MHR_B	MHR_03m	**0.3596**	0.0679	0.2088	0.003	0.0949	0.1479	0.1179
-->	IS_B	IS_3m	**0.3477**	0.027	0.1029	0.006	0.2807	0.03	0.2058
-->	MOT_B	RF_B	**0.3427**	0.1439	0.0889	0.1648	0.1808	0.027	0.01
o->	IS_3m	LN_3m	0.3367	0.1339	**0.2597**	0.033	-	0.015	0.2218
o-o	ageill	log_age	0.018	0.026	0.2008	0.3297	**0.3347**	0.023	0.0679

APPENDIX I

The Experience of Loneliness Among People Participating in Early Psychosis Treatment Programs Semi-Structured Interview Script

(Questions that are **BOLD** are asked to everyone. Questions that are *ITALICIZED* are examples of probing questions.)

The purpose of this interview is to explore and better understand the experience of loneliness among people participating in our early psychosis treatment programs.

"So, as we discussed in the consenting process, I am going to you questions about your experience of loneliness and your treatment program. At any point you can decline to answer a question or stop the interview."

How do you define loneliness?

How do you experience loneliness (how do you know when you are lonely)?

When do you think you first started feeling lonely?

- ***How has that changed?***
- *Probe: Has psychosis affected your experience of loneliness?*

What gets in the way of social relationships/connections? *(Alternate question: What makes it hard to find or keep social relationships?)*

- ***Do mental health symptoms influence your experience of loneliness?***
- *Probe for stigma? Does stigma play a role in feeling lonely?*

Can you find companionship when you want it?

How do you try to connect with others?

- *Probe for stress: Is it stressful?*
- *Probe for places/spaces that feel more welcoming to connections*

Who relies on you?

- *Probe: What types of things do people rely on you for?*

- *If response is nobody or minimal: Why do you think people don't rely on you?*
    - *Does this contribute to feeling lonely or disconnected from others?*

- *Probe: Do people rely on you differently since your diagnosis?*
    - *Why do think that is?*
    - *Does being relied upon, or not, contribute to feeling lonely or disconnected from others?*

What qualities are the most important for you in close social relationships (friendships, romantic partners, family, etc.)?

Has treatment helped with loneliness?

- *If yes: what helped?*
    - *Was there anything that was not helpful?*

- *If no: Is there anything that would have been helpful? What was missing?*

In general, what do you think would help you, or other folks with early psychosis, feel less lonely?

Appendix J

Study 1 Generalized Psychosis Sample Standardized Causal Effect Sizes

Edge Type (MAG)	Nodes		Standardized Effect Size	Standard Error	z-score	p-value	Confidence Interval	
							lower	upper
-->	BDI-II_B	BDI-II_4m	0.36928	0.089328	4.133999	3.57E-05	0.194201	0.544359
-->	BDI-II_4m	BDI-II_6m	0.833927	0.035196	23.69353	0	0.764944	0.902911
-->	BDI-II_4m	QSANS_3	0.382128	0.080768	4.731178	2.23E-06	0.223825	0.54043
-->	DB_B	DB_4m	0.730099	0.059275	12.31705	0	0.613921	0.846277
-->	DB_B	DB_6m	0.353671	0.100269	3.52722	0.00042	0.157147	0.550195
-->	DB_4m	DB_6m	0.485414	0.097858	4.960376	7.04E-07	0.293615	0.677213
-->	ISMI_1	DB_B	0.390324	0.107024	3.647051	0.000265	0.180559	0.600088
-->	IS_B	IS_4m	0.357795	0.091018	3.931021	8.46E-05	0.179402	0.536187
-->	IS_4m	IS_6m	0.838502	0.035059	23.91659	0	0.769787	0.907217
-->	MEA_B	BDI-II_B	-0.65143	0.064889	-10.0391	0	-0.77861	-0.52425
-->	MEA_B	IS_B	-0.62486	0.069446	-8.99772	0	-0.76097	-0.48875
-->	MEA_B	MCR_B	0.627712	0.068963	9.102171	0	0.492547	0.762877
-->	MEA_B	RWP_B	0.759468	0.04534	16.75069	0	0.670604	0.848332
-->	MEA_B	ULS_B	-0.56051	0.079966	-7.00937	2.39E-12	-0.71725	-0.40378
-->	MEA_6m	SP_6m	0.552906	0.077899	7.097755	1.27E-12	0.400227	0.705584
-->	MCR_B	SP_B	0.629186	0.075536	8.329621	0	0.481138	0.777233
-->	MCR_B	SF_B	0.570641	0.084555	6.748719	1.49E-11	0.404916	0.736367
-->	MCR_4m	MCR_6m	0.604303	0.056583	10.68002	0	0.493403	0.715203
-->	RWP_B	RWP_6m	0.349083	0.074206	4.70426	2.55E-06	0.203642	0.494523
-->	RWP_4m	BDI-II_4m	-0.38363	0.082869	-4.62933	3.67E-06	-0.54605	-0.22121
-->	RWP_4m	MEA_4m	0.715507	0.046191	15.49013	0	0.624974	0.80604
-->	RWP_4m	RWP_6m	0.50926	0.065575	7.766055	7.99E-15	0.380735	0.637785

-->	RWP_6m	MEA_6m	0.72396	0.057396	12.6135	0	0.611466	0.836453
-->	SP_B	SP_4m	0.581127	0.075027	7.745552	9.55E-15	0.434076	0.728178
-->	SP_4m	SP_6m	0.378268	0.08631	4.382675	1.17E-05	0.209104	0.547433
-->	SP_6m	MCR_6m	0.300571	0.070906	4.238995	2.25E-05	0.161597	0.439545
-->	QSANS_1	MOT_B	-0.75099	0.05534	-13.5706	0	-0.85946	-0.64253
-->	QSANS_1	ER40_rtcr_6m	-0.25296	0.064558	-3.91824	8.92E-05	-0.37949	-0.12642
-->	QSANS_2	MOT_4m	-0.58115	0.049434	-11.7561	0	-0.67804	-0.48426
-->	QSANS_2	SF_4m	-0.64742	0.061734	-10.4872	0	-0.76842	-0.52642
-->	QSANS_3	MOT_6m	-0.76125	0.052264	-14.5654	0	-0.86369	-0.65882
-->	QSAPS_1	QSAPS_2	0.684572	0.05905	11.59314	0	0.568836	0.800307
-->	QSAPS_2	BDI-II_6m	0.085992	0.058373	1.473161	0.140708	-0.02842	0.2004
-->	QSAPS_2	QSAPS_3	0.7259	0.054078	13.42319	0	0.619909	0.831891
-->	ULS_B	ULS _4m	0.738071	0.057034	12.94081	0	0.626286	0.849857
-->	ULS_B	MOT_4m	-0.31545	0.060905	-5.17942	2.23E-07	-0.43482	-0.19608
-->	ULS _4m	BDI-II_4m	0.294527	0.090421	3.257294	0.001125	0.117306	0.471749
-->	ULS _4m	ISMI_2	0.510509	0.084707	6.026788	1.67E-09	0.344487	0.676531
-->	ULS _4m	MEA_4m	-0.23783	0.070334	-3.3815	0.000721	-0.37569	-0.09998
-->	ULS _4m	SP_4m	-0.36401	0.085284	-4.26822	1.97E-05	-0.53117	-0.19686
-->	ULS _4m	ULS _6m	0.815194	0.040553	20.10175	0	0.73571	0.894677
-->	age	age1sx	0.45891	0.085598	5.36124	8.27E-08	0.291141	0.626678
-->	OF_B	MCR_6m	0.226688	0.069659	3.254252	0.001137	0.090159	0.363217
-->	OF_B	OF_4m	0.800368	0.044226	18.09741	0	0.713687	0.887048
-->	OF_B	OF_6m	0.661283	0.071463	9.253461	0	0.521217	0.801348
-->	OF_B	MOT_4m	0.400592	0.062971	6.36149	2E-10	0.277171	0.524014
-->	OF_6m	QSANS_3	-0.21516	0.082974	-2.59315	0.00951	-0.37779	-0.05254
-->	MOT_B	OF_B	0.417765	0.104829	3.98521	6.74E-05	0.212304	0.623226
-->	MOT_6m	RWP_6m	0.319712	0.074772	4.275833	1.9E-05	0.173162	0.466262
-->	SF_B	QSANS_1	-0.71404	0.062118	-11.4949	0	-0.83579	-0.59229
-->	SF_B	SF_6m	0.744125	0.056548	13.15915	0	0.633292	0.854957
-->	SF_6m	QSANS_3	-0.5498	0.074449	-7.38495	1.53E-13	-0.69572	-0.40388
-->	ER40_cr_B	ER40_cr_4m	0.594108	0.074571	7.967024	1.55E-15	0.447952	0.740264

-->	ER40_cr_B	ER40_cr_6m	0.27829	0.097447	2.855808	0.004293	0.087297	0.469282
-->	ER40_cr_4m	ER40_cr_6m	0.485063	0.094419	5.137335	2.79E-07	0.300005	0.670122
-->	ER40_rtcr_B	ER40_rtcr_4m	0.611708	0.071659	8.536416	0	0.47126	0.752157
-->	ER40_rtcr_B	ER40_rtcr_6m	0.368144	0.07648	4.813627	1.48E-06	0.218247	0.518042
-->	ER40_rtcr_4m	ER40_rtcr_6m	0.510707	0.075751	6.7419	1.56E-11	0.362237	0.659177

ULS = UCLA Loneliness Scale, IS = Internalized Stigma of Mental Illness Scale – Abbreviated, DB = Defeatist Beliefs Subscale, MEA = MAPS-SR Motivation to Engage in Activities, SP = MAPS-SR Social Pleasure, MCR = MAPS-SP Motivation for Close Relationships, RWP = MAPS-SP Recreation and Work Pleasure, MOT = QLS Intrapsychic Foundations Subscale, BDI-II = Beck Depression Inventory – II, SF = QLS Interpersonal Relations subscale, OF = QLS Occupational Role Functioning subscale, ER40 = ER-40 Emotion Recognition task (cr = total correct responses, rtcr = reaction time for correct responses), QSAPS = Quick Scale for the Assessment of Positive Symptoms, QSANS = Quick Scale for the Assessment of Negative Symptoms, age = age at study enrollment, age1sx = reported age of first symptoms

Appendix K

Study 1 Generalized Psychosis Sample Raw Causal Effect Sizes

Edge Type (MAG)	Nodes		Effect Size	Standard Error	z-score	p-value	Confidence Interval	
							lower	upper
-->	BDI-II_B	BDI-II_4m	0.357261	0.090333	3.954938	7.66E-05	0.180212	0.534311
-->	BDI-II_4m	BDI-II_6m	0.746673	0.052562	14.20551	0	0.643653	0.849693
-->	BDI-II_4m	QSANS_3	0.547125	0.119032	4.596438	4.3E-06	0.313826	0.780423
-->	DB_B	DB_4m	0.685832	0.081523	8.412782	0	0.526051	0.845614
-->	DB_B	DB_6m	0.335635	0.096656	3.472454	0.000516	0.146192	0.525078
-->	DB_4m	DB_6m	0.490393	0.102839	4.768548	1.86E-06	0.288832	0.691954
-->	ISMI_1	DB_B	1.124916	0.336982	3.338204	0.000843	0.464443	1.785389
-->	IS_B	IS_4m	0.350546	0.092608	3.785266	0.000154	0.169038	0.532054
-->	IS_4m	IS_6m	0.849743	0.055898	15.20157	0	0.740184	0.959302
-->	MEA_B	BDI-II_B	-1.54518	0.228556	-6.76059	1.37E-11	-1.99314	-1.09721
-->	MEA_B	IS_B	-0.59016	0.093647	-6.30194	2.94E-10	-0.7737	-0.40661
-->	MEA_B	MCR_B	0.327229	0.051538	6.349332	2.16E-10	0.226217	0.428241
-->	MEA_B	RWP_B	0.440121	0.047879	9.192394	0	0.346281	0.533962
-->	MEA_B	ULS_B	-1.42569	0.267516	-5.32937	9.86E-08	-1.95002	-0.90137
-->	MEA_6m	SP_6m	0.30426	0.049346	6.165894	7.01E-10	0.207544	0.400975
-->	MCR_B	SP_B	0.663559	0.104104	6.373985	1.84E-10	0.459518	0.867599
-->	MCR_B	SF_B	0.347463	0.063504	5.471551	4.46E-08	0.222998	0.471928
-->	MCR_4m	MCR_6m	0.630141	0.074278	8.483548	0	0.484559	0.775723
-->	RWP_B	RWP_6m	0.272698	0.059516	4.581961	4.61E-06	0.156049	0.389346
-->	RWP_4m	BDI-II_4m	-1.73301	0.409458	-4.23245	2.31E-05	-2.53554	-0.93049
-->	RWP_4m	MEA_4m	1.263669	0.12388	10.20071	0	1.020867	1.50647
-->	RWP_4m	RWP_6m	0.453844	0.067672	6.706534	1.99E-11	0.321209	0.586478

-->	RWP_6m	MEA_6m	1.411119	0.170767	8.263431	2.22E-16	1.076422	1.745815
-->	SP_B	SP_4m	0.529738	0.079645	6.651215	2.91E-11	0.373636	0.68584
-->	SP_4m	SP_6m	0.366502	0.086882	4.218375	2.46E-05	0.196216	0.536788
-->	SP_6m	MCR_6m	0.319342	0.075685	4.219334	2.45E-05	0.171001	0.467683
-->	QSANS_1	MOT_B	-0.03572	0.003988	-8.95539	0	-0.04353	-0.0279
-->	QSANS_1	ER40_rtcr_6m	-0.00937	0.002316	-4.0452	5.23E-05	-0.01391	-0.00483
-->	QSANS_2	MOT_4m	-0.02646	0.002668	-9.91495	0	-0.03169	-0.02123
-->	QSANS_2	SF_4m	-0.05819	0.007997	-7.27671	3.42E-13	-0.07387	-0.04252
-->	QSANS_3	MOT_6m	-0.03793	0.004103	-9.24368	0	-0.04597	-0.02989
-->	QSAPS_1	QSAPS_2	0.733685	0.099218	7.394687	1.42E-13	0.539222	0.928149
-->	QSAPS_2	BDI-II_6m	0.069732	0.047049	1.48212	0.138308	-0.02248	0.161946
-->	QSAPS_2	QSAPS_3	0.544596	0.055649	9.786338	0	0.435527	0.653665
-->	ULS_B	ULS_4m	0.727245	0.084433	8.613284	0	0.56176	0.892731
-->	ULS_B	MOT_4m	-0.02012	0.0038	-5.29624	1.18E-07	-0.02757	-0.01268
-->	ULS_4m	BDI-II_4m	0.269678	0.084468	3.192651	0.00141	0.104123	0.435233
-->	ULS_4m	ISMI_2	0.188484	0.034899	5.400895	6.63E-08	0.120084	0.256885
-->	ULS_4m	MEA_4m	-0.08514	0.025064	-3.39686	0.000682	-0.13426	-0.03601
-->	ULS_4m	SP_4m	-0.07279	0.017472	-4.16626	3.1E-05	-0.10703	-0.03855
-->	ULS_4m	ULS_6m	0.849074	0.066307	12.8052	0	0.719115	0.979033
-->	age	age1sx	0.335174	0.073254	4.575511	4.75E-06	0.191599	0.478749
-->	OF_B	MCR_6m	0.314019	0.095536	3.286927	0.001013	0.126772	0.501266
-->	OF_B	OF_4m	0.7816	0.067724	11.54104	0	0.648864	0.914336
-->	OF_B	OF_6m	0.67297	0.096951	6.941329	3.88E-12	0.482949	0.862991
-->	OF_B	MOT_4m	0.174544	0.026797	6.513624	7.34E-11	0.122023	0.227065
-->	OF_6m	QSANS_3	-1.86527	0.719187	-2.59358	0.009498	-3.27485	-0.45569
-->	MOT_B	OF_B	0.893368	0.246748	3.620568	0.000294	0.409751	1.376985
-->	MOT_6m	RWP_6m	0.884164	0.208399	4.242659	2.21E-05	0.47571	1.292618
-->	SF_B	QSANS_1	-8.23767	1.025771	-8.03071	8.88E-16	-10.2481	-6.22719
-->	SF_B	SF_6m	0.66202	0.07548	8.770789	0	0.514082	0.809958
-->	SF_6m	QSANS_3	-6.39682	0.97288	-6.57513	4.86E-11	-8.30363	-4.49001
-->	ER40_cr_B	ER40_cr_4m	0.407988	0.070154	5.815631	6.04E-09	0.270489	0.545486

-->	ER40_cr_B	ER40_cr_6m	0.223873	0.080521	2.780301	0.005431	0.066055	0.381692
-->	ER40_cr_4m	ER40_cr_6m	0.568227	0.117115	4.851893	1.22E-06	0.338687	0.797767
-->	ER40_rtcr_B	ER40_rtcr_4m	0.457079	0.075071	6.088609	1.14E-09	0.309942	0.604216
-->	ER40_rtcr_B	ER40_rtcr_6m	0.221894	0.047602	4.661408	3.14E-06	0.128595	0.315193
-->	ER40_rtcr_4m	ER40_rtcr_6m	0.411957	0.063661	6.471104	9.73E-11	0.287184	0.536731

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Appendix L

Study 2 Early Psychosis Sample Pooled Summary of Standardized Causal Effect Sizes

Edge Type (MAG)	Nodes		Pooled Std. Effect Size	Pooled Std. Effect Size		Pooled Standard Error	Pooled z-score	Pooled p-value	Pooled Confidence Interval	
				Low	High				Lower	Upper
-->	BIS_B	BIS_6m	0.54045	0.31	0.67	0.07063	7.83167	1.10439E-05	0.4020	0.65514
-->	BIS_6m	LN_6m	0.26800	0.14	0.33	0.06984	3.81610	0.00637164	0.13111	0.40488
-->	BIS_6m	IMR-SD_6m	-0.42548	-0.37	-0.51	0.07289	-5.84268	6.7301E-08	-0.56834	-0.28261
-->	CDSS_B	SI_B	-0.36106	-0.28	-0.41	0.09620	-3.77452	0.001258319	-0.54962	-0.22644
-->	CDSS_6m	SI_6m	-0.35843	-0.33	-0.4	0.08384	-4.28160	4.48948E-05	-0.52276	-0.19410
-->	CDSS_6m	ANX_6m	0.37303	0.31	0.46	0.08660	4.35555	0.000170103	0.20329	0.43779
-->	IMR-FI_B	IMR-SD_B	0.78271	0.74	0.82	0.04121	19.35692	0	0.70191	0.85104
-->	IMR-FI_B	IMR-SD_6m	0.35584	0.29	0.44	0.08154	4.37028	0.000207617	0.19602	0.51565
-->	IMR-FI_6m	IMR-SD_6m	0.60506	0.52	0.7	0.06030	10.27173	5.27356E-15	0.48685	0.72326
-->	IMR-FI_6m	ANX_6m	-0.46222	-0.35	-0.58	0.07982	-6.07508	4.52071E-05	-0.61866	-0.30576
-->	IMR-FI_6m	DEP_6m	-0.38571	-0.26	-0.54	0.07130	-5.42714	0.000116282	-0.52547	-0.32376
-->	IMR-SD_B	IMR-SD_6m	0.41658	0.27	0.52	0.07753	5.30742	4.4279E-05	0.26462	0.46526
-->	IMR-SD_6m	IMR-FI_6m	0.56295	0.47	0.7	0.06969	8.43312	9.4612E-11	0.42634	0.65894
-->	IMR-SD_6m	ANX_6m	-0.44977	-0.37	-0.61	0.07322	-6.28792	4.17012E-06	-0.59329	-0.41598
-->	InDI_A_B	InDI_A_6m	0.52674	0.22	0.65	0.07159	7.51325	0.000457202	0.38642	0.64157
-->	InDI_A_6m	IMR-FI_6m	-0.31245	-0.28	-0.34	0.08193	-3.83240	0.000183433	-0.47304	-0.15185
-->	InDI_A_6m	InDI_D_6m	0.62849	0.57	0.66	0.06040	10.45980	0	0.51010	0.70279
-->	InDI_D_B	InDI_A_B	0.62018	0.58	0.65	0.06782	9.17048	3.77476E-16	0.48723	0.72664
-->	InDI_D_B	InDI_D_6m	0.53558	0.53	0.54	0.07878	6.79828	1.34219E-11	0.38115	0.68999
-->	InDI_D_6m	InDI_A_6m	0.46448	0.34	0.56	0.07137	6.87924	3.19489E-05	0.32458	0.60436
-->	LEC_B	InDI_D_B	-0.53535	-0.51	-0.59	0.06686	-8.03662	2.83912E-13	-0.66640	-0.43570
-->	LN_B	InDI_D_B	0.37653	0.32	0.46	0.08231	4.60197	7.65394E-05	0.21519	0.50757
-->	LN_B	DEP_6m	0.30637	0.24	0.4	0.06886	4.44650	8.70669E-05	0.17140	0.44133
-->	LN_6m	CDSS_6m	0.57686	0.53	0.62	0.07096	8.30565	4.63318E-12	0.43777	0.63803
-->	race	ANX_B	-0.30028	-0.25	-0.4	0.07719	-3.87344	0.000225141	-0.45158	-0.17816
-->	SI_B	SI_6m	0.45978	0.39	0.53	0.08018	5.74682	7.72521E-07	0.30262	0.58523
-->	ANX_B	BIS_B	0.50533	0.38	0.56	0.08125	6.30682	7.39796E-06	0.34608	0.63024
-->	ANX_B	IMR-FI_B	-0.5360	-0.45	-0.59	0.07719	-7.02007	1.1553E-08	-0.68729	-0.38471

-->	ANX_6m	BIS_6m	0.39652	0.2	0.53	0.07412	5.46695	0.002505723	0.25125	0.46665
-->	ANX_6m	MOT_6m	0.52285	0.35	0.65	0.07269	7.56528	1.52062E-05	0.38038	0.66532
-->	DEP_B	LN_B	0.64518	0.61	0.68	0.06095	10.64536	0	0.52570	0.73889
-->	DEP_B	CDSS_B	0.62586	0.57	0.64	0.06303	10.03626	1.70234E-15	0.50232	0.71903
-->	DEP_B	ANX_B	0.65189	0.62	0.68	0.05557	11.74142	0	0.54297	0.73330
-->	DEP_B	MOT_B	0.75769	0.71	0.78	0.04112	18.76438	0	0.67708	0.83829
-->	DEP_6m	LN_6m	0.59402	0.52	0.76	0.06238	9.99295	2.77873E-14	0.47174	0.67578
-->	DEP_6m	MOT_6m	0.66281	0.48	0.8	0.05515	13.58215	1.53479E-09	0.55470	0.73327
-->	MOT_B	DEP_B	0.75342	0.73	0.78	0.04089	18.59621	0	0.67327	0.78600
-->	MOT_6m	DEP_6m	0.63698	0.56	0.75	0.05909	11.20426	9.76996E-16	0.52116	0.75280

LN = LN composite score, InDI-D = Intersectional Discrimination Index – day-to-day discrimination, InDI-A = Intersectional Discrimination Index – anticipated discrimination, DEP = Minnesota Symptom Severity Checklist (MSSC), ANX = Minnesota Symptom Severity Checklist (MSSC), MOT = Minnesota Symptom Severity Checklist (MSSC), CDSS = Calgary Depression Scale for Schizophrenia, BIS and BAS = Behavioral Inhibition and Behavioral Activation Scale, LEC = Life Events Checklist for DSM-5, IMR-SD = Illness Management and Recovery Scale – Symptom Distress, IMR-FI = Illness Management and Recovery Scale – Functional impairment, race = binary race variable, SI = suicidal ideation.

Appendix M

Study 3 First-Episode Psychosis Sample Standardized Causal Effect Sizes

Edge Type (MAG)	Nodes		Standardized Effect Size	Standard Error	z-score	p-value	Confidence Interval	
							lower	upper
-->	ANX_B	CDSS_B	0.450996	0.059503	7.579374	3.46E-14	0.334372	0.56762
-->	ANX_B	POS_B	0.286879	0.068127	4.210921	2.54E-05	0.153352	0.420406
-->	ANX_B	IS_B	0.275064	0.071457	3.849362	0.000118	0.135011	0.415117
-->	ANX_m6	POS_m6	0.350603	0.063178	5.549419	2.87E-08	0.226776	0.474431
-->	ANX_m12	POS_m12	0.268448	0.064864	4.138641	3.49E-05	0.141317	0.395578
-->	LN_B	LN_m3	0.442196	0.056665	7.803693	6E-15	0.331135	0.553258
-->	LN_m3	LN_m6	0.402025	0.060356	6.660905	2.72E-11	0.283729	0.52032
-->	LN_m6	LN_m12	0.555502	0.054361	10.21868	0	0.448955	0.662048
-->	LN_m6	SF_m6	-0.19314	0.056653	-3.40922	0.000651	-0.30418	-0.0821
-->	LN_m6	MHR_m6	-0.25196	0.051963	-4.84875	1.24E-06	-0.3538	-0.15011
-->	LN_m12	SF_m12	-0.23217	0.059762	-3.88495	0.000102	-0.3493	-0.11504
-->	MOT_B	SAC_B	0.281002	0.058302	4.819777	1.44E-06	0.166732	0.395271
-->	MOT_B	POS_B	-0.28469	0.069518	-4.09518	4.22E-05	-0.42094	-0.14844
-->	MOT_m6	MOT_m12	0.259213	0.060359	4.294533	1.75E-05	0.140912	0.377514
-->	MOT_m6	SF_m6	0.272649	0.05665	4.812903	1.49E-06	0.161618	0.38368
-->	MOT_m6	RF_m6	0.429115	0.057761	7.429203	1.09E-13	0.315906	0.542323
-->	MOT_m6	MHR_m6	0.24352	0.050354	4.836127	1.32E-06	0.144827	0.342212
-->	SAC_B	SAC_m12	0.230622	0.056351	4.092613	4.27E-05	0.120176	0.341067
-->	SAC_m6	NEG_m6	-0.63871	0.044606	-14.3188	0	-0.72613	-0.55128
-->	SAC_m6	NEG_m12	-0.45052	0.055296	-8.14743	4.44E-16	-0.55889	-0.34214
-->	SF_B	MOT_B	0.422986	0.057209	7.39364	1.43E-13	0.310858	0.535115
-->	SF_B	SF_m6	0.341879	0.056444	6.056958	1.39E-09	0.231251	0.452508

-->	SF_B	SF_m12	0.309712	0.06611	4.684791	2.8E-06	0.180138	0.439285
-->	SF_B	NEG_B	-0.47845	0.057187	-8.36648	0	-0.59053	-0.36637
-->	SF_m6	SF_m12	0.365242	0.066732	5.473302	4.42E-08	0.23445	0.496033
-->	SF_m12	NEG_m12	-0.40907	0.056279	-7.26869	3.63E-13	-0.51938	-0.29877
-->	ageill	log_age	0.356703	0.064937	5.493082	3.95E-08	0.229429	0.483976
-->	ageill	POS_m6	-0.22868	0.064517	-3.54453	0.000393	-0.35513	-0.10223
-->	CDSS_B	MHR_B	-0.28524	0.072338	-3.94321	8.04E-05	-0.42702	-0.14346
-->	CDSS_m6	ANX_m6	0.491713	0.056028	8.776248	0	0.381901	0.601525
-->	CDSS_m6	SI_m6	0.47246	0.054158	8.723734	0	0.366312	0.578607
-->	CDSS_m6	CDSS_m12	0.351695	0.065382	5.379049	7.49E-08	0.223548	0.479842
-->	CDSS_m12	ANX_m12	0.54182	0.055529	9.757443	0	0.432986	0.650655
-->	CDSS_m12	SI_m12	0.462329	0.060874	7.594805	3.09E-14	0.343017	0.581641
-->	GCog_B	GCog_m12	0.759915	0.032905	23.09446	0	0.695423	0.824407
-->	GCog_B	NEG_m6	-0.22729	0.055606	-4.08746	4.36E-05	-0.33627	-0.1183
-->	RF_B	MOT_B	0.347489	0.059701	5.820515	5.87E-09	0.230477	0.4645
-->	RF_B	RF_m6	0.290844	0.062619	4.644659	3.41E-06	0.168113	0.413575
-->	RF_B	RF_m12	0.279061	0.066032	4.226161	2.38E-05	0.149641	0.408481
-->	RF_m6	RF_m12	0.405909	0.064356	6.307194	2.84E-10	0.279772	0.532045
-->	RF_m6	POS_m6	-0.29537	0.064413	-4.58559	4.53E-06	-0.42162	-0.16912
-->	RF_m12	MOT_m12	0.27888	0.06099	4.572526	4.82E-06	0.159341	0.398419
-->	MHR_B	MHR_m3	0.524691	0.055443	9.46367	0	0.416025	0.633356
-->	MHR_m3	MHR_m6	0.642044	0.042172	15.22459	0	0.559389	0.724698
-->	MHR_m3	MHR_m12	0.277825	0.066916	4.151847	3.3E-05	0.146672	0.408978
-->	MHR_m6	MHR_m12	0.424611	0.065441	6.488446	8.67E-11	0.296349	0.552873
-->	NEG_B	SAC_B	-0.55557	0.051236	-10.8432	0	-0.65599	-0.45514
-->	NEG_B	SAC_m6	-0.5424	0.05541	-9.78893	0	-0.65101	-0.4338
-->	NEG_B	SI_m6	-0.19883	0.063769	-3.11799	0.001821	-0.32381	-0.07385
-->	NEG_B	GCog_B	-0.35349	0.06885	-5.13419	2.83E-07	-0.48843	-0.21855
-->	NEG_m6	SF_m6	-0.36048	0.055855	-6.4538	1.09E-10	-0.46995	-0.251
-->	NEG_m12	MOT_m12	-0.38513	0.058039	-6.63572	3.23E-11	-0.49889	-0.27138
-->	NEG_m12	SAC_m12	-0.61027	0.046731	-13.059	0	-0.70186	-0.51868

-->	POS_B	POS _m12	0.32438	0.062964	5.151797	2.58E-07	0.200972	0.447788
-->	POS s_m6	CDSS _m12	0.233495	0.069839	3.343336	0.000828	0.096613	0.370377
-->	POS _m6	POS _m12	0.280603	0.064576	4.345322	1.39E-05	0.154037	0.40717
-->	IS_B	IS_m3	0.502506	0.058889	8.533106	0	0.387086	0.617926
-->	IS_m3	LN_m3	0.316727	0.06336	4.998847	5.77E-07	0.192544	0.440911
-->	IS_m3	MHR_m3	-0.22859	0.063398	-3.60564	0.000311	-0.35285	-0.10433
-->	IS _m3	IS _m6	0.66804	0.043638	15.30879	0	0.582512	0.753568
-->	IS _m6	LN_m6	0.362998	0.061478	5.904537	3.54E-09	0.242503	0.483492
-->	IS _m6	IS _m12	0.656835	0.044809	14.65853	0	0.569011	0.744659
-->	IS _m12	MHR_m12	-0.29499	0.050894	-5.79617	6.78E-09	-0.39474	-0.19524

LN = Loneliness composite score, IS = Self Stigma Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, MOT = Heinrichs-Carpenter Quality of Life Scale items, SAC = Heinrichs-Carpenter Quality of Life Scale items, SF = Heinrichs-Carpenter Quality of Life Scale items, RF = Heinrichs-Carpenter Quality of Life Scale Role Functioning subscale, POS/NEG = Positive and Negative Syndrome Scale (PANSS), ANX = Positive and Negative Syndrome Scale items, GCog = z-score of total Brief Assessment of Cognition in Schizophrenia (BACS) tasks, SI = Suicidal ideation, ageill = age of first illness, log_age = log-transformed age variable

Appendix N

Study 3 First-Episode Psychosis Sample Raw Causal Effect Sizes

Edge Type (MAG)	Nodes		Raw Effect Size	Standard Error	z-score	p-value	Confidence Interval	
							lower	upper
-->	ANX_B	CDSS_B	0.716452	0.111743	6.411581	1.44E-10	0.497439	0.935465
-->	ANX_B	POS_B	0.623835	0.157617	3.957924	7.56E-05	0.314912	0.932757
-->	ANX_B	IS_B	0.925248	0.254875	3.630199	0.000283	0.425702	1.424794
-->	ANX_m6	POS_m6	0.800618	0.152514	5.249469	1.53E-07	0.501696	1.09954
-->	ANX_m12	POS_m12	0.561093	0.139294	4.028124	5.62E-05	0.288082	0.834104
-->	LN_B	LN_m3	0.427764	0.063831	6.701535	2.06E-11	0.302658	0.55287
-->	LN_m3	LN_m6	0.405169	0.065259	6.208603	5.35E-10	0.277263	0.533074
-->	LN_m6	LN_m12	0.538455	0.063522	8.476722	0	0.413955	0.662955
-->	LN_m6	SF_m6	-0.49852	0.14725	-3.38556	0.00071	-0.78713	-0.20992
-->	LN_m6	MHR_m6	-1.32159	0.27331	-4.83552	1.33E-06	-1.85727	-0.78592
-->	LN_m12	SF_m12	-0.6576	0.171644	-3.83119	0.000128	-0.99401	-0.32118
-->	MOT_B	SAC_B	0.168384	0.035653	4.722836	2.33E-06	0.098505	0.238263
-->	MOT_B	POS_B	-0.41978	0.106876	-3.92773	8.58E-05	-0.62925	-0.21031
-->	MOT_m6	MOT_m12	0.241043	0.058494	4.120804	3.78E-05	0.126397	0.35569
-->	MOT_m6	SF_m6	0.561129	0.121817	4.606317	4.1E-06	0.322372	0.799887
-->	MOT_m6	RF_m6	0.895518	0.138714	6.455878	1.08E-10	0.623644	1.167392
-->	MOT_m6	MHR_m6	1.018495	0.217051	4.692422	2.7E-06	0.593083	1.443907
-->	SAC_B	SAC_m12	0.228765	0.056403	4.055891	4.99E-05	0.118217	0.339314
-->	SAC_m6	NEG_m6	-1.52295	0.133308	-11.4243	0	-1.78423	-1.26167
-->	SAC_m6	NEG_m12	-1.0496	0.139543	-7.52167	5.42E-14	-1.3231	-0.7761
-->	SF_B	MOT_B	0.214236	0.032702	6.551248	5.71E-11	0.150142	0.27833
-->	SF_B	SF_m6	0.364311	0.064368	5.659855	1.52E-08	0.238153	0.49047

-->	SF_B	SF_m12	0.351047	0.078535	4.469965	7.82E-06	0.197122	0.504972
-->	SF_B	NEG_B	-0.38433	0.055591	-6.91351	4.73E-12	-0.49329	-0.27538
-->	SF_m6	SF_m12	0.388497	0.074198	5.235987	1.64E-07	0.243073	0.533922
-->	SF_m12	NEG_m12	-0.29068	0.042561	-6.82976	8.51E-12	-0.3741	-0.20726
-->	ageill	log_age	0.004793	0.000963	4.974998	6.52E-07	0.002905	0.006681
-->	ageill	POS_m6	-0.18512	0.054148	-3.41879	0.000629	-0.29125	-0.07899
-->	CDSS_B	MHR_B	-1.34903	0.357243	-3.77621	0.000159	-2.04921	-0.64884
-->	CDSS_m6	ANX_m6	0.273728	0.038203	7.165186	7.77E-13	0.198853	0.348604
-->	CDSS_m6	SI_m6	0.068157	0.00932	7.313269	2.61E-13	0.049891	0.086423
-->	CDSS_m6	CDSS_m12	0.288981	0.058762	4.917788	8.75E-07	0.173809	0.404153
-->	CDSS_m12	ANX_m12	0.365177	0.044645	8.179625	2.22E-16	0.277675	0.452679
-->	CDSS_m12	SI_m12	0.081897	0.012132	6.750661	1.47E-11	0.058119	0.105675
-->	GCog_B	GCog_m12	0.774813	0.050769	15.26166	0	0.675309	0.874318
-->	GCog_B	NEG_m6	-1.35466	0.333219	-4.06539	4.8E-05	-2.00776	-0.70157
-->	RF_B	MOT_B	0.179433	0.03334	5.381932	7.37E-08	0.114088	0.244777
-->	RF_B	RF_m6	0.320403	0.073224	4.375641	1.21E-05	0.176886	0.46392
-->	RF_B	RF_m12	0.30076	0.074559	4.033844	5.49E-05	0.154626	0.446893
-->	RF_m6	RF_m12	0.397111	0.067681	5.867436	4.43E-09	0.26446	0.529763
-->	RF_m6	POS_m6	-0.20639	0.046723	-4.41729	9.99E-06	-0.29797	-0.11481
-->	RF_m12	MOT_m12	0.12702	0.028456	4.463667	8.06E-06	0.071246	0.182793
-->	MHR_B	MHR_m3	0.481288	0.059102	8.143304	4.44E-16	0.36545	0.597126
-->	MHR_m3	MHR_m6	0.587442	0.04767	12.32304	0	0.49401	0.680874
-->	MHR_m3	MHR_m12	0.255802	0.062365	4.101691	4.1E-05	0.133569	0.378035
-->	MHR_m6	MHR_m12	0.42729	0.068497	6.238076	4.43E-10	0.293038	0.561542
-->	NEG_B	SAC_B	-0.20991	0.02248	-9.33748	0	-0.25397	-0.16585
-->	NEG_B	SAC_m6	-0.23343	0.028495	-8.1921	2.22E-16	-0.28928	-0.17759
-->	NEG_B	SI_m6	-0.02121	0.006896	-3.07549	0.002102	-0.03472	-0.00769
-->	NEG_B	GCog_B	-0.06086	0.012693	-4.79485	1.63E-06	-0.08574	-0.03598
-->	NEG_m6	SF_m6	-0.46599	0.075288	-6.1895	6.04E-10	-0.61355	-0.31843
-->	NEG_m12	MOT_m12	-0.23023	0.03681	-6.25465	3.98E-10	-0.30238	-0.15809
-->	NEG_m12	SAC_m12	-0.22811	0.021267	-10.726	0	-0.26979	-0.18643

-->	POS_B	POS _m12	0.298614	0.06047	4.938201	7.88E-07	0.180095	0.417134
-->	POS s_m6	CDSS _m12	0.150926	0.046226	3.264994	0.001095	0.060326	0.241527
-->	POS _m6	POS _m12	0.255507	0.060665	4.211743	2.53E-05	0.136605	0.374409
-->	IS_B	IS_m3	0.563125	0.076358	7.374833	1.65E-13	0.413466	0.712783
-->	IS_m3	LN_m3	0.100222	0.020879	4.800034	1.59E-06	0.059299	0.141144
-->	IS_m3	MHR_m3	-0.41792	0.117797	-3.54777	0.000389	-0.6488	-0.18704
-->	IS _m3	IS _m6	0.679926	0.059689	11.39119	0	0.562938	0.796914
-->	IS _m6	LN_m6	0.113737	0.020289	5.605892	2.07E-08	0.073972	0.153503
-->	IS _m6	IS _m12	0.683968	0.061881	11.05295	0	0.562683	0.805252
-->	IS _m12	MHR_m12	-0.46853	0.081126	-5.77532	7.68E-09	-0.62753	-0.30952

LN = Loneliness composite score, IS = Self Stigma Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, MOT = Heinrichs-Carpenter Quality of Life Scale items, SAC = Heinrichs-Carpenter Quality of Life Scale items, SF = Heinrichs-Carpenter Quality of Life Scale items, RF = Heinrichs-Carpenter Quality of Life Scale Role Functioning subscale, POS/NEG = Positive and Negative Syndrome Scale (PANSS), ANX = Positive and Negative Syndrome Scale items, GCog = z-score of total Brief Assessment of Cognition in Schizophrenia (BACS) tasks, SI = Suicidal ideation, ageill = age of first illness, log_age = log-transformed age variable