LONGITUDINAL CHARACTERIZATION OF PSYCHOSIS AMONG ADULTS LIVING IN MARGINAL HOUSING

by

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B.Sc., Queen's University, 2011

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Neuroscience)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

April 2018

Abstract

People living in marginal or inadequate housing experience increased risk for premature mortality and face accumulating health challenges associated with poverty, substance use, and physical and mental illness. In particular, psychotic disorders, such as schizophrenia or schizoaffective disorder, may be more common. Psychosis, or grossly impaired reality testing, is a key feature of these disorders, but remains poorly understood, due to the heterogeneous course, multifaceted etiology, and complex clinical presentation. As part of a five-year longitudinal study of adults living in urban marginalized housing in Vancouver, Canada, we sought to characterize the consequences, risk factors, and dynamics of psychosis over time. First, we demonstrated that psychotic disorders were a significant risk factor for premature mortality over the study period, beyond other potentially treatable illnesses. Second, through direct clinical interviews each month, we observed a high prevalence of psychosis and psychosis risk factors. Among those without schizophrenia or schizoaffective disorder, the number of days of methamphetamine, powder cocaine, cannabis, or alcohol use predicted dose-related increases in odds of psychosis, without evidence of interaction or reverse causation. Recent trauma, and histories of early-life trauma or brain injury, also had independent effects on psychosis. No relationships with risk factors were demonstrated in the schizophrenia/schizoaffective group. Lastly, we examined how psychosis may evolve over time through the interplay between psychotic symptoms themselves. By assessing symptoms monthly and applying a multilevel dynamic network analytic approach, we disentangled the within-individual temporal dynamics of psychotic symptoms from the stable between-individual differences. Psychotic symptoms fluctuated and were positively reinforcing over time. Delusions had a central role in the symptom

network, at both the between-individual and within-individual levels. Delusions were associated with more severe unusual thought content or suspiciousness, but not conceptual disorganization. In the dynamic symptom network, suspiciousness was upstream and hallucinations were downstream in the symptom activation cascade. Dynamic network connectivity was greatest in the group with schizophrenia or schizoaffective disorder. Overall, these studies identify multiple risk factors and psychopathological processes that contribute to the longitudinal characteristics of psychosis and suggest potential targets for intervention and prevention strategies among adults at risk for psychosis.

Lay Summary

People living in unstable housing conditions experience greater risk for co-occurring illness, including psychotic disorders such as schizophrenia. As part of a five-year prospective study, this thesis characterized the consequences, risk factors, and dynamics of psychosis experienced by adults in urban, marginalized housing. Psychotic disorders were associated with premature mortality, beyond other potentially treatable illnesses. Early-life and ongoing psychosis risk factors were prevalent. Early-life trauma, past traumatic brain injury, and ongoing trauma and methamphetamine, powder cocaine, cannabis, or alcohol use independently predicted psychosis in adults without schizophrenia over time. Applying a network approach, psychotic symptoms fluctuated and positively reinforced each other over five years. Delusions had a central role in the psychotic symptom network and suspiciousness was upstream in the symptom activation cascade. Adults with schizophrenia had the greatest dynamic network connectivity. Overall, this work identifies potential targets for intervention and prevention strategies among adults at risk for psychosis.

Preface

All of the studies presented were conducted as part of the Hotel Study, a longitudinal study of adults living in marginalized housing in Vancouver, Canada. This study was approved by the Clinical Research Ethics Board of the University of British Columbia (certificate number H08-00521). In collaboration with the Hotel Study investigators and under the supervision of Dr. William Honer, I was the lead investigator for the studies described in Chapters 3, 4, and 5 of this dissertation.

A version of Chapter 3 has been published [Jones AA, Vila-Rodriguez F, Leonova O, Langheimer V, Lang DJ, Barr AM, Procyshyn RM, Smith GN, Schultz K, Buchanan T, Krausz M, Montaner JSG, MacEwan GW, Rauscher A, Panenka WJ, Thornton AE, Honer WG. Mortality from treatable illnesses in marginally housed adults: A prospective cohort study. BMJ Open doi: 10.1136/bmjopen-2015-008876]. As lead author, I was responsible for study design, data analysis, and manuscript composition. Vila-Rodriguez F, Leonova O, Langheimer V, Lang DJ, Barr AM, Smith GN, Schultz K, and Buchanan T were involved in acquisition, analysis, and interpretation of the data, administrative and technical support, and editing the manuscript. Krausz M, Montaner JSG, MacEwan GW, Rauscher A, Panenka WJ, and Thornton AE contributed to study concept and design, obtaining funding, interpretation of the data, and critical revision of the manuscript for important intellectual content. Honer WG was the supervising author and was involved throughout project from study concept and design to final manuscript preparation.

A version of Chapter 4 has been prepared as a manuscript for submission. I was responsible for the study design, data analysis, and drafting the text and figures of the manuscript. Willi TS, Seyedin S, Smith GN, Schmitt TA, and Gicas KM contributed to data

management, analysis, and interpretation, and editing the manuscript. Leonova O, Vila-Rodriguez F, and Procyshyn RM provided critical expertise to inform the study concept and design, data interpretation, and manuscript revisions. Buchanan T, Vertinsky AT, Barr AM, and Lang DJ were involved in acquisition, analysis, and interpretation of the data, administrative, and technical support, and editing the manuscript. MacEwan GW, Rauscher A, Panenka WJ, and Thornton AE contributed to study concept and design, obtaining funding, interpretation of the data, and critical revision of the manuscript for important intellectual content. Honer WG was the supervisory author and was involved throughout the projects from study concept and design to manuscript preparation.

The study described in Chapter 5 will be prepared as a manuscript for submission. As lead investigator, I developed the study concept and design, conducted all data analysis, and drafted the manuscript text and figures. Gicas KM, Leonova O, Vila-Rodriguez F, and Cheng A contributed to study concept and critical revisions for intellectual content. Mostafavi S contributed to the supervision of the study design and data modeling. Buchanan T, Lang DJ, Procyshyn RM, and Smith GN were involved in acquisition, analysis, and interpretation of the data, as well as administrative and technical support. MacEwan GW, Barr AM, Rauscher A, Panenka WJ, and Thornton AE contributed to study design, obtaining funding, and interpretation of the data. As in the previous studies, Honer WG was the supervisory author and was involved throughout the entire project development process.

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List of Abbreviations

AIC – Akaike Information Criterion

AIDS – autoimmune deficiency syndrome

APRI – aspartate aminotransferase:platelet ratio index

AR Group – At-Risk Group (no schizophrenia or schizoaffective disorder diagnosis)

CI – confidence interval

COPD – chronic obstructive pulmonary disease

CS Index – centrality stability index

DCC – Downtown Community Court

DIC – disseminated intravascular coagulation

DNA – deoxyribonucleic acid

DSM – Diagnostic and Statistical Manual of Mental Disorders

DVT – deep vein thrombosis

EBIC – extended Bayesian information criterion

EP Group – Endorsing Psychosis at Study Entry Group

HAART – highly active antiretroviral therapy

HBV – hepatitis B virus

HCV – hepatitis C virus

HIV – human immunodeficiency virus

HR – hazard ratio

IQR – interquartile range

LTF – lost to follow-up

MRI – magnetic resonance imaging

MRSA – methicillin-resistant Staphylococcus aureus

MSSA – methicillin-sensitive Staphylococcus aureus

NP Group – Not Endorsing Psychosis at Study Entry Group

NS – not significantly different between groups

OR – odds ratio

PANSS – Positive and Negative Syndrome Scale

PE – pulmonary embolism

PNOS – psychosis not otherwise specified

SD – standard deviation

SMR – standardized mortality ratio

SOFAS – Social and Occupational Functioning Assessment Scale

SSA Group – Schizophrenia/ Schizoaffective Disorder Group

TBI – traumatic brain injury

THQ – Trauma History Questionnaire

THQ18 – Trauma History Questionnaire adapted for events prior to age 18

rTHQ – Trauma History Questionnaire adapted for events in the past month

TMS – transcranial magnetic stimulation

VAR – vector autoregression

Acknowledgements

Dedication

To my parents:

thank you for your infinite support, trust, and love.

Chapter 1: General introduction

1.1   Outline

This dissertation characterizes the longitudinal consequences, risk factors, and dynamics of psychosis experienced by adults living in marginal housing conditions in Vancouver, Canada. These studies consider psychosis as three nested components: a disorder, a mental state, and characteristic symptoms. In Chapter 2, we will outline the methodological approach for the three studies. In Chapter 3, we explore the mortality risk associated with psychotic disorders and other potentially treatable conditions. In Chapter 4, we examine psychosis, a mental state of impaired reality testing, and its relationships with past and ongoing risk factors. Last, in Chapter 5, we deconstruct psychosis into the cardinal psychotic symptoms to understand how these symptoms may dynamically interact and evolve over time.

1.2   Psychosis and psychotic disorders

1.2.1   Phenomenology

Our current understanding of psychosis is heavily informed by clinical descriptions from the turn of the 20th century. Most notably, Emil Kraepelin wrote several texts describing "dementia praecox," a deteriorating condition with poor prognosis characterized by diverse signs and symptoms, including "disconnectedness of thought," auditory hallucinations, or delusions with an "absurd" character (Kraepelin, 1899 as cited by Kendler, 2016; McKenna, 2017). He described that "in the early stages, ideas of persecution predominate" (Kraepelin, 1896 as cited by Kendler, 2016) and attributed the illness to underlying physical brain disease (Falkai et al., 2015). Bleuler (1908) built on these descriptions through longitudinal study of the varied illness course, and redefined the illness

as the "Group of Schizophrenias" (Bleuler, 1908 as cited by Falkai et al., 2015), to capture

the observed heterogeneity. Notably, he described a defining feature of the Group of

Schizophrenias was "disturbance of associations" (Bleuler, 1924 as cited by Kendler, 2016)

in the individual's thought pattern, as well as "los[ing] contact with reality" (Bleuler, 1924 as

cited by Kendler, 2016). In parallel, Jaspers (1913) provided detailed phenomenological

descriptions that emphasized the presence of bizarre thoughts as "un-understandable" from

the perspective the clinician (McKenna, 2017; Walker, 1991). Schneider (1939), a student of

Jaspers, defined the First Rank Symptoms of schizophrenia informed by the importance of

this bizarre quality (Table 1.1) (Cermolacce, Sass, & Parnas, 2010; Fish, 1984; McKenna,

2017). First Rank Symptoms have demonstrated utility in the diagnosis of schizophrenia with

moderate sensitivity and specificity, but may not be endorsed by all individuals with the

disorder (Soares-Weiser et al., 2015).

Table 1.1 First Rank Symptoms (from Fish, 1984; Soares-Weiser et al., 2015)

	Symptom	Example
1	Hearing one's own thoughts spoken aloud	"I hear my thoughts outside my head."
2	Hallucinatory voices in the form of statement and reply, so that the patient hears voices speaking about him/herself in third person	"The first voice says 'he used that fork in an odd way' and then the second replies 'Yes, he did.'"
3	Hallucinatory voices in the form of a running commentary	"They say 'he is sitting down now talking to a psychiatrist.'"
4	Bodily sensations which he/she attributes to external agencies	"I feel them crawling over me."
5	Thought withdrawal, thought insertion, and other influences on thought by an external agency	"My thoughts are fine except when Michael Jackson stops them."
6	Thought broadcasting whereby others share the individual's thoughts in unison	"My thoughts filter out of my head and everyone can pick them up if they walk past."
7	Delusional perception, where the individual attributes a false meaning to a true perception	The traffic lights turning red may be interpreted as meaning that Martians are about to land.
8	Feelings or actions experienced as made or influenced by external agents	"The CIA controlled my arm."

Taken together, there are several key signs and symptoms that have come to be understood as indicators for psychosis, or grossly impaired reality testing (American Psychiatric Association, 1980). These symptoms will be used to indicate presence psychosis for the studies to follow. Hallucinations are aberrant perceptions which are not generated by external stimuli and may be indistinguishable from reality. Delusions are fixed false beliefs that are held in the face of contrary evidence. Unusual or bizarre thoughts are outside what is expected by physical laws and cultural understanding. Paranoia is characterized by unrealistic ideas of persecution or suspicious hypervigilance. Thought disorder is marked by disorganized thinking processes often presenting as loose associations and incoherence in speech. Indeed, these symptoms have been the cornerstone for identifying psychosis as part

of the operationalization of psychotic disorder diagnosis (American Psychiatric Association, 2000; Kendler, 2016; Spitzer, Endicott, & Robins, 1978).

In addition to patterns described clinically, in the past 25 years the field of psychiatry has employed analytic approaches to reduce heterogeneity by grouping symptoms that are empirically similar. An early form of this approach was Liddle's three-syndrome model, comprised of reality distortion (positive), thought form disorders (disorganization), and psychomotor poverty (negative) symptom dimensions (Liddle, 1987). Since then, other models have been proposed, ranging from three to six groupings (or factors) (Emsley et al., 2003; Malla, Norman, Williamson, Cortese, & Diaz, 1993; van der Gaag et al., 2006; Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012). Coupling this strategy with other modes of inquiry, such as neurobiology research, has revealed potential underlying mechanisms for these phenomena.

1.2.2 Neurobiological correlates

For nearly half a century, through technical advancement and rigorous inquiry, the dopamine hypothesis has been central to our understanding of psychosis pathogenesis (Howes & Kapur, 2009; Meltzer & Stahl, 1976). This hypothesis was generated based on the observations that dopaminergic agonists could induce or exacerbate psychosis (Angrist, Sathanathan, Wilk, & Gershon, 1975), and that dopamine antagonists could attenuate psychosis (Seeman & Lee, 1975). Following this foundational research, positron emission tomography (Lindström et al., 1999) and single photon emission computerized tomography (Abi-Dargham et al., 2000) studies identified elevated dopamine synthesis and release in the striatum in people with psychotic disorder. These changes to the brain have regional and clinical specificity: increased dopamine transmission in the mesolimbic pathway correlates

strongly with positive psychotic symptoms and response to antipsychotic treatment, and not with other psychiatric symptoms such as depression, anxiety, or negative symptoms (Agid et al., 2007; Howes et al., 2009; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999).

While striatal dopamine has been implicated in reward prediction (Schultz, Dayan, & Montague, 1997), it may also have a significant role in salience attribution, whereby abnormal dopamine transmission may lead to difficulty distinguishing relevant and irrelevant stimuli (Berridge & Robinson, 1998). Reality distortion, such as hallucinations and delusions, may thus be due to increased salience of innocuous internal (e.g., own voice) or external (e.g., conversing couple) stimuli, shaped by one's own culture and experience (Kapur, 2003). Striatal dopamine dysregulation may be specific to some aspects of psychosis, but may not explain all symptoms. Thus, alternative neurobiological mechanisms have been studied, including glutamatergic transmission, which may underlie dissociative characteristics of psychosis (Javitt & Zukin, 1991).

Ultimately, the etiology of dysregulated neural transmission is thought to be the result of complex interactions between genetic and environmental factors. As with other complex diseases, comprehensive genetic studies have identified a large number of genes that have small effects on the risk for psychosis (Allen et al., 2008). Subsequent sections will explore critical environmental factors, such as non-prescription substance use, trauma, and head injury, that may contribute to psychosis risk.

1.2.3 Health-related consequences of psychosis and psychotic disorders

Psychosis may range in its duration and impact on the health and functioning of the individual. For some individuals, perceptual disturbances may not be distressing or of clinical concern (Baumeister, Sedgwick, Howes, & Peters, 2017); however, for many

individuals living with psychotic disorder such as schizophrenia, there may be devastating impacts on life expectancy and quality of life. Schizophrenia is considered the most disabling mental health condition (Salomon et al., 2012) with significant global disease burden (Murray et al., 2012). A recent meta-analysis demonstrated a significant pooled mortality risk of 2.54 (95% confidence interval [CI] 2.35 to 2.75) for persons with psychotic disorders (Walker, McGee, & Druss, 2015). In the early stages of illness, premature mortality is likely attributed to higher suicide risk (Melle et al., 2006). Co-morbid acute and chronic illness, treatment side effects, behavioral health factors, and accidents also contribute to mortality risk and a life expectancy shortened by 10 to 20 years (Laursen, Nordentoft, & Mortensen, 2014; Lawrence, Hancock, & Kisely, 2013). A population-based study identified that 78% of excess deaths were attributed to co-morbid physical illness, particularly cardiovascular disease (Lawrence et al., 2013). Individuals with psychotic disorder may experience delays in diagnosis and/or further inequities in health service quality (Kisely et al., 2007; Kisely, Campbell, & Wang, 2009; Laursen et al., 2014). Supporting the recovery and minimizing the consequences of psychotic disorders involves addressing the complex factors that govern the course of psychosis.

1.3   Environmental influence on psychosis risk

1.3.1   Biopsychosocial framework

Contemporary models of the development and expression of psychosis include the dynamic interaction of genetic, neurodevelopmental, environmental, cognitive, and social factors (Howes & Murray, 2014; Walker & Diforio, 1997; Zubin & Spring, 1977). Based on these models, researchers postulate that the causes of psychosis are the combined effects of pre-existing vulnerability (genetic or early life factors) and the continued exposure to risk

factors across the lifespan. Psychiatric epidemiology and related fields aim to identify which factors may potentially cause psychosis in order to mitigate onset, exacerbation, and associated consequences. This line of inquiry is guided by key principles for considering potential causal relationships. Notably, the Bradford Hill viewpoints or criteria may be used as a guide to examine associations, explore the possibility of a causal relationship, and test if there is "any other answer that is equally more likely than cause and effect" (Hill, 1965) (Table 1.2). The biopsychosocial factors explored in the present studies were selected based on the consistency, plausibility, analogy, and coherence of their effects on psychosis across studies, as well as their prevalence and relevance to urban, marginally housed populations.

Table 1.2 Summary of Bradford Hill viewpoints (based on Hill, 1965)

Criteria	Definition
Strength	Magnitude of the effect associated with the outcome
Consistency	Repeatedly observed across populations, settings, and time
Specificity	The effect of exposure is limited to the outcome
Temporality	The factor precedes the outcome
Biological gradient	Dose-response effect – increasing the dose of the factor is associated with increasing the response of the outcome
Plausibility	The effect aligns with current scientific understanding
Coherence	The effect does not conflict with current scientific knowledge
Experiment	Intervention on the factor changes the outcome
Analogy	Similar causal relationships have been observed

1.3.2   Marginal housing context

Marginal housing is defined as housing that is below Canadian standards for adequacy (i.e., need for repair), affordability (i.e., rental costs less than 30% of before-tax household income), or suitability (i.e., makeup of bedrooms and household) (Canada Mortgage and Housing Corporation, 2014). In Canada, approximately 150,000 to 300,000

people spend time homeless each year (Fazel, Geddes, & Kushel, 2014). Marginal housing facilities such as single room occupancy (SRO) hotels are one of few alternatives to sleeping on the street or relying on temporary shelters in many urban centers. Individuals living in marginalized housing or experiencing homelessness face increased mortality risk, beyond the effects of low income (Hwang, Wilkins, Tjepkema, O'Campo, & Dunn, 2009). Mortality risk was elevated for both men and women living in shelters or SRO hotels compared to those with stable housing, with men younger than 45 in shelters being the most vulnerable (Hwang et al., 2009). Substance use, human immunodeficiency viral (HIV) and hepatitis C viral (HCV) infection have been identified as predictors of premature mortality among homeless or marginally housed adults (Deans et al., 2013; Grebely et al., 2011; Hwang et al., 2009; Nielsen, Hjorthøj, Erlangsen, & Nordentoft, 2011). The devastating impact of these treatable conditions suggests these may be a proxy for barriers to health.

Rates of psychotic disorders are also elevated in urban communities (Kirkbride et al., 2006; McGrath et al., 2004), particularly among people at risk of homelessness (Fazel et al., 2014). These increased rates may be shaped by early-life and ongoing risk exposures. A recent study demonstrated increased psychosis risk with both early-life and adulthood exposure to social disadvantage indicators, such as long-term separation from caregiver, income below poverty line, and unstable and overcrowded housing (Stilo et al., 2017). Adults living in marginal housing endure significant socioeconomic inequities, and may also have complex histories of early-life trauma, head injury, as well as ongoing exposure to trauma and substance use (Hwang et al., 2008, 2011; Lazarus, Chettiar, Deering, Nabess, & Shannon, 2011; Schmitt et al., 2017; Shannon, Ishida, Lai, & Tyndall, 2006; Vila-Rodriguez

et al., 2013). The impacts of these factors, however, are often examined in isolation, neglecting the realities of cumulative risk exposure.

1.3.3 Sex differences

Epidemiological and clinical studies have found patterns in the expression and onset of psychosis by age and biological sex. Over the life course, men are more likely to develop schizophrenia (Aleman, Kahn, & Selten, 2003), particularly at younger ages (Rabinowitz, Levine, & Häfner, 2006). However, examinations of potential differences in psychopathology have mixed findings, describing psychotic symptoms that were similar or perhaps more severe among women (Leung & Chue, 2000). Sex differences in psychosis may be confounded by sex differences in psychosis risk factors, and the investigation of these potentially interacting factors is necessary.

1.3.4 Substance use exposure

Non-prescription, psychoactive substance use and substance use disorders commonly co-occur with psychotic disorders (Regier et al., 1990). Conversely to antipsychotic medications that block dopamine transmission; substances that increase dopamine transmission have consistently been linked to greater psychosis risk. Acutely, psychosis may be induced or augmented by methamphetamine (Glasner-Edwards & Mooney, 2014), cocaine (Vorspan et al., 2012), cannabis (Murray et al., 2017), or alcohol use (Jordaan & Emsley, 2014).

For individuals with psychotic disorder, evidence consistently suggests that methamphetamine use may exacerbate symptoms (Batki & Harris, 2004), but for cannabis and alcohol, the evidence of use tied to symptom exacerbation is more inconsistent (Addington & Addington, 2007; Zammit et al., 2008). Cannabis use has been shown to be

associated with exacerbations in psychotic symptoms (van der Meer & Velthorst, 2015), but this effect is potentially bidirectional (Foti, Kotov, Guey, & Bromet, 2010), meaning that psychosis may increase subsequent use. Tobacco may also increase risk for psychosis, but the reverse is possible (Gurillo, Jauhar, Murray, & MacCabe, 2015).

Among individuals without pre-existing psychotic disorder, the profile of psychotic symptom exacerbation may vary by substance type. Methamphetamine use is associated with hallucinations (visual, tactile, auditory), delusions (persecutory, thought interference), paranoia, and/or unusual thought (Alexander et al., 2017; Bousman et al., 2015; McKetin, Baker, Dawe, Voce, & Lubman, 2017; Wang et al., 2016), but not disorganization (McKetin et al., 2017; Wang et al., 2016). Similarly, paranoia and hallucinations (auditory, visual, tactile) are associated with cocaine use (Mooney, Sofuoglu, Dudish-Poulsen, & Hatsukami, 2006; Vorspan et al., 2012), or periods of heavy alcohol use (Glass, 1989). Indeed, research indicates that increases in symptom severity are associated with greater frequency of use or periods of binge use (Smith, Thirthalli, Abdallah, Murray, & Cottler, 2009; Ujike & Sato, 2004; Willi et al., 2016). Route of administration of the substance is also a suggested contributory factor for experiencing psychosis. For example, cocaine may be ingested by insufflation, intravenous injection, or smoked in its crack cocaine form. Differences in the bioavailability, pharmacokinetic, and subjective effects of these routes of administration (Jeffcoat, Perez-Reyes, Hill, Sadler, & Cook, 1989; Volkow et al., 2000) may underlie differences in psychosis expression (Honer, Gewirtz, & Turey, 1987).

Upon ingestion, these substances enhance the transmission of monoamines dopamine, serotonin, and norepinephrine. Cocaine and methamphetamine directly increase extracellular dopamine in the nucleus accumbens by blocking reuptake or facilitating dopamine release at

presynaptic neurons (Koob & Volkow, 2010). Based on pre-clinical work, methamphetamine is more potent and has longer half-life than cocaine (Barr et al., 2006; Izawa, Yamanashi, Asakura, Misu, & Goshima, 2006), which may have implications for psychosis risk. Cannabis and alcohol indirectly enhance mesolimbic dopamine transmission by altering dopamine cell firing (Pierce & Kumaresan, 2006). How these cellular mechanisms interact is currently unknown. Augmented mesolimbic dopamine release and subsequent D2 receptor activation are implicated in the pathogenesis of both addiction and psychosis (Koob & Volkow, 2010; Ross & Peselow, 2012).

There are significant limitations in the contemporary understanding of the combined effects of substance use. Most human and non-human studies to date have examined each substance in isolation, with a few exceptions. One study of individuals with methamphetamine dependence experienced independent, dose-related increases in risk of psychosis with past-month polysubstance use, specifically methamphetamine, alcohol, and cannabis use frequency (McKetin, Lubman, Baker, Dawe, & Ali, 2013). Among individuals with psychostimulant dependence, the frequency of methamphetamine and cannabis use, but not cocaine use, were independently associated with positive symptom severity (Willi et al., 2016). A population-based study found cumulative effects of cannabis use and traumatic event exposure (Morgan, Reininghaus, Reichenberg, et al., 2014). Together, these findings underscore the importance of considering the combined effects and frequency of polysubstance use on psychosis exacerbation, in addition to other risk exposures. We aim to disentangle these combined effects in the present studies (Chapter 4).

1.3.5   Traumatic event exposure

Extensive evidence indicates that traumatic events early in life are associated with psychosis and psychotic disorders in adulthood (Morgan & Fisher, 2007; Trotta, Murray, & Fisher, 2015). Traumatic events include maltreatment (including neglect, physical, emotional, or sexual abuse or exploitation), natural disaster, or loss of caregiver or parent. Cumulative traumatic exposures may increase psychosis risk, and delusions and hallucinations seem to link most closely with these early life experiences (Muenzenmaier et al., 2015; Oher et al., 2014; Rosen et al., 2017). A recent mixed methods study in an urban disadvantaged community found that the content of these reality distortions often directly mirrored the traumatic experience, such as voices of abusive or gang-related figures (Rosen et al., 2017). In other cases, the hallucinations or delusions were related to protection against future violence. Indeed, the impact of both childhood personal and socioeconomic adversity on the expression of psychotic symptoms is complex and significant.

Limited research has assessed the effects of ongoing traumatic events on psychosis expression. Brown and Birley (1968) performed a case-control study that identified increased likelihood of a serious life event in the three weeks prior to psychosis onset. However, across the studies to follow, the definitions of the events (i.e., an occurrence involving change versus violent abuse) and psychosis (i.e., screening tool versus clinical assessment) varied considerably and warrants further study (Beards et al., 2013).

Preclinical and clinical evidence has demonstrated that adversity during development is associated with increased striatal dopamine transmission and stress reactivity (Mizrahi et al., 2012; Trainor, 2011). In adulthood, acute traumatic events may dysregulate the hypothalamic-pituitary-adrenal axis to subsequently increase striatal dopamine transmission

(Walker & Diforio, 1997). These observations may be driven by sensitization of dopamine system, whereby repeated exposure (e.g., early-life and ongoing trauma, psychostimulant use) results in response amplification. Indeed, evidence of cross-sensitization between different risk factors (Prasad, Sorg, Ulibarri, & Kalivas, 1995) suggests several psychosis risk factors could converge on this neurobiological mechanism. Moreover, repeated traumatic events may bias cognitive schema to interpret salient stimuli as threatening and outside of one's control, as in paranoia or persecutory delusions (Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007). Certainly, these experiences themselves may induce further stress, and may continue to perpetuate these aberrant neurobiological and cognitive processes.

The potential cumulative impact of early life and ongoing traumatic events is a necessary and emerging area of investigation. Few studies have examined the relationship between past and ongoing traumatic events on expression of psychosis in adulthood (Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2012; Mansueto & Faravelli, 2017; Morgan, Reininghaus, Fearon, et al., 2014; Morgan, Reininghaus, Reichenberg, et al., 2014). Thus far, evidence suggests the effects of childhood and adulthood traumatic events are additive (Mansueto & Faravelli, 2017) or synergistic (Lataster et al., 2012; Morgan, Reininghaus, Fearon, et al., 2014; Morgan, Reininghaus, Reichenberg, et al., 2014). Further research is necessary to investigate these relationships, particularly in the context of polysubstance use, and other co-occurring risk factors.

1.3.6 Traumatic brain injury

In recent years, there has been growing understanding and attention on the impact of traumatic brain injury (TBI) (Zgaljardic et al., 2015). Among marginally housed individuals,

TBI prevalence is 6.9% to 52.5% (Hwang et al., 2008; McHugo et al., 2017; Schmitt et al., 2017). TBI is frequently associated with poor mental health outcomes among vulnerably housed adults (Hwang et al., 2008; Schmitt et al., 2017). However, the evidence of psychosis following a brain injury is conflicting, and phenomenological study is limited (Molloy, Conroy, Cotter, & Cannon, 2011). Psychotic symptoms may follow TBI even years after the injury (Achte, Hillbom, & Aalberg, 1969; Koponen et al., 2002; Sachdev, Smith, & Cathcart, 2001). One study suggested that individuals may gradually (over greater than six months) experience bizarre behavior and social withdrawal, followed by the onset of paranoia, delusions, and hallucinations, without thought disorder (Sachdev et al., 2001). Further complicating the study of this injury sequelae is the delay of symptom onset, which is proposed to extend more than ten years, suggesting injury may confer more permanent vulnerability (Achte et al., 1969; Koponen et al., 2002). Further still, psychosis may be more common with diffuse brain injury, particularly to the temporal and frontal regions (Fujii & Ahmed, 2002; Sachdev et al., 2001), and evidence is inconclusive whether mild (Achte et al., 1969; Molloy et al., 2011) or severe (Koponen et al., 2002; Sachdev et al., 2001) injuries are more likely to lead to symptom onset. This neurological insult may confer additional vulnerability, perhaps enhancing the impact of existing risk factors, such as childhood trauma (Song et al., 2017). Thus, the relationship between TBI and psychosis needs to be clarified in the context of ongoing polysubstance use, trauma, and other risk factors.

1.4 Emerging approaches to understand psychosis

1.4.1 Network approach to psychopathology

While the exploration of potential risk factors has made substantial progress, the examination of the risk factors and potential therapies for psychosis will benefit from

refining our understanding of the outcome of psychosis itself. In recent years, network-based

models have been developed to complement and extend the current approaches (Borsboom,

2017; Cramer, Waldorp, van der Maas, & Borsboom, 2010; Kendler, Zachar, & Craver,

2011; Vinogradov, King, & Huberman, 1992). Based on theory and methodology from the

network sciences field (Wasserman & Faust, 1994), a network is a representation of the

relationships ("edges") among a set of variables ("nodes"). Network theory has influenced

recent advances in ecological, biological, and genetics research by permitting the study of

millions of relationships in a single model (Barabási, 2009). For psychopathological

networks, symptoms are re-conceptualized as nodes with potentially causal relationships

(edges) connecting one symptom to the others. A network model proposes that the

heterogeneity in symptom presentations is the result of complex interactions between the

symptoms themselves. For example, envision an individual, in whom sleep disturbances may

lead to fatigue which could lead to anxiety which may subsequently impact sleep (Figure

1.1). In a symptom network model, the symptoms themselves interact to sustain and mutually

reinforce each other, and, thus, may appear together upon clinical presentation (i.e., in Figure

1.1, at time t6). Indeed, such feedback loops have been described clinically (Beck, Rush,

Shaw, & Emery, 1979; Hayes et al., 2007). Of note, the mechanisms giving rise to these

pathways may be multifaceted: each edge in the network may be the manifestation of

biological and psychological processes, influenced by genetic, early-life, and ongoing

environmental exposures (Wichers, 2014).

Figure 1.1 Schematic of symptom network concept.
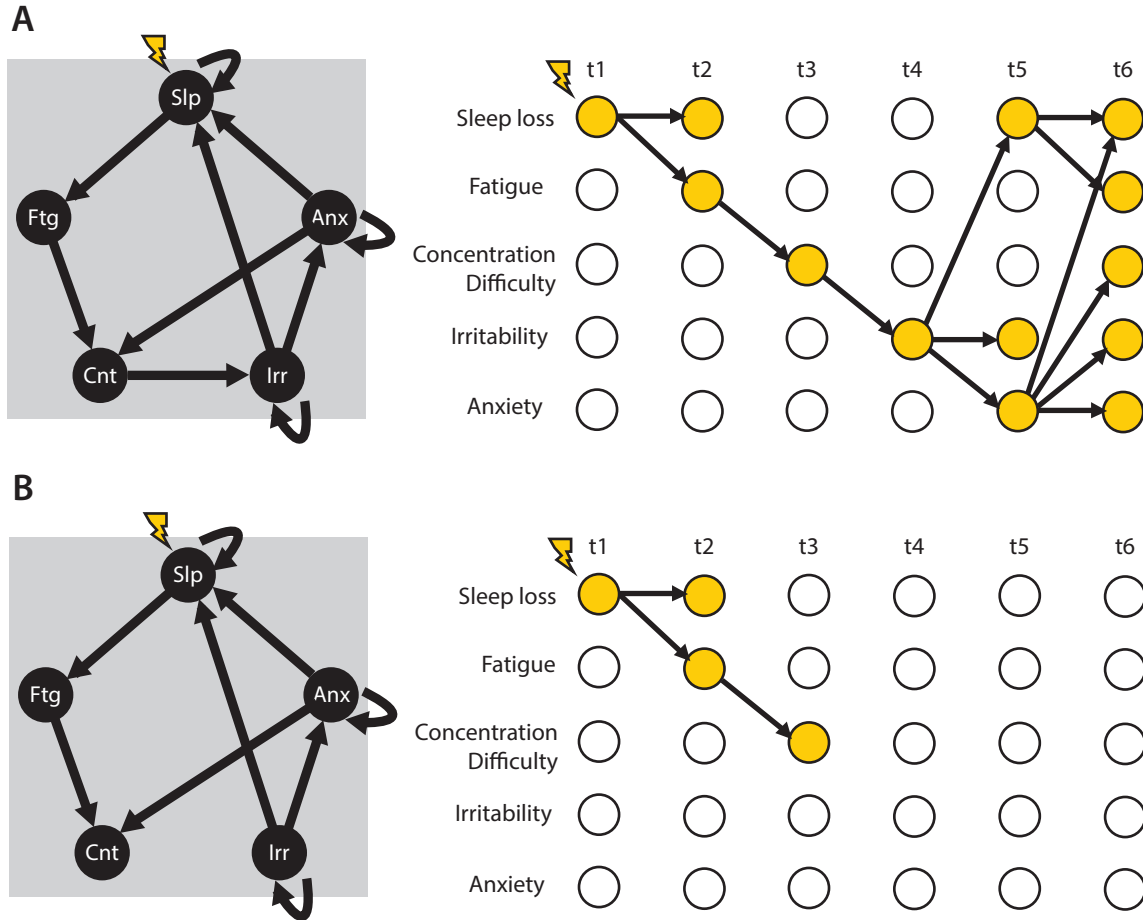
(A) Two schematic representations of a fictitious symptom network within an individual. Nodes (circles) are symptoms and directed edges (arrows) are the relationships between symptoms. The left panel represents the relationships between symptoms, which may have a biological or psychological basis. The right panel represents the activation cascade over time (t1 to t6) when a stressor activates "Sleep Loss." Presenting symptoms (activated) are orange, inactive symptoms are white. (B) Two schematic representations of another individual's symptom network, where the edge between "Concentration Difficulty" and "Irritability" is absent, perhaps due to intervention or inter-individual biological or psychological differences. The structure of this symptom network results in different symptom presentation with the same stressor. Slp = Sleep loss, Ftg = Fatigue, Cnt = Concentration difficulty, Irr = Irritability, Anx = Anxiety, Lightning bolt = stressor. (Figure is adapted from figure in Wichers et al., 2015 and informed by Borsboom et al., 2011; Borsboom, 2017.)

Similar to the hierarchy of symptoms in Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria, symptoms may play different roles in the network. Symptoms that have more connections with other symptoms are considered central, and those with fewer connections are considered peripheral in the network. With this framework applied to psychopathology, central symptoms can reach other symptoms and control the evolution of psychopathology more readily, while the peripheral symptoms may have less influence on the other symptoms. Centrality measures include strength, closeness, or betweenness of the nodes (Opsahl, Agneessens, & Skvoretz, 2010).

When examining a symptom network, the density of the connections is also assessed. The connection between symptoms form the routes for activation and evolution of psychopathology. Compared to a network that is sparsely connected, the effect of a perturbation (e.g., stressful event) may spread more rapidly along the edges of a dense network. Along this line, it has been postulated that individuals with more severe illness may have more densely connected symptom networks, allowing perturbations to spread rapidly to exacerbate multiple symptoms (van Borkulo et al., 2015; Wichers, Wigman, & Myin-Germeys, 2015). It is also conceivable, that a single edge may play a significant role in the cascade of activation (Figure 1.1B). Importantly, ongoing discussion has cautioned the generalization of group-level results to individual-level inference (Bos & Wanders, 2016; Schuurman, Ferrer, de Boer-Sonnenschein, & Hamaker, 2016). The distinction of individual within-person effects versus group-level between-person effects is made possible by emerging longitudinal analysis techniques explored in the studies to follow.

1.4.2 Dynamic network approaches

Although many psychiatric symptoms may fluctuate considerably over time, the study of the role of these dynamics in the evolution of symptoms over time is limited. The emerging psychopathological network studies to date are limited to cross-sectional designs. Consideration of the complex, dynamic interplay of psychopathology over time is likely a vital next step (Borsboom, 2017; Nelson, McGorry, Wichers, Wigman, & Hartmann, 2017; Odgers et al., 2009). Indeed, as described above, a triggering stimulus to a strongly connected network may lead to rapid onset and self-sustaining symptoms, persisting long after the stimulus has passed (Wichers et al., 2015). However, if these edges are modified or prevented from forming, as in a sparse network, effects of the stimuli may be brief and the progression to persistent psychopathology may be halted (e.g., Figure 1.1B). In addition, the resistance to change (or inertia) of a symptom may be an important marker for progression of illness (Koval, Kuppens, Allen, & Sheeber, 2012).

In dynamic networks, the present state of all nodes is predicted by the past state of all nodes, including itself. An examination of symptoms longitudinally in the context of a network could inform our understanding of the temporal ordering of the relationships and potential causality (Granger, 1969). For example, Granger causality theory asserts that if past suspiciousness predicts subsequent delusions, above and beyond what is predicted by past delusions, suspiciousness potentially causes delusions (Granger, 1969). When the magnitudes of these connections are compared, the most influential paths driving change in the network can be identified.

1.4.3 Psychotic symptom networks

Cross-sectional and longitudinal studies of psychotic symptom networks are novel areas of inquiry. To date, only three cross-sectional studies have examined psychotic symptoms (Isvoranu et al., 2017; van Rooijen, Isvoranu, Kruijt, et al., 2017; van Rooijen, Isvoranu, Meijer, et al., 2017). Researchers observed that the central symptoms of the network were delusions or unusual thought content for individuals with non-affective psychotic disorder (Isvoranu et al., 2017; van Rooijen, Isvoranu, Kruijt, et al., 2017). When using a different symptom scale in the same sample of participants, van Rooijen et al. (2017) found that the central symptoms in the network were chaotic speech, thought insertion, and auditory hallucinations. There is one cross-sectional study of negative symptoms as well (Levine & Leucht, 2016). To date, there are no longitudinal, dynamic network studies of psychotic symptoms.

The exploration of related phenomena, psychotic-like experiences, have been explored using dynamic network analysis. Experience sampling methods have been utilized to collect repeated (e.g., hourly) measures of self-reported psychotic-like experiences in clinical and non-clinical samples. Similarly, mental states (e.g., cheerful, irritated, suspicious) have also been tracked this way. To date, there are four cross-sectional studies examining these types of experiences in adult (Isvoranu, Borsboom, van Os, & Guloksuz, 2016; Murphy, McBride, Fried, & Shevlin, 2017) or adolescent populations (Guloksuz et al., 2016; Wigman, De Vos, Wichers, Van Os, & Bartels-Velthuis, 2017). Longitudinal studies of mental state networks in individuals with psychotic disorder have been conducted for one single-participant (Bak, Drukker, Hasmi, & Os, 2016) and two studies combining multiple study samples (N=654 and N=599, respectively) (Klippel et al., 2017; Wigman et al., 2015).

Klippel et al. (2017) found that among individuals with psychotic disorder (N=245), mental state networks had a greater number of significant connections and that suspiciousness, loss of control, and anxiety states were more likely to be activated. While rich in temporal precision, these approaches are limited by the screening nature of their measurement tools and the duration of their follow-up (i.e., five to six days in these two studies). Additionally, these studies to date have focused only on within-individual dynamics. In Chapter 5, we build on this work by using clinical assessment and studying the dynamics in the context of group-level psychotic symptom patterns.

1.5   Goals of the current study

1.5.1   Specific aims and hypotheses

Since Kraepelin's original descriptions, clinicians and researchers have described a heterogeneous presentation and potentially devastating consequences for psychosis and related disorders. While attention to the biopsychosocial factors that shape psychosis has increased, the examination of this multifactorial, complex illness is only just emerging. This dissertation examines the longitudinal features of psychosis in three distinct ways that progress in complexity. First, given the increased mortality risk experienced by individuals with psychotic disorder and individuals experiencing marginal housing, we hypothesize that mortality rates experienced by a population of marginally housed adults will exceed rates of the general population. We expect that substance use, HIV and HCV infection, and psychotic disorders will be significant risk factors for premature mortality. Second, when psychosis and several risk factors are examined over time, we hypothesize that early-life and recent traumatic events and ongoing frequent use of methamphetamine, cocaine, cannabis, and alcohol will be independently associated with an increase in the probability of experiencing

psychosis. We also hypothesize that psychosis is characterized by multiple co-occurring symptoms for those with psychotic disorders. Third, building on this work, we aimed to investigate the complex interplay between these symptoms as a dynamic network. We expected psychotic symptoms to co-occur and mutually reinforce one another, particularly in individuals with psychotic disorder. Overall, this dissertation is designed to test these hypotheses by examining the experiences and characteristics of a community-based sample of marginally housed adults and employing longitudinal analytic techniques to address the following aims:

1. Evaluate psychotic disorder as a risk factor for premature mortality
2. Longitudinally assess psychosis and psychosis risk factors
3. Characterize psychotic symptom dynamics over time

Each aim will be presented in the chapters to follow, documenting the longitudinal characterization of the consequences, risk factors, and dynamics of psychosis.

Chapter 2: General methods

2.1 Context of the community of study

The Downtown Eastside is a region on the traditional territories of the Musqueum, Tsleil-Waututh, and Sḵwx̱wú7mesh Nations. At the turn of the 20th century, this region supported the workers of the port and rail industries and the Japanese and Chinese communities. Like other major cities at the time, SRO hotels were built as temporary living quarters for transient workers. These buildings typically comprised of rooms less than 30 m^2 in size, include a sink, hot plate, and shared washroom facilities. Following World War II, this region expanded and became home to individuals affected by poverty who relied on the SRO housing stock. Increasing rates of cocaine and heroin injection in the context of criminalization and supply-focused drug policy contributed to an epidemic of HIV infection and overdose-related deaths in the 1990s, resulting in the implementation of the Four Pillar drug strategy, the opening of a safe injection facility, and expansion of HIV treatment and harm reduction services (Fischer, Popova, Rehm, & Ivsins, 2006; Linden, Mar, Werker, Jang, & Krausz, 2013; Marshall, Milloy, Wood, Montaner, & Kerr, 2011; Montaner et al., 2010; Tyndall, Currie, & Spittal, 2003; Werb et al., 2013; Wood et al., 2003).

In the 21st century, the Downtown Eastside has been referred to as "Canada's poorest postal code" (Lazarus et al., 2011). Individuals living in this area are reported to live with severe co-occurring physical and mental illnesses and endure significant socioeconomic challenges and housing insecurity (Deans et al., 2013; Palepu, Marshall, Lai, Wood, & Kerr, 2010; Vila-Rodriguez et al., 2013). Risk factors for premature all-cause mortality in this community have changed over the years: community-based studies identified HIV infection and cocaine injection as primary risk factors in 2001 (Tyndall et al., 2001), HIV infection in

2011 (Grebely et al., 2011), and both HIV, HCV, and HCV/HIV co-infection in 2013 (Deans et al., 2013). Risk factors examined in these studies focused on substance use, infectious disease, and sociodemographic factors, with limited attention to mental health.

The majority of the SRO buildings (94%) in Vancouver are located in the Downtown Eastside region. These buildings are a low-income, non-market housing option, and one of an often limited number of alternatives to street homelessness. More than half of SRO buildings are privately owned and operated, and the quality of conditions depend on a number of factors including location and management/ownership philosophy (Knight et al., 2014; Lazarus et al., 2011). Many SRO hotels have substandard living conditions and are unsanitary, unsafe, and lacking supports for tenants (Lazarus et al., 2011; Shannon et al., 2006). While SRO buildings provide an alternative to homelessness for individuals living on low incomes, the political, social, and psychological factors of these built spaces may interact to create environments that negatively impact mental health overall (Knight et al., 2014). Additionally, in response to the complex circumstances in the Downtown Eastside, the Downtown Community Court (DCC) was initiated to improve the coordination among the justice, social, and health care services for individuals experiencing housing instability, co-occurring illness, and criminal involvement (BC Justice Review Task Force, 2005; Somers, Moniruzzaman, Rezansoff, & Patterson, 2014). Indeed, the Downtown Eastside is home to many individuals who may struggle at the intersecting gaps in the social, justice, health, and economic systems that govern our society.

2.2   Participant recruitment

The Hotel Study is a longitudinal prospective study following a community-based sample of adults living in urban marginalized housing in Vancouver (Honer et al., 2017;

Vila-Rodriguez et al., 2013). The study aims to characterize the health needs of this population, with a particular focus on mental health, to advance understanding of the determinants of complex illness and to inform policy. Individuals were invited to participate in SRO hotels and the DCC in Vancouver, Canada between November 1, 2008 to October 31, 2015. Participants primarily resided in SRO hotels in the Downtown Eastside, but also in other parts of downtown Vancouver at the time of study entry, all of which are classified as marginal housing by not meeting the requirements of adequacy, affordability, and suitability of the Canada Mortgage and Housing Corporation (Canada Mortgage and Housing Corporation, 2014). All participants (age 18 or older) provided written informed consent once procedures were completely described. Clinically significant laboratory findings were shared with participants and their physicians. This study was approved by the Clinical Research Ethics Board of the University of British Columbia (certificate number H08-00521).

2.3   Measures

2.3.1   Psychiatric diagnoses

All psychiatric diagnoses, including psychotic disorders, were made by study psychiatrists using all available clinical information in a Best Estimate Clinical Evaluation and Diagnosis process (Endicott, 1988) modified to make diagnoses according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). Psychiatric evaluation included the Mini-International Neuropsychiatric Interview and a mental status examination. Healthcare records for previous psychiatric hospitalizations were obtained as part of the consent process. Baseline psychiatric symptoms were assessed using the 30-item Positive and Negative

Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), which is sensitive to a broad range of symptom severity (Santor, Ascher-Svanum, Lindenmayer, & Obenchain, 2007). Social functioning was assessed by the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 2000).

2.3.2 Psychotic symptoms

Five cardinal symptoms of psychosis from the PANSS (Kay et al., 1987) were assessed monthly over five years by trained interviewers: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness and persecution, and unusual thought content. The severity of each symptom in the past week is assessed. PANSS item ratings (seven-point scale) demonstrated good to excellent inter-rater reliability in participants with same-day assessments by two independent interviewers including a research psychiatrist (weighted κ = 0.46-0.83, p<0.01) (Table 2.1), similar to other studies of psychosis (Bebbington et al., 2006; Chen et al., 2010; Keller et al., 1981). Additionally, presence of psychosis (binary variable) at baseline assessment was defined by threshold scores for each of the five symptoms of psychosis (Chen et al., 2010; Hui et al., 2018). In a previous longitudinal study of patients with first episode psychosis who were free of all positive symptoms after treatment, these threshold scores were used to define relapse into psychosis (Chen et al., 2010).

Table 2.1 Criteria for psychosis

Assessments	Threshold Indicating Presence of Psychosis	Inter-rater Reliability (weighted kappa) [a]
Delusions	≥3	0.829**
Conceptual disorganization	≥4	0.459**
Hallucinatory behavior	≥3	0.737**
Suspiciousness / persecution	≥5	0.469**
Unusual thought content	≥4	0.739**
Presence/absence of any of the above symptoms exceeding threshold score for psychosis	—	0.690** [b]

[a] – using independent interviews of the same participant on the same day by different interviewers (N=26)

[b] – unweighted kappa statistic for psychosis state

**p<0.01

2.3.3 Mortality

For participants who died during the study, Coroner's reports were requested, health care providers interviewed, and hospital records from the year prior to death were obtained to determine primary cause and date of death.

2.3.4 Baseline measures

Each participant completed a comprehensive baseline assessment of sociodemographic, physical, mental, and social health variables. Sociodemographic factors, including age, sex, years of education, and previous periods of homelessness were recorded (e.g., living on the street, in shelter, couch surfing, or having no fixed address).

Physical health measures included self-reported medical conditions and treatment history. Participants also provided blood samples for serological testing for infectious disease and complete blood count. Positive serology indicated HCV exposure and viral DNA

detection by qualitative polymerase chain reaction indicated active HCV infection. HIV exposure was identified by antibody detection. HBV exposure was identified by core antibody detection. Hepatic fibrosis was estimated using the surrogate serological measure aspartate aminotransferase:platelet ratio index (APRI) (Wai et al., 2003). Significant hepatic fibrosis is indicated by APRI values greater than 0.7 (Wai et al., 2003).

A history of TBI was determined by clinical interview demonstrating persistent sequelae, and/or high-field (3T) magnetic resonance imaging (MRI) findings identified by a neuroradiologist. Evidence of persistent sequelae included first reporting serious head injury with clinical manifestations (loss of consciousness ≥5 minutes or confusion ≥1 day), then either: seizures in the past year attributable to TBI, need for seizure prophylaxis, or persistent neurological findings attributable to TBI. All participants were offered the opportunity to participate in 3T imaging. At baseline, 348/437 (79.6%) participants completed a scan.

Past traumatic events prior to age 18 were assessed using the semi-structured Trauma History Questionnaire (THQ) modified to record age of event(s) (Green, 1996). Events involved objective threat of death or serious injury to which an individual reacted with extreme fear, horror, or helplessness according to DSM-IV-TR criteria. The THQ is scored as the number of types of traumatic events endorsed to a maximum of 23, including physical, sexual, disaster-related, or crime-related events (Hooper, Stockton, Krupnick, & Green, 2011). For the present analyses, the semi-structured THQ was used to assess traumatic events prior to age 18 (THQ18).

2.3.5 Prospective measures

At monthly follow-up visits, several additional measures of health were captured. Ongoing traumatic events were reported for the month prior to each visit using the THQ (recent trauma, rTHQ). Periods of homelessness were also captured.

Prescription and non-prescription substance use was reported using the Timeline Followback method (Sobell et al., 2003). The number of days, dose, route of administration, and type of non-prescription substance use were reported for the four weeks prior to each visit. Methamphetamine, powder and crack cocaine, cannabis, opioid, alcohol, and tobacco use were reported. The urine testing for methamphetamine, cocaine, cannabis, and opioids demonstrated substantial agreement with self-reported use ($\kappa = 0.62\text{-}0.70$, $p<0.001$). Pipe and needle sharing were also reported (Marsden et al., 1998).

Prescribed medications were also recorded each month, and included methadone therapy for opioid dependence, antiretroviral medication for HIV infection, and antipsychotic medication for psychotic illness. A history of any treatment for HCV was also obtained. Antipsychotic treatment (medication type, dose, route of administration, days of use) was reported for the past four weeks. Reliability of self-reported antipsychotic use was confirmed with PharmaNet, the province-wide records of dispensing prescription medication ($\kappa = 0.71$, $p<0.001$). Adequacy of treatment for managing psychosis was determined according to the Clinical Handbook of Psychotropic Drugs guidelines (Procyshyn, Bezchlibnyk-Butler, & Jeffries, 2015) and reported adherence (i.e. depot or ≥80% of past 28 days taking oral medication) in consultation with a psychopharmacologist. Prescribed methadone therapy was reported and considered adequate if taken ≥80% of past 28 days. Adequate methadone reports exhibited high concordance with urine testing ($\kappa = 0.82$, $p<0.001$).

2.4   Longitudinal analytic approaches

2.4.1   Prospective sample description

According to specific study inclusion criteria and the date of analysis, study sample

size and follow-up duration differed. In the mortality study (Chapter 3), of the 514

potentially eligible individuals, 375 SRO tenants and DCC participants were recruited from

November 1 2008 to October 31, 2012. These individuals were followed for a median 3.8

years (interquartile range, IQR: 1.9 – 5.0 years) as of June 1, 2014. Participants from DCC

(N = 65) were followed for less time (1.9 years, IQR: 1.9 – 1.9 years) than SRO participants

(N = 306) (4.3 years, IQR: 3.1 – 5.0 years) at the time of analysis. Eighty percent of DCC

participants were living in an SRO hotel at study entry and were more likely to report a

previous history of homelessness (83% vs. 65%) and opioid dependence (54% vs. 39%)

compared to participants recruited from SRO hotels.

In the risk factor study (Chapter 4), the first year of follow up was examined. The

additional 62 participants who were recruited from November 27, 2013 to October 31, 2015

from youth-oriented marginal housing were included in this study sample as they had been

potentially enrolled in the study for at least one year at the time of analysis (January 16,

2017). The total sample was 437 participants, of whom 385 (88.1%) were followed for the

entire year (mean, standard deviation (SD): 12.0, 3.0 months).

Lastly, the symptom network study (Chapter 5) examined the first five years of

longitudinal data. The original 375 participants had been enrolled at least five years prior to

analysis (October 21, 2017), and thus were eligible for inclusion in this study. Of this

sample, 251 (66.9%) of participants were followed for the five year period (mean, SD: 49.3,

19.8 months).

2.4.2   Survival analysis for mortality risk factor evaluation

All analyses described were performed using R (R Core Team, 2017). The impact of potentially treatable illnesses on mortality risk was assessed using left-truncated Cox proportional hazards modeling with age as the time-scale (see Chapter 3). This survival analysis approach accounts for deaths before or after study participation and the effect of aging on mortality risk. Loss to follow up and study exit were censored. As well, left-truncation accounts for deaths that cannot be observed during the study period as they occurred prior to study entry or prior to the minimum entry age of 18. This is necessary as the modeling examines survival across the lifespan (i.e., time-scale is age). This analysis was performed using the R *survival* package (Therneau, 2015).

Cox proportional hazards modeling approach relies on two key assumptions that must be considered and tested before interpreting results. First, the model assumes non-informative censoring, where the mechanisms underlying censoring (e.g., exiting the study before death) are not related to the probability of death. In our study, the continuation of follow-up was not dependent on a participants' health or illness status. Sensitivity analyses were performed. Second, these models assume that the hazard ratio of an independent variable is constant over the time-scale (in this case, age). The proportional hazard assumption for Cox models was verified by visual and statistical assessment of Schoenfeld residuals plotted against the time-scale. In the case of non-proportionality (Schoenfeld residual global test p<0.05), we used a change-point estimate approach (Quandt, 1958) to account for distinct effects on mortality at younger and older ages, in this case.

To visualize the effect of statistically significant predictors on mortality, the Kaplan-Meier method was used. This survival anaylysis approach estimates the time to death,

accounting for censored data. While it has utility in several settings, this survival analysis

approach is limited in its ability to estimate survival adjusting for covariates or multiple

independent variables. Thus, we chose to use the Cox proprotional hazards model for

estimating the impact of several illnesses on mortality.

2.4.3   Mixed effects modeling for longitudinal psychosis risk factor assessment

The associations between longitudinally ascertained psychosis (binary outcome) and

the multiple risk factors and covariates were estimated by logistic mixed effects models

using the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015) (see Chapter 4). Mixed

effects (multilevel) regression models were used to account for the hierarchical structure of

longitudinal observations within individuals (Gelman & Hill, 2007; Singer & Willett, 2003;

Wu, 2009).

Mixed effects modeling was used for several reasons. First, this modeling approach

allows all repeated measures observations to be considered, as opposed to change score or

adjusted end-point approaches. This allows for more powerful hypothesis testing and precise

estimates. Second, the random effects component of this modeling approach enables us to

capture the inter-individual unobserved heterogeneity in the population, while identifying the

unique contributions of multiple time-invariant and time-varying risk factors in question (i.e.,

fixed effects). The combined advantages of both fixed and random effects underlie the

decision to use mixed effects models as opposed to random effects models or fixed effects

models. Third, this modeling approach can be applied to a variety of outcome measures,

including binary outcomes, as in our data. This is an advantage over a repeated measures

analysis of variance approach. Fourth, mixed effects models are robust to missing data that

are missing at random, as in our study. This is an advantage over approaches such as

repeated measures analysis of variance, growth curve models, and generalized estimating

equations (Wu, 2009). Fifth, when estimated by restricted maximum likelihood estimation,

mixed effects models yield individual-specific estimates. This is an advantage over many

longitudinal analytic approaches, including generalized estimating equations and growth

curve modeling.

Mixed effects models extend the classic regression models that are used for cross-

sectional data by including both fixed and random effects. Fixed effects are the main effect

of an independent variable, averaged across the sample of participants. Random effects are

the individual-specific deviation from the population mean effect. In the present study

(Chapter 4), we included the random effects of time and individual to account for the within-

individual correlation across repeated measures, as well as the between-individual variability

around the fixed effects estimates, respectively. Thus, a trajectory with a unique intercept and

slope (i.e., random intercept and random slope) is estimated for each individual. The model

is:

$$\text{Logit } Y_{it} = \beta_0 + b_{0i} + (\beta_1 + b_{1i}) \text{ Time}_{it} + \beta_2 \, x_2 + \ldots + \beta_n \, x_n + \varepsilon_{it},$$

where Y_{it} is the binary dependent variable for individual i at time t, x are the independent

variables, β_0 is the mean intercept across individuals, β_1 is the fixed effect estimate of time

(i.e. this is the slope of the population trajectory of the dependent variable), β_n are the fixed

effect estimates of the independent variables x, b_{0i} is the random effect of the intercept for

each individual i, b_{1i} is the random effect of time for each individual i, and ε_{it} is the random

error. The fixed effects are interpreted as the conditional odds ratio that is adjusted for

covariates and for random effects.

Mixed effects models do not require equal number of assessments per participant, nor the same measurement schedule (Wu, 2009). Also, unlike regression models, mixed effects models do not require independence of the observations, as observations from the same individual are expected to be correlated. The model assumes linearity, constant variance, and normal distribution of the residuals, which are tested by visual inspection of diagnostic plots. In addition, the person-specific random effects are estimated from a multivariate normal distribution. The covariance structure is assumed to be the product of the variance component and the design matrix. As with any model building procedure, outliers (high leverage observations) and overdispersion (sum of residuals is greater than the degrees of freedom) are assessed, which could affect estimation accuracy if violated. Adjusted models were estimated by a stepwise model fitting process iteratively adding and removing fixed and random effects (Bolker et al., 2009). Nested models were compared by likelihood ratio test and Akaike Information Criterion (AIC) values to identify the best fitting model.

Importantly, independent variables included both time-invariant and time-varying risk factors. The fixed effects of time-invariant risk factors are interpreted as the conditional effect of the factor on the odds of psychosis. Likewise, the fixed effects of time-varying risk factors are estimated as the conditional effect of that factor on psychosis, averaged across people and time, controlling for all other factors in the model. Linearity of these effects was tested by modeling factors first as ordinal predictors, simultaneously estimating the linear and quadratic effects. If the linear effect but not the quadratic effect was significant ($p<0.05$), the variable was included in the final model as a continuous variable. Multiplicative interactions with time were also explore for each explanatory variable to see if the effect changed over the course of follow-up.

2.4.4 Multilevel vector autoregressive modeling for dynamic psychotic symptom network estimation

In Chapter 5, psychotic symptom networks were constructed to estimate the relationships between psychotic symptoms across time. Autoregressive models allow for the estimation of the stability or change in a variable over time within an individual. For autoregressive models with a lag of one time point, a variable at time point *t-1* is used to predict that same variable at time point *t*. Vector autoregressive (VAR) models extend this approach by modeling these lagged effects for multiple variables. In doing so, the VAR models estimate both the autoregressive effects (how well a variable predicts itself at the next time point) as well as the cross-regressive effects (how well one symptom predicts a different symptom at the next time point). When a multilevel framework is used, a VAR model is estimated for each individual and the population overall to capture the within-individual dynamic interactions between variables over time (Epskamp, Waldorp, Mõttus, & Borsboom, 2016a).

Recently, theoretical and empirical evidence has shown that the patterns observed in the population may not be generalizable to the processes that occur within the individual. As an example, people who exercise more may have lower risk of heart attack (negative between-person effect), while one is more likely to experience a heart attack while exercising (positive within-person effect) (Curran & Bauer, 2011). This phenomenon is known as Simpson's paradox. The between-person and within-person effects can differ in both magnitude and direction and have different clinical implications. In addition, the relationship between symptoms may differ when examined at one moment versus over time. For example, hunger may predict subsequent eating, but hunger and eating may not co-occur.

Thus, it is necessary to disaggregate the between-individual and within-individual effects, as well as the cross-sectional and the temporal effects, which is possible when the outcome and predictors are both tracked repeatedly over time in longitudinal study design.

In order to disentangle the within-person psychotic symptom dynamics from within-person cross-sectional ("state") and stable between-person differences ("trait"), we used a multilevel VAR modeling approach (Bringmann et al., 2013; Epskamp, Waldorp, et al., 2016a). We applied the two-step multilevel VAR strategy outlined in Epskamp et al. (2016) and executed in *mlVAR* package (Epskamp, Deserno, & Bringmann, 2017). We extended this strategy in four ways, detailed below, and compared our estimated networks to the findings obtained from using the R *mlVAR* package.

This multilevel VAR modeling approach was selected for several reasons. First, this model allows for the study of multivariate responses, and thus the interrelationships between several outcomes (i.e., psychotic symptoms), unlike other longitudinal approaches such as mixed effects modeling, as described above. Second, the multilevel framework enables the examination of both within-person and between person effects, which may better capture personal change over time and how that may differ from trends seen across the population. This approach has been demonstrated as robust with a similar number of nodes in simulation study (Epskamp, Waldorp, Mõttus, & Borsboom, 2016b). Third, Gaussian Graphical Models have been estimated and found to fit the present scale, PANSS (Kay et al., 1987) well (Isvoranu et al., 2017). Fourth, this is the first longitudinal study of psychotic symptom networks and thus prior knowledge of expected relationships is limited. Thus, this probabilistic (i.e., frequentist) approach permits the estimation of effects using available data, perhaps to inform priors of future Bayesian inquiry.

We sought to deconstruct the psychotic symptom interrelationships into three

networks representing the "trait", "state", and "dynamic" components. First, to separate

between-person and within-person effects, symptom scores were person-mean centered prior

to multilevel VAR analysis (Hamaker & Grasman, 2014; Wang & Maxwell, 2015). This

yielded two sets of data: (1) participants' mean symptom severity across assessments and (2)

participants' time-varying fluctuations around their own mean in symptom severity score.

The first set of data was used to estimate the stable between-person similarities and

differences in the population (Person-Mean Network), while the second dataset was used to

estimate how symptoms interact to influence these fluctuations over time (Dynamic

Network). Then, the residuals from multilevel VAR analysis were used to estimate the

Contemporaneous Network, a map of how symptoms correlated within an individual at a

given moment (cross-sectional relationships). For clarity, we begin by explaining the

Dynamic Network construction, followed by Contemporaneous Network and the Person-

Mean Network construction.

The multilevel VAR model can be understood as:

Level 1 Model:

$$\mathbf{Y}_{it} \mid \mathbf{y}_{it} = N\,(\mu_i + \mathbf{B}_i\,(\mathbf{y}_{i(t-1)} - \mu_i\,),\,\Theta_i)$$

Level 2 Model:

$$\mu_i \qquad \sim N\,(\mathbf{f}\,,\Omega)\ ,$$

$$\mathrm{Vec}\,(\mathbf{B}_i)$$

where, $\mathbf{y}$ is a vector of symptoms at time t for each individual i, μ denotes the stationary

mean symptom scores, $\mathbf{B}$ encodes the matrix of within-person temporal effects (Dynamic

Network), and Θ denotes the partial correlation matrix of model residuals (i.e.,

Contemporaneous Network). In the Level 2 model, **f** represents the matrix of fixed effects

(Person-Mean Network) and Ω denotes the random effects distribution.

As in previous dynamic network analysis studies, in our dynamic psychotic symptom

network each node represents a symptom and each edge represents the lagged effect

coefficient between two nodes. Multilevel VAR modeling was used to estimate the directed

edge weights between psychosis symptoms over time. Specifically, a multilevel VAR(1)

model was fit for each symptom, where a symptom at time point t served as a dependent

variable and the five time-lagged symptoms at time point t-1 (past month) served as

predictors. For example, the following equation estimates the temporal effects of time-lagged

symptoms on delusions at t, adjusting for time:

$$\text{Delusions}_{it} = \beta_{0i} + (\beta_{1i} + b_{1i}) * \text{Delusions}_{it-1} +$$

$$(\beta_{2i} + b_{2i}) * \text{Conceptual Disorganization}_{it-1} + \ldots +$$

$$(\beta_{5i} + b_{5i}) * \text{Unusual Thought Content}_{it-1} + (\beta_{6i} + b_{6i}) * \text{Time}_{it} + \varepsilon_{it} \,,$$

where β_{0i} is the intercept, β_{1i} to β_{6i} are the (Level 1) fixed effects coefficients for participant i

at month t-1, b_{1i} to b_{6i} are the random effects for participant i. Note that random effects are

estimated for each lagged variable as well as time and represent the individual-specific

deviation from the fixed effects (population mean) of each lagged effect. Thus, the within-

individual effect is $\beta_{ni} + b_{ni}$ for symptom n. The *lme4* package (Bates et al., 2015) was used

for estimation.

From these models, a 5-by-5 matrix of fixed effects regression coefficients (β) was

constructed (network adjacency matrix). Each regression coefficient corresponds to a

directed edge and indicates the extent to which a past month symptom predicts another symptom at time t, controlling for the effects of all other variables. The effect of a symptom on itself in the subsequent month (autoregressive effects or self-loops, i.e., the matrix diagonal) and on other symptoms in the subsequent month (cross-regressive effects) are estimated. Autoregressive effects have been postulated to represent the inertia or resistance to change of a symptom (Hamaker & Grasman, 2014; Pe & Kuppens, 2012). Differing from the *mlVAR* package, we account for multiple testing by controlling the False Discovery Rate at 5%, since several edges are estimated simultaneously (Benjamini et al., 1995). In addition, while *mlVAR* used maximum likelihood estimation, we used restricted maximum likelihood estimation for unbiased estimates of the random effects parameter (Singer & Willett, 2003).

The model has several assumptions. First, stationarity over time is assumed. Time was included as both a fixed and random effect to allow for differences in intercept and slope across individuals and to account for any time trends in the independent and dependent variables (i.e., to "detrend") (Wang & Maxwell, 2015). Second, the model also assumes normality of the joint conditional distribution and the marginal distribution of each variable tested by visual inspection of diagnostic plots. The person-specific random effects are estimated from a multivariate normal distribution. Third, multilevel VAR models assume equal intervals between time points (Bringmann et al., 2016; Epskamp, Waldorp, et al., 2016a).

Recently, there has been increased discussion about the impact of symptom score variance on network estimation. In accordance with Bulteel et al. (2016) and Schuurman et al. (2016), symptom scores were within-person standardized to limit the impact of any differences in symptom variance. To test whether symptom variance may contribute to

observed network differences, unstandardized and within-person standardized estimates were compared (Bulteel, Tuerlinckx, Brose, & Ceulemans, 2016; Schuurman et al., 2016). Of note, only participants that experienced change in their symptom severity could be included in the Dynamic Network (n=294, 78.4%). Additionally, while centering the data allows for separation of within-person and between-person effects, this transformation may lead to under-estimation of the autoregressive effects (Hamaker & Grasman, 2014). Additionally, there has been concern that using single item measures may introduce measurement error (McNally, 2016). We address this concern by examining the inter-rater reliability of the symptom scores (Table 2.1) and test the stability of network estimates using permutation approaches described below. Previous item response analysis identified that these cardinal symptoms were good to very good for discriminating symptom severity (Santor et al., 2007). We also examine for structural equivalence between highly correlated items (Fried & Cramer, 2017; Lorrain & White, 1971), to test if the items are in fact representing the same clinical phenomena (i.e. have equivalent connections to other symptoms and therefore an equivalent role in the network). Last, as with any multiple regression analysis, the edge weights represent only the independent, unique direct effects and do not include the shared effect of multiple symptoms (Bulteel et al., 2016).

In addition to examining within-person dynamics, between-person similarities and differences were estimated to determine the aggregate tendency for pairs of psychotic symptoms to be associated in the population. In the Person-Mean Network, the edges represent the partial correlation matrix between individuals' mean symptom severity scores (i.e., dataset 1 from above). In this way, we estimate the tendency of symptoms to co-occur in a population. For example, do individuals with severe delusions, on average, tend to

experience severe suspiciousness? The relationships between the person-specific means represent the Level 2 part of the multilevel VAR model and is the vector of the intercepts for each symptom model. These relationships are not ordered over time, and, thus, the partial correlation matrix is symmetric. The partial correlation matrix is the association between two variables, given all other variables in the network. The partial correlation matrix can be estimated by either standardizing the inverse variance-covariance matrix of the network, or by performing node-wise multiple regression with all other variables as covariates (Epskamp & Fried, 2016). Thus, partial correlations values equaling zero (visualized as an absent edge) mean that the two variables are independent, conditioning on all other variables in the network.

Specifically, we estimated a Gaussian Graphical Model (Epskamp, Borsboom, & Fried, 2016; Epskamp, Waldorp, et al., 2016a) to the participant mean symptom severity data and visualized these partial correlation coefficients as an undirected weighted network (Person-Mean Network). This model also assumes multivariate normality, which was tested by comparing networks estimated by correlation methods that vary in this assumption, namely, polychoric correlations, Spearman correlations, and polychoric correlation with non-paranormal transformation (Epskamp & Fried, 2016). All methods of edge estimation yielded equivalent networks (r > 0.95, p<0.001), supporting the multivariate normality assumption. In order to reduce Type 1 errors and improve estimation accuracy, network analysis studies estimate partial correlation networks using L_1-regularization (also known as graphical least absolute shrinkage and selection operator) (Friedman, Hastie, & Tibshirani, 2007). The regularization process utilizes several values of the tuning parameter λ to adjust the sparsity of the network. To optimize model fit, networks estimated under different λ

values are compared using the extended Bayesian Information Criterion (EBIC) (Chen and Chen, 2008), with a hyperparameter γ set to 0.5 as a conservative control of network sparsity to remove false positive edges (Epskamp & Fried, 2016). Though the *mlVAR* function estimates the partial correlation network by node-wise multiple regression, we chose to estimate regularized partial correlation networks instead in order to improve accuracy and sparsity of the Person-Mean Network.

Lastly, the Contemporaneous Network is an undirected network representing the co-occurrence of symptoms within an individual at a given time. Multilevel VAR model residuals were used to estimate how much of the unexplained variance in symptoms at time t were explained by another co-occurring symptom, conditioning on other co-occurring symptoms. As for the Person-Mean Network, the Contemporaneous Network represents the L_1-regularized partial correlations between symptoms. Person-Mean and Contemporaneous Networks were estimated by the *bootnet* package (Epskamp, Borsboom, et al., 2016). All networks were visualized using the *qgraph* package (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012).

Finally, we chose to estimate these networks manually in order to (1) account for multiple testing by adjusting for False Discovery Rate of 5%, (2) improve accuracy of random effects estimation of Dynamic Network by using restricted maximum likelihood estimation, (3) enable group comparison by including fixed effects interactions, and (4) estimate more accurate and sparse Person-Mean and Contemporaneous Networks by using L_1-regularization. We expect the three networks to be almost identical to those obtained by the *mlVAR* package when these specific changes were absent from the model. We tested this

by correlating the coefficient matrices obtained from the automated and manual estimation processes.

Centrality measures were calculated for each symptom within the Person-Mean, Contemporaneous, and Dynamic Networks. The centrality measures include strength, closeness, and betweenness (Freeman, 1978; Opsahl et al., 2010). Strength is the sum of the edge weights for each node and thus is a measure of local structure. In a directed graph (Dynamic Network), the sum of outgoing edges is called out-strength and is a measure of the symptom's influence on other symptoms in the network. The in-strength is the sum of incoming edges and is an indicator of how downstream a symptom is in the activation cascade. Closenessness is estimates how proximate the symptom is to all other nodes in the network and is the sum of the inverse shortest paths to each other node. Closeness estimates the efficiency by which a symptom may exert its influence. Lastly, betweenness is the number of paths the symptom mediates, and thus represents its role as a gatekeeper, transmitting activation between other pairs of nodes.

Recently, methods for assessing the certainty of the edges and centrality measures of undirected networks have been developed (Epskamp, Borsboom, et al., 2016) which we applied to the Person-Mean and Contemporaneous Networks. A bootstrapping procedure was used to estimate the 95% confidence interval of edges by refitting the networks 10,000 times. Non-significant edges (with 95% confidence intervals that included zero) were removed from the visualized network to prevent interpretation of spurious edges. Further, in an additional bootstrapping procedure, 10,000 subsamples of varying sizes were used to estimate the stability of the centrality measures. A Centrality Stability (CS) index (Epskamp, Borsboom, et al., 2016) is generated. The index indicates the maximum percent reduction in

subsample size to retain a correlation of at least 0.70 across subsample centrality measures. A CS index value of at least 0.70 is considered adequate and suggests that a sample size could be reduced by 70% of its original size (ie. subsample size 30% or original size) and still have a similar ($r > 0.70$) centrality measure. The CS index was estimated for strength, closeness, and betweenness centrality measures. The bootstrapping procedure was performed using the *bootnet* package (Epskamp, Borsboom, et al., 2016). Currently, there is no accepted approach to assess centrality measure stability for dynamic networks. For the Dynamic Network, the standard error of the effect coefficients is used to determine certainty of the edges.

Lastly, networks were estimated for three groups of participants with varying psychosis risk (Chapter 5). Currently there is no gold standard approach for comparing dynamic networks between groups. However, Bringmann et al. (2013) compared groups of participants by including an interaction term between group membership and the cross-regressive and autoregressive effects in the model directly. We applied this approach in our current study to compare the dynamic networks between groups. Further, in a recent study, Klippel et al. (2017) proposed a permutation procedure to estimate group differences in average whole network connectivity (density), including both autoregressive and cross-regressive connectivity, as well as group differences in each edge weight. Group membership was reshuffled between participants 10,000 times, models were re-fitted, and the permutation distributions of the size of the group differences were obtained under the null hypothesis. The size of the observed group differences for connectivity or edge weight were compared to the permutation distribution to determine level of significance of group differences in Dynamic Network characteristics (Klippel et al., 2017). The Person-Mean and Contemporaneous Networks of these groups were compared using the Network Comparison

Test (van Borkulo et al., 2015). The Network Comparison Test is a similar permutation procedure that randomly re-assigns participants to the groups and re-estimates undirected networks 10,000 times. The distributions of global connectivity are estimated across the permutations to determine if there are significant group differences in network connectivity.

2.4.5 Missing data assessment

Missing data is highly common in longitudinal studies. Thus, data were first assessed for the rate and pattern of missingness, including missing visits or missing variables. When data are considered missing completely at random, the probability of missingness is independent of both the variable itself and other observed variables (Wu, 2009). In the case of data being missing at random, the probability of a variable being missing is unrelated to the values of the variable itself, but may be dependent on observed variables. To test whether data are missing at random and whether the patterns of missingness alter our findings, we performed several sensitivity and multiple imputation analyses (Bieling et al., 2015). Sensitivity analyses were performed to compare participants with missing versus available data on factors that may be related to the variable in question, including any available observations of the variable itself. Further, groups of participants with differing number of total visits made or differing reasons for discontinuation were compared.

Overall, participants who remained engaged in the study for five years were similar to those who discontinued. Notably, measures related to our primary outcomes of psychosis were not associated with whether a psychotic symptom assessment was missed (Appendix Table A.1). Younger age, however, was associated with psychosis missingness over the five years. See Appendix Tables A.2 to A.5 for comparisons of engaged versus discontinued participants, engaged participants with greater than or equal to 50 versus those with less than

50 assessments (60th percentile), and participants who discontinued participation due to death

or being lost to follow up. Discontinuation occurred due to death (41, 11.0% individuals;

contributing 1176, 5.1% months during follow-up), lost to follow-up (77, 20.5% individuals;

contributing 3671, 16.0% months; e.g., moved away from Vancouver, incarceration, or living

in a treatment facility may precede discontinuation), or withdrawal from the study (6, 1.6%

individuals; contributing 255, 1.1% months). There were differences between individuals

who died versus those who were lost to follow-up for other reasons (LTF): older age (mean,

SD: Died 49.4, 8.4 versus LTF 39.7, 10.4, p<0.001), and less likely to have

methamphetamine dependence (proportion: Died 7.7% versus LTF 32.9%, p=0.006), or a

history of homelessness (proportion: Died 52.6% versus LTF 79.7%, p=0.005). Thus,

participants censored in the survival analysis study (Chapter 3) did not seem to discontinue

due to greater co-occurring morbidity or illness (i.e., non-informative censoring). Altogether,

data appeared to be missing at random and unrelated to psychosis, though differences in

reasons for discontinuation (i.e. death) should be considered in multiple imputation analysis.

Multiple imputation analysis was performed using the *mice* package (van Buuren &

Groothuis-Oudshoorn, 2011). First, imputed values are generated from regression models

with relevant predictors, including covariates from the main model of interest, and other

variables that related to a variable's missingness (Bieling et al., 2015). Based in the

sensitivity analyses, death (time-varying indicator), THQ18, history of homelessness, and

methamphetamine, cannabis, and alcohol dependence were included as potentially relevant

predictors. Continuous variables were predicted by posterior mean matching and binary

variables were predicted by logistic regression. We imputed ten completed datasets with ten

iterations for each imputation analysis (Chapter 4 and 5), as is recommended by standard

multiple imputation procedures (Rubin, 1987). Second, the main model of interest was fit to each of the completed datasets. Last, the parameter estimates from the second step were pooled to produce final parameter estimates. Pooled parameter estimates from the imputed datasets were compared to those from the complete-case analysis to test whether our findings and inferences were affected by missing data.

Chapter 3: Identification of psychotic disorder as a risk factor for premature mortality among marginally housed adults

3.1   Brief introduction

As discussed in Chapter 1, individuals living in marginal housing conditions experience increased risk of premature mortality and face accumulating health challenges. We sought to examine the role of psychotic disorders and other potentially treatable illnesses on premature mortality risk among adults living in marginal housing. We hypothesized that this community-based sample would experience greater mortality risk compared to age- and sex-matched Canadians and that having a psychotic disorder diagnosis would be a significant risk factor for premature mortality.

3.2   Brief methods

3.2.1   Measures

Recruitment and study design details are outlined in Chapter 2. In brief, for participants who died during the study, Coroner's reports were requested, health care providers interviewed, and hospital records for the year prior to death were obtained to determine cause of death. Mental and physical illnesses were identified at baseline to assess their impact on mortality risk, including psychiatric illness, viral infection, and serological markers for liver dysfunction. Substance use and pipe and needle sharing was reported for the four weeks before baseline assessment. Medications recorded included methadone maintenance therapy, antiretroviral medication, antiviral or interferon-based medication for HCV infection, and antipsychotic medication.

3.2.2 Statistical analysis

The indirect method of standardization was used to determine the standardized mortality ratio (SMR) for this cohort. The SMR was calculated as the ratio of the observed number of deaths to the number of deaths expected if the cohort experienced the same age- and sex-specific mortality rates as the general Canadian population in 2009. The Boice-Monson method was used to calculate the 95% confidence interval.

The impact of mental illness (psychosis and mood disorder), addiction (stimulant, opioid, and alcohol dependence, and injection drug use), and physical illness (HIV exposure, HCV active infection or exposure, and hepatic fibrosis) on mortality risk was assessed using left-truncated Cox proportional hazards modeling with age as the time-scale. The effect of psychotic disorder exhibited non-proportionality across ages (Schoenfeld residual global test p<0.05). The change-point was selected by visual inspection of Schoenfeld residual plots, which showed an inflection between 44 and 59 years of age and an inflection point at age 55. Thus, we selected 55 years of age as the change-point. Other change-points were examined, but results were similar.

The Kaplan-Meier method was used to plot the effect of statistically significant predictors on mortality. Multiple logistic regression was used in secondary analyses to evaluate factors associated with hepatic fibrosis. Variables were considered for inclusion in the final adjusted models if they fit the scientific framework, were associated with mortality risk (p-values ≤ 0.10), and changed unadjusted effect coefficients by more than 10%. Interactions between mortality risk factors were examined.

Each variable had less than 5.0% missing data, except HBV (5.9% missing). Participants with missing data were compared to the rest of the cohort (Appendix Table A.2

to A.5). Complete cases were used for each regression analysis. Significance was set at p<0.05.

3.3   Results

3.3.1   Participants

Of the 514 potentially eligible, 375 (73%) SRO tenants and DCC participants met inclusion criteria and agreed to enroll. As of June 1, 2014, participants were followed for a median of 3.8 years (interquartile range (IQR) 1.9 - 5.0 years), including 60/375 (16%) who were lost to follow up (Table 3.1). Participants were mostly middle-aged males, many of whom had been homeless (no fixed address) for at least one period in their life. Substance use was prevalent across the cohort, with tobacco, crack cocaine, and cannabis among the most commonly used. Half the cohort injected drugs, while few reported sharing needles. Conversely, pipe sharing was common (52%) among those using crack cocaine.

Table 3.1 Participant baseline characteristics and mortality

Sociodemographic Factors

	N	%
Female Sex	82	21.9
Income Assistance or Long-Term Disability	362	97.3
History of Homelessness	268	72.6
Visit with Family Physician (6 months)[a]	311	84.3
	Mean	SD
Age	43.4	9.4
Monthly Income[b]	898.3	442.3

Mortality		
	Mean	SD
Mortality	31	8.4
Causes of Death		
Physical Disease	15	48.4
Accidental Drug Overdose	8	25.8
Trauma	4	12.9
Suicide	1	3.2
Undetermined	3	9.7
	Mean	SD
Age at Death, N=31	53.0	8.5
Mental Illness		
	N	%
Psychotic Disorder	175	47.2
Mood Disorder	105	28.3
Substance Dependence	355	95.7
Stimulant Dependence	305	82.2
Opioid Dependence	202	54.4
Alcohol Dependence	67	18.1
Physical Illness		
	N	%
HIV Exposure	63	17.5
Hepatitis B Exposure	141	40.5
Current Hepatitis B Infection	5	3.5
Hepatitis C Exposure	244	68.3
Current Hepatitis C Infection	180	73.8
HIV/HCV Co-Infection	43	17.6
Hepatic Fibrosis (APRI>0.7)[c]	73	20.7
Substance Use[d]		
	N	%
Any Injection Drug Use	194	53.0
Any Tobacco Use	336	92.3
Any Crack Cocaine Use	210	57.7
Any Powder Cocaine Use	86	23.6
Any Cannabis Use	173	47.5
Any Heroin Use	127	34.9
Any Methamphetamine Use	91	24.3
Any Alcohol Use	180	49.2
Users Sharing Crack Pipes	108	52.2
Users Sharing Needles	3	1.5

[a] - Reported for first six months of study follow-up

[b] - Canadian dollars

[c] - AST-to-Platelet Ratio Index, surrogate measure of hepatic fibrosis

[d] - Reported for month prior to baseline

3.3.2 Mortality

During 1,269 person-years of observation, 31/375 (8%) of participants died. Coroner's reports were obtained for 14 participants who died outside of hospital. Fifteen deaths were attributed to physical disease, eight were accidental drug overdose-related, four were due to trauma (i.e. motor vehicle or blunt trauma), one was attributed to suicide and the causes of three deaths were unclear. Cocaine and opioids together were implicated in half of the deaths attributed to accidental drug overdose (Table 3.2).

Table 3.2 Demographic and clinical characteristics of participants who died

Age	Sex	Concurrent or contributing illnesses	Cause of death
55	M	COPD, hypertension, hyperlipidemia	Accidental drug overdose - cocaine
50	M	None	Accidental mixed drug intoxication - cocaine, morphine, methadone, methamphetamine
44	M	Chronic alcohol consumption, respiratory failure, substance intoxication, chronic pancreatitis, HCV, seizure disorder, severe steatohepatitis, acute bronchopneumonia	Acute subdural hematoma due to blunt force head injury
59	M	Respiratory failure, septic shock, acute kidney injury, DIC, COPD, hepatic dysfunction	Pneumonia
43	M	Subarachnoid hemorrhage, cardiac arrest, HIV, chronic renal failure, chronic microcytic anemia, thrombocytopenia, remote AIDS dementia	Subarachnoid hemorrhage
41	M	Recurring bronchopneumonia, recurrent infective endocarditis, remote tricuspid valve replacement, HCV, polysubstance abuse, chronic renal failure, adrenal insufficiency, severe peripheral vascular disease, dilated cardiomyopathy	Accidental mixed intoxication with cocaine and opioids
52	M	Corneal ulcer, harmful use of alcohol	Natural disease process - pneumonia
57	M	Uremic encephalopathy, AIDS, bilateral renal cell cancer, chronic renal failure	Uremia
64	M	COPD, alcohol dependence, DVT/PE	Metastatic non-small cell lung cancer

Age	Sex	Concurrent or contributing illnesses	Cause of death
59	F	MSSA bacteremia, mitral valve endocarditis, atrial fibrillation, multiple embolic strokes, polyneuropathy, myelopathy, chronic renal disease secondary to sepsis, respiratory failure requiring tracheostomy	Multiple organ failure
55	M	None	Acute myelogenous leukemia
47	F	HCV, MRSA infection, bipolar disorder	Accidental mixed drug intoxication - cocaine and methadone
59	M	HIV, HCV	Natural disease process - sepsis as a consequence of streptococcal pneumonia and bleeding duodenal ulcer
39	M	Cryptococcal septicemia, HCV, cirrhosis, hepatic failure, bleeding esophageal varices, MRSA positive	Respiratory failure
30	F	HCV, psychosis NOS, polysubstance abuse	Mixed drug toxicity - morphine, cocaine, methamphetamine
54	M	Illicit drug use	Accidental morphine and amitriptyline toxicity
54	M	Polysubstance abuse, COPD	Adenocarcinoma of the stomach
56	M	HIV, HCV, HIV-related thrombocytopenia	Unknown, coroner's report unavailable
51	M	HIV, HCV, traumatic brain injury, alcohol dependence, hypertension	Accidental inhalation of volatile substances (xylene and toluene in paint thinner) and pneumonia
58	M	Alcoholism, diabetes, HCV	Subdural hematoma after a fall
44	M	HIV, HCV, opioid and stimulant addiction	Found dead in jail cell, coroner's report unavailable
41	M	Heroin and crack cocaine	Suicide by hanging
56	M	None	Hit by a car while a pedestrian
45	F	Alcohol misuse	Gastrointestinal hemorrhage
64	M	HIV, HCV, polysubstance abuse, end-stage cirrhosis and liver failure	Respiratory failure secondary to pneumonia
57	M	Myotonic dystrophy, coronary artery disease, atrial flutter, hypertension, type II diabetes, previous stroke	Respiratory failure, COPD, pneumonia

Age	Sex	Concurrent or contributing illnesses	Cause of death
65	M	Cocaine use (coroner), substance-induced mania and psychosis (notes)	Blunt force head injury from being struck by a car
56	F	HCV, esophageal varices, hepatic encephalopathy, diabetes type II, depression	Metastatic hepatocellular carcinoma
50	M	Schizophrenia	Thought to be accidental overdose, coroner's report unavailable
59	F	HIV, HCV, pneumonia, past endocarditis	Small cell lung carcinoma
63	M	Chronic congestive heart failure	Thought to be suicide by overdose, related to wife's death, coroner's report unavailable

The crude mortality rate was 24 deaths per 1,000 person-years. The mean age at death was 47 (IQR: 23 - 72). Overall, 25/31 (81%) of decedents were male, similar to remaining participants. Compared with age- and sex-matched Canadian population data, the SMR was 8.29 (CI: 5.83-11.79). Deaths were particularly over-represented in the younger (20 - 39) and middle (40 - 59) age groups at 10.73 (CI: 3.46 - 33.25) and 10.54 (CI: 7.12 - 15.59) times the national rates, while in the older (60+) group, the SMR was elevated but not different (2.76; CI: 0.89 - 8.56) from the national rate. The SMR was elevated for both women (14.48; CI: 6.50 - 32.22) and men (7.52; CI: 5.08 - 11.13).

3.3.3 Illness prevalence

Physical and mental illness were prevalent at baseline assessment (Table 3.1). Psychiatric disorders, including psychotic disorder (175/375, 47%), mood disorder (105/375, 28%), and substance dependence disorders (355/375, 96%) were common. Psychotic disorders included schizophrenia (29/175, 17%), schizoaffective (20/175, 11%), mood disorder with psychosis (12/175, 7%), post-anoxic or interferon-related psychosis (2/175, 1%) substance-induced psychosis (70/175, 40%), and psychosis not otherwise specified (42/175, 24%). HCV exposure (244/357, 68%) was prevalent, including several participants

(12/244, 5%) who reported never testing positive for HCV previously. Many had persistent

HCV infection (180/244, 74%). Hepatic fibrosis (APRI >0.7) was detected in 73/353 (21%)

of the cohort.

3.3.4   Impact of illness on mortality risk

Survival analysis was employed to evaluate the association between illnesses

amenable to treatment and mortality risk (Table 3.3). Notably, baseline HIV or HCV

exposure, and opioid or stimulant dependence were not associated with increased risk of

mortality. The effect of psychotic disorder on mortality interacted with age as determined by

a significant Schoenfeld residual global test (Table 3.3). For participants younger than the

change-point age 55, psychotic disorder was significantly associated with earlier death, but

not in those 55 or older (Figure 3.1). The probability that an individual with psychotic

disorder would survive to age 50 was 68% compared to 94% for those without the diagnosis

among marginally housed individuals.

Table 3.3 Survival analysis of illnesses amenable to treatment as risk factors of earlier mortality

			Unadjusted regression models		
Factor	N	HR	95% CI	Log-Rank p-value	Schoenfeld p-value
Mental Illness					
Psychotic Disorder	371	1.18	0.56, 2.47	0.660	0.008
Mood Disorder	371	0.88	0.39, 2.00	0.767	0.147
Stimulant Dependence	371	0.90	0.37, 2.22	0.819	0.852
Opioid Dependence	371	1.18	0.56, 2.45	0.665	0.644
Alcohol Dependence	371	2.05	0.93, 4.53	0.075	0.996
Physical Illness					
HIV Exposure	359	1.42	0.59, 3.41	0.431	0.118
HCV Exposure	357	1.32	0.52, 3.35	0.558	0.765
Current HCV Infection	244	1.00	0.36, 2.78	0.993	0.427
Hepatic Fibrosis (APRI>0.7)[a]	353	3.42	1.63, 7.17	<0.001	0.259
Substance Use [b]					
Any Injection Drug Use	366	1.45	0.65, 3.21	0.365	0.619

[a] - AST-to-Platelet Ratio Index, surrogate measure of hepatic fibrosis

[b] - Reported for month prior to baseline

Figure 3.1 Kaplan-Meier curves for the probability of survival by age among marginally housed adults (Above) ≥ 55 years old (N=82) and (Below) < 55 years old (N=289) with psychotic disorder as compared to those without the diagnosis.
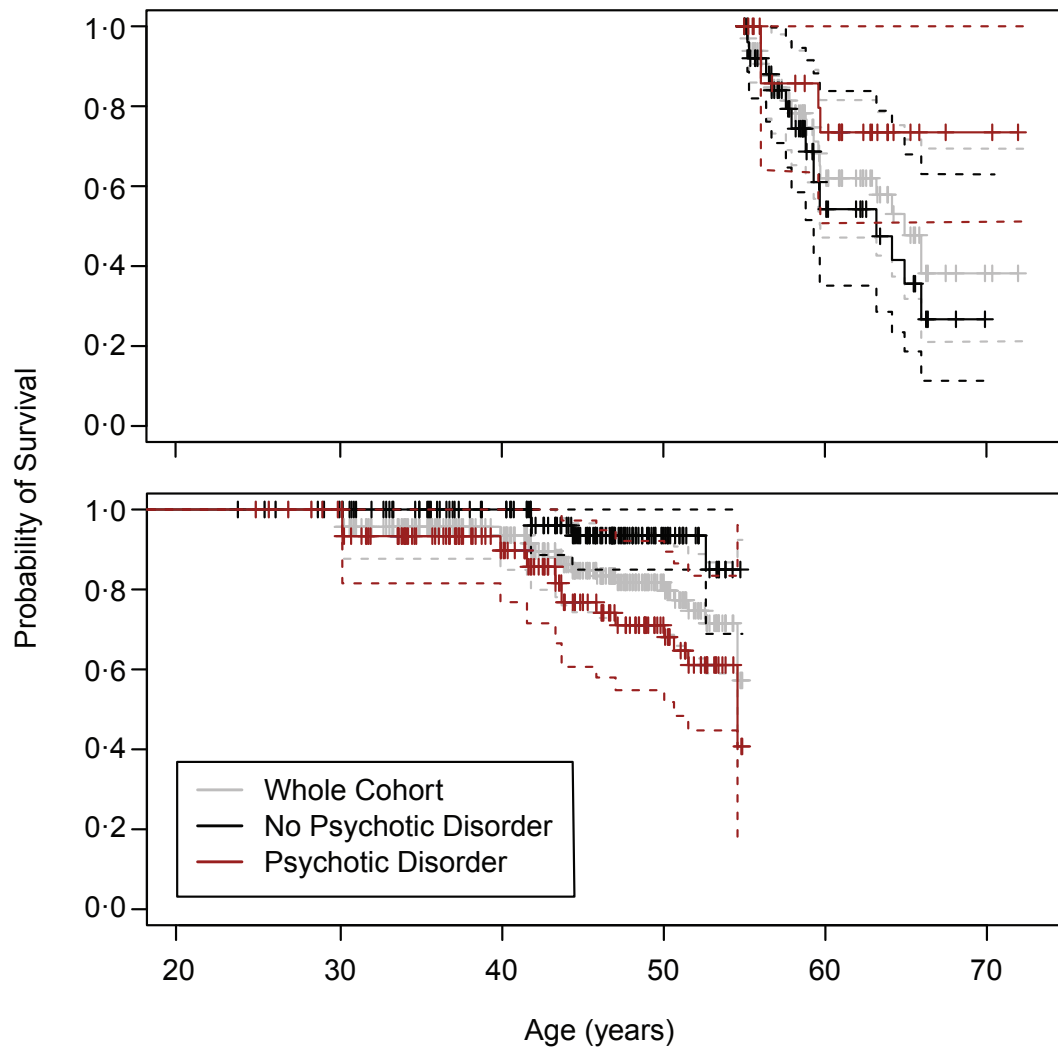
Survival curves coloured grey for population average, red for those with psychotic disorder and black for those without psychotic disorder.

Surpassing the threshold APRI value of 0.7 (suggesting hepatic fibrosis) was also significantly associated with earlier mortality (Figure 3.2). The probability that an individual with hepatic fibrosis in this cohort would survive to age 50 is 34% compared to 89% for those without evidence of fibrosis. Active HCV infection was not independently associated with earlier mortality. However, active HCV infection was associated with evidence of fibrosis. As compared to those that had cleared the infection, current HCV infection was a significant predictor of above threshold APRI, adjusting for age and alcohol dependence (Table 3.4).

Figure 3.2 Kaplan-Meier curves for the probability of survival by age among marginally housed adults with evidence of hepatic fibrosis (APRI>0.7) as compared to those with APRI<0.7. (N=353)
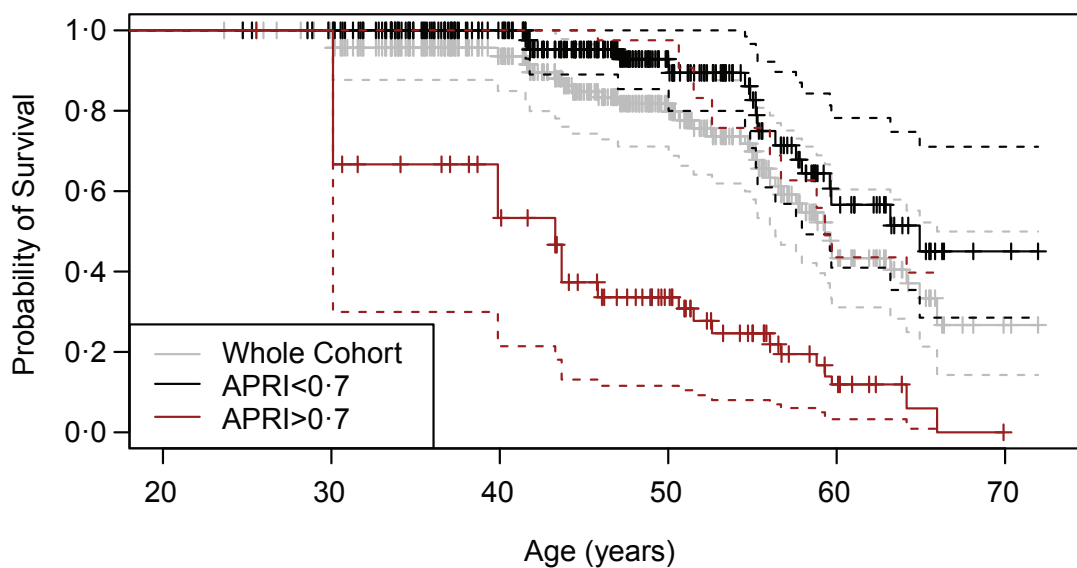
Survival curves coloured grey for population average, red for those with APRI>0.7 and black for those with APRI<0.7.

Table 3.4 Logistic regression analysis of factors associated with hepatic fibrosis

Factor	N	OR	95% CI	p-value	OR	95% CI	p-value
		Unadjusted Models			**Adjusted Model (n=239)**		
Female	353	0.73	0.07, 1.39	0.354	--	--	--
Age at Entry (years)	353	1.05	1.02, 1.08	<0.001	1.04	1.01, 1.08	0.015
Current HCV Infection	240	2.57	1.23, 5.92	0.017	2.96	1.37, 7.08	0.009
Any Alcohol Use	350	1.15	0.68, 1.95	0.593	--	--	--
Alcohol Dependence	353	1.74	0.93, 3.18	0.074	1.90	0.83, 4.29	0.122

For participants younger than 55 years of age, hepatic fibrosis and psychosis were significantly associated with earlier mortality (Table 3.5). Alcohol dependence did not meet inclusion criteria for the adjusted model. Interactions between predictors were not significant (p=0.367).

Table 3.5 Unadjusted and adjusted survival analysis of risk factors of earlier mortality for younger (age <55, N=289) and older (age≥55, N=82) adults

Factor	N	HR	95% CI	Log Rank p-value	HR	95% CI	Log Rank p-value
		Unadjusted Models			**Adjusted Model (n=273)**		
Age < 55							
Psychotic Disorder	289	3.78	1.03-13.84	0.032	8.12	1.55-42.47	0.013
Hepatic Fibrosis[a]	273	8.90	2.83-27.93	<0.001	13.01	3.56-47.57	<0.001
Alcohol Dependence	289	2.91	0.95-8.96	0.051	--	--	
Age ≥ 55							
Psychotic Disorder	82	0.36	0.10-1.31	0.107	--	--	
Hepatic Fibrosis[a]	80	2.14	0.79-5.82	0.128	--	--	
Alcohol Dependence	82	1.83	0.57-5.91	0.304	--	--	

[a] - APRI>0.7. AST-to-Platelet Ratio Index, surrogate measure of hepatic fibrosis

3.3.5 Treatment rates

The majority of participants (84%) reported seeing a family physician during the first six months of study follow-up (Table 3.1). However, baseline treatment rates were low for illnesses associated with earlier mortality in this cohort. Treatment for psychotic disorder and HCV infection were less common than treatment for HIV and opioid dependence (Figure 3.3). Of those who died, 15/31 (48%) were psychotic at the last visit before death; available data indicated 2/12 (17%) with psychotic disorder were receiving antipsychotic drug treatment.

Figure 3.3 Stacked bar plot comparing baseline treatment rates for those with HIV infection, opioid dependence, psychotic disorder, and liver fibrosis (APRI>0.7) with current HCV infection (qPCR+).
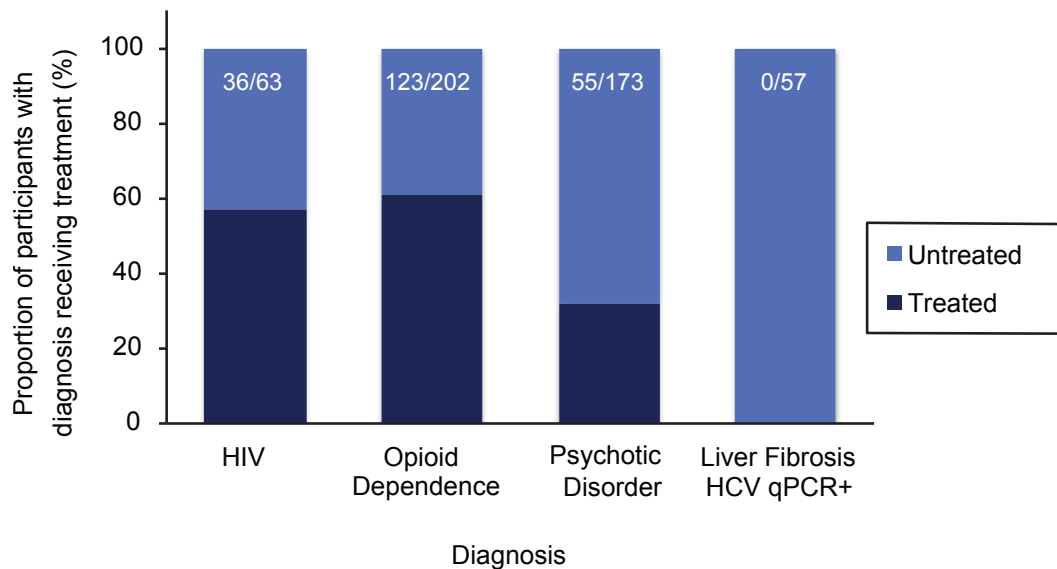
Proportions of diagnosed participants receiving treatment (n/N) are reported here.

3.4   Discussion

3.4.1   Excess premature mortality among marginally housed adults

Adults living in marginalized conditions have significantly greater all-cause mortality rates than other Canadians. We found a greater than eight-fold increase in mortality rate. Deaths were over-represented in younger participants. The excess mortality in the present cohort is comparable or greater than other reports of marginally housed individuals (Fazel et al., 2014; Nielsen et al., 2011; Phipps, 2003), except one cohort study of homeless women in Toronto (Cheung & Hwang, 2004). Causes of death included overdose and acute and chronic diseases. Mental and physical multimorbidities were common, many of which are complex but potentially treatable. We found that having psychotic disorder and hepatic fibrosis (APRI > 0.7) were significantly associated with earlier mortality in participants less than 55 years old.

3.4.2   Psychotic disorder as a significant risk factor for premature mortality

Individuals with psychotic disorder may face a greater than eight-fold increase in mortality risk compared to those without psychotic disorder, adjusting for hepatic fibrosis. The associated mortality risk is higher than reported estimates from a meta-analysis demonstrating a pooled mortality risk of 2.54 (95% CI 2.35 - 2.75) for psychotic disorder (Walker et al., 2015). The majority of the studies included in the meta-analysis focused on inpatient schizophrenia while other psychotic illnesses and untreated psychotic disorder were less represented (Walker et al., 2015). Psychosis itself is a devastating biological insult in addition to the effects of co-occurring social factors, including poverty and social connectedness, access to quality health care, and behavioural and lifestyle factors (Laursen et al., 2014).

3.4.3   Hepatic fibrosis as an independent risk factor for premature mortality

Biochemical evidence of hepatic fibrosis was also associated with earlier death across the cohort and was strongly associated with active HCV infection. Prior to age 55, hepatic fibrosis conferred a 13-fold increase in premature mortality, adjusting for the effects of psychotic disorder. These findings are consistent with other studies supporting persistent untreated HCV infection can lead to hepatic fibrosis and shorten life expectancy (Backus et al., 2011; Grebely et al., 2011). Historically, HIV infection and needle sharing were associated with high rates of mortality in urban Vancouver (Grebely et al., 2011). However, low rates of HIV and needle sharing and high rate of antiretroviral treatment seen here may reflect the impact of harm reduction initiatives and increased access to highly active antiretroviral therapy (HAART) (Hyshka, Strathdee, Wood, & Kerr, 2012; Marshall et al., 2011; Montaner et al., 2010).

Many participants also suffered from a substance use and/or mood disorder, but neither illness was associated with premature death. There was a trend suggesting alcohol dependence may have a weak association with earlier death, but this was not statistically significant in adjusted analyses. Alcohol dependence also demonstrated a trend association with evidence for hepatic fibrosis, however this effect was not significant, particularly when adjusting for active HCV infection.

3.4.4   Low treatment rates for illnesses with significant mortality risk

The majority of participants saw a family physician during the first six months of the study. This is consistent with high primary care and emergency department utilization seen among people experiencing unstable housing (Hwang et al., 2013). Despite being connected to primary care, less than one third of participants with psychotic disorder were receiving

pharmacological treatment for their illness. Antipsychotic medications reduce the risk of suicide, the leading cause of premature death in people with schizophrenia (Lehman et al., 2010). Low treatment rates may be attributed to financial barriers associated with lack of supplemental insurance for prescription medications (Mulvale & Hurley, 2008). Limited psychiatric care access and challenges in diagnosis, treatment engagement, and comorbidity management may also contribute.

Successful treatment of HCV infection with antiviral therapy reduces all-cause mortality (Backus et al., 2011). Here we show that none of the participants with HCV infection and evidence of hepatic fibrosis were receiving antiviral treatment at baseline. As of 2009, the American Association for the Study of Liver Diseases guidelines outlined that persons who inject drugs and/or have psychiatric illness should be considered for treatment of active/chronic HCV infection with monitoring and the support of a multi-disciplinary team (Ghany, Strader, Thomas, & Seeff, 2009). Effective HCV management may be impeded by factors including limited access to care, cost of treatment, education about illness, low perceived need for treatment, and physician expertise in managing comorbidities (Donepudi, Paredes, Hubbard, Awad, & Sterling, 2015). Treatment may also be postponed due to other pressing health concerns (Donepudi et al., 2015). In this study, several participants with HCV exposure at baseline screening were unaware of their status. Despite inconsistencies in treatment accessibility, high-risk populations have demonstrated an interest in knowing their HCV status (Norton et al., 2014), supporting increased community-based HCV screening for inner city populations.

3.4.5 Study strengths and limitations

There are several limitations to the study. Treatment self-report has the advantage of capturing adherence but accuracy and precision may be affected by participants' memory or understanding of their care. Follow-up was limited to median 3.8 years; this is similar to other survival reports (Backus et al., 2011; Grebely et al., 2011; Walker et al., 2015) but should be considered when interpreting results. Also, since illness measures were assessed at baseline only, it is not possible to draw conclusions of the impact of the course of illness on mortality. Longitudinal trajectories of illness progression and mortality risk may offer further insights into health risks and care prioritization.

This study also has several strengths. Participants were recruited from marginalized housing operations and the DCC to better capture the population living in inner city conditions. Our findings may be generalizable to other marginalized populations facing multimorbidities, though cost and availability of treatment may underlie variations between other health care systems.

Chapter 4: Longitudinal assessment of psychosis and psychosis risk factors among marginally housed adults

4.1   Brief introduction

As described in Chapter 1, multiple biopsychosocial risk factors are proposed to accumulate across the lifespan increasing the likelihood of psychosis and associated psychotic disorders. We sought to determine (1) the one-year prevalence of psychosis among adults in marginal housing, and (2) the combined effects of early-life and recent exposures, including trauma, substance use, and brain injury, on psychosis risk over one year. We hypothesized that early-life and recent traumatic events and ongoing frequent use of methamphetamine, cocaine, cannabis, or alcohol would independently increase the probability of experiencing psychosis over the year.

4.2   Brief methods

4.2.1   Measures

Detailed description of recruitment and study design are included in Chapter 2. Diagnoses were determined by study psychiatrists according to DSM-IV-TR criteria using all available information. Those who met criteria for schizophrenia or schizoaffective disorder were included in the Schizophrenia/Schizoaffective Disorder (SSA) group; the remaining participants were included in the At-Risk (AR) group. Baseline psychiatric symptoms and social functioning were assessed using the 30-item PANSS (Kay et al., 1987) and SOFAS (American Psychiatric Association, 2000).

The binary outcome variable indicated the presence of psychosis. Psychosis was identified according to threshold scores for each of the five key symptoms at monthly assessments for the past week: delusions, conceptual disorganization, hallucinatory behavior,

suspiciousness and persecution, and unusual thought content (see Table 2.1). Retrospective and prospective psychosis risk factors were assessed. Retrospective factors included the number of types of traumatic events prior to age 18 (THQ18), and persistent sequelae of past TBI. Time-varying (prospective) factors were assessed at monthly visits and included recent traumatic events (rTHQ), prescribed and non-prescribed substance use, and housing status (Figure 4.1). The rTHQ was recorded and analyzed as an ordinal variable truncated at 2, since only 3.0% had 3 or more types of events in the past month. Non-prescription substance use in the week concurrent with psychosis evaluation was examined to capture acute effects of substance exposure on symptom severity. Days of use and route of administration were reported. Tobacco use was dichotomized to indicate daily use due to the high prevalence (82.9%) among participants. Antipsychotic treatment and methadone maintenance therapy were reported and assessed for the past four weeks at each monthly visit. Housing status at the time of assessment was analyzed as a binary variable of homeless versus housed, and excluded periods in jail (1.2%) or inpatient treatment (1.4%) due to low rates.

4.2.2   Statistical analysis

Descriptive statistics of participant time-invariant and time-varying psychosis risk factors were reported as mean (SD) for continuous variables and number (proportion) for categorical variables. For participants without psychosis at baseline, the incidence rate for a new episode of psychosis was calculated (Incident Episode Subgroup of the AR group). Incidence proportion and time-to-episode were estimated by the Kaplan-Meier method. SSA and AR groups were compared on categorical variables using the Chi-squared test. Within-subject diagnostic stability was tested by McNemar's test.

Mixed effects logistic regression models with random intercept and slope for longitudinal binary outcome data were used to assess the relationships between psychosis (presence or absence) and time-varying and time-invariant risk factors over time. Fixed effects estimated the main effects of risk factors on odds of psychosis. Time-invariant factors included persistent sequelae from past TBI (categorical effect estimate) and THQ18 (dose-effect estimate). Time-varying risk factors included number of days (zero to seven days) of non-prescription substance use and rTHQ (dose-effect estimates). The number of days of each substance had an linear effect with psychosis. When the days of substance use was included as an ordinal variable (with several cutpoints compared), the quadratic effects were not significant ($p > 0.05$) and including the quadratic effects did not improve model fit. Effects were also visualized by plotting the predicted probability of psychosis by days of substance use. Thus, days of non-prescription substance use were included as continuous variables. Covariates were age, sex, time point, antipsychotic treatment, and methadone therapy. Random effects standard deviations were reported. No evidence overdispersion was found ($\chi^2 = 1624.18$, p=1.000). We tested multiplicative interactions using the Wald test. Unstandardized fixed effects coefficients are reported for interpretation, and were compared against standardized estimates. Predicted probabilities of psychosis were estimated for combinations of significant risk factors.

Several approaches were employed to test the robustness of results (Figure 4.1). Reverse causation was investigated by estimating the effect of psychosis presence or absence on the frequency of substance use in the subsequent week using linear mixed effects models, and likelihood of a traumatic event in the subsequent month using logistic mixed effects models, adjusting for covariates. Time-lagged substance use in the week prior to the week of

psychosis assessment was included in the adjusted model to estimate the persistence of

substance use effects. Further, the relationships between psychosis and same-day urine drug

screen results were also assessed. Sensitivity analyses assessed for evidence of systematic

bias by comparing participants who were included or excluded from longitudinal analyses

and findings were compared between models with and without outlier observations. A

multiple imputation procedure was also performed using all risk factors and covariates to

predict missing values by posterior mean matching and logistic regression analysis. The

adjusted model was estimated for ten completed datasets, and estimates were pooled to

obtain fixed effects estimates that were compared to the complete-case analysis by Pearson

correlation.

Figure 4.1 Schematic of design for one-year study of psychosis in tenants living in marginal housing.
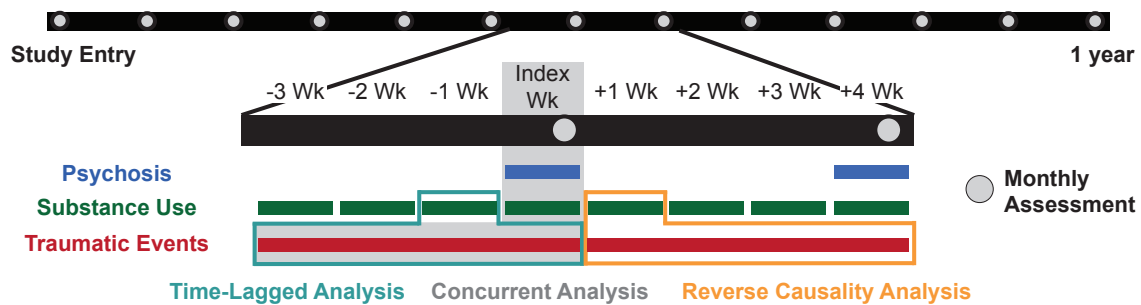
The schematic depicts the study design to evaluate time-varying factors at monthly assessments over one year. At each assessment (grey circle), psychosis in the past week is evaluated by a five-item PANSS (dark blue bars). Substance use in the past four weeks is evaluated by the Drug Timeline Followback approach (green bars). Traumatic events in the past month are evaluated by the Trauma History Questionnaire (THQ) (red bars). The grey box indicates the time-varying factors included in concurrent analyses estimating the acute effects of substance use and traumatic events on psychosis. The teal boxes indicate the factors included in analyses with time-lagged substance use variables, while the orange boxes indicate the factors included in the analyses testing potential reverse causality of effects.

4.3 Results

4.3.1 Participant characteristics

Participant enrollment and flow through the one-year study period appears in Figure 4.2. Demographic and clinical characteristics of participants (n=437) appear in Table 4.2. At baseline, 425 (97.3%) participants were living in an SRO hotel and 12 (2.7%) were homeless. For 208 participants with available follow-up data, schizophrenia and schizoaffective disorder diagnoses exhibited significant stability at five years (93.8% determined to have the same diagnosis five years later; $\chi^2 = 1.23$, p=0.267).

Figure 4.2 Flow chart of participants in one-year study of psychosis in adults living in marginal housing.
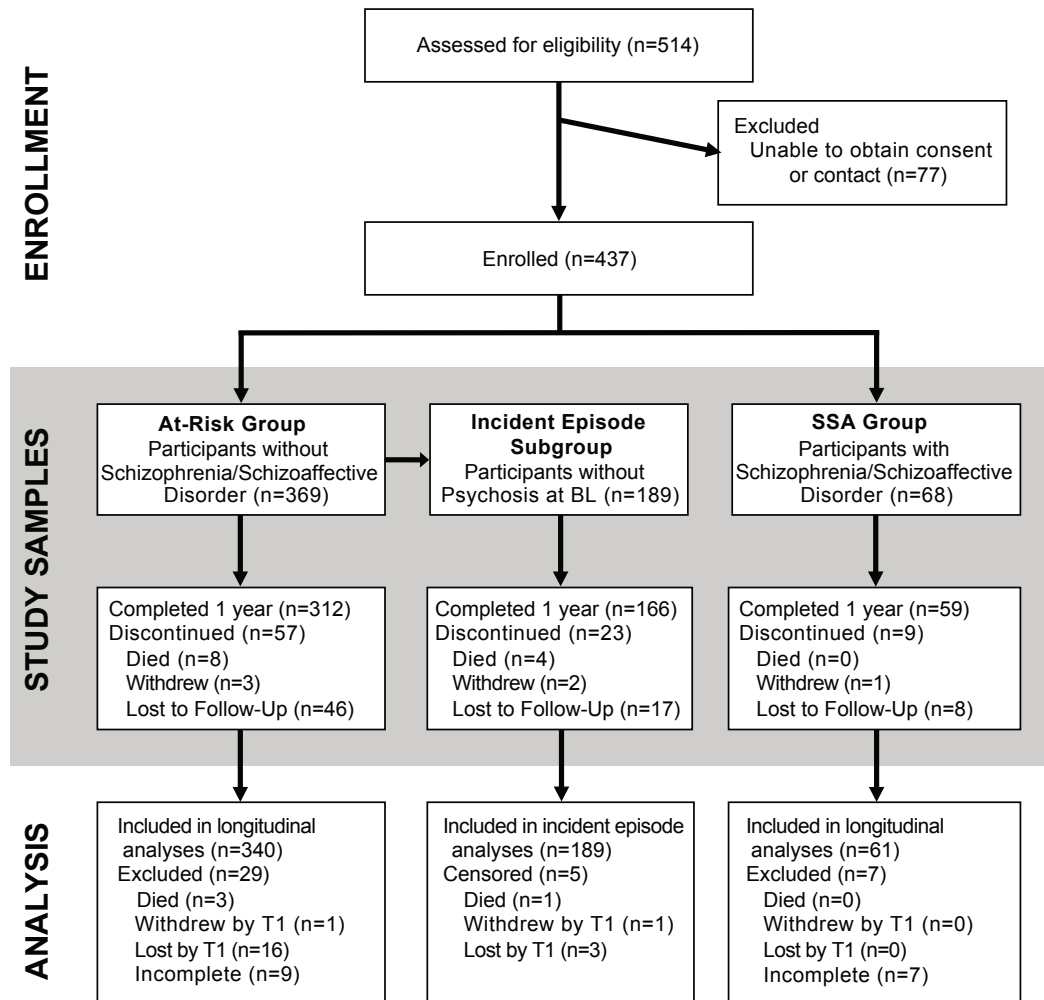
Schematic depicts participant flow in enrollment, study groups, and data analysis. BL = baseline assessment at study entry; T1 = assessment one month after study entry.

Table 4.1 Baseline and psychosis characteristics of adults living in marginal housing

Characteristic	All Enrolled (N=437)		AR Group (N=369)		IE Subgroup (N=189)		SSA Group (N=68)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	40.6	11.2	41.5	11.0	42.7	10.7	35.6	11.2
SOFAS score	39.9	10.6	40.7	10.6	43.0	10.8	35.7	9.6
	N	%	N	%	N	%	N	%
Sex								
Male	340	77.8	281	76.2	145	76.7	59	86.8
Female	97	22.2	88	23.9	44	23.3	9	13.2
Ethnicity/Race								
White	261	59.7	215	58.3	112	59.3	46	67.6
Aboriginal	113	25.9	99	26.8	50	26.5	14	20.6
Other	63	14.4	55	14.9	27	14.3	8	11.8
Completed high school or equivalent	186	43.0	159	43.4	88	46.8	27	40.3
Any formal employment	53	12.1	41	11.1	25	13.2	12	17.6
Past homelessness	323	74.9	278	76.4	138	73.4	45	67.2
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
30-item PANSS								
Positive subscale score	16.0	6.0	14.6	4.9	13.3	4.0	22.7	6.5
Negative subscale score	16.5	5.8	15.7	5.3	15.3	5.0	20.1	7.0
General psychopathology subscale	37.3	8.6	36.0	8.1	34.5	7.5	43.7	8.0
Total score	69.7	17.5	66.3	15.0	63.1	13.7	85.5	19.7
Monthly assessment visits – no.	9.8	3.6	9.9	3.7	10.2	3.4	9.2	3.3
Monthly visits with psychosis (%)	45.0	37.6	37.6	35.2	15.1	21.6	84.0	23.4
	N	%	N	%	N	%	N	%
Monthly visits with psychosis								
Participants with 0 visits over 1-year	93	21.7	92	25.6	92	48.7	1	1.5
Participants with 1 visit over 1-year	51	11.9	51	14.2	32	16.9	0	0.0
Participants with ≥2 visits over 1-year	284	66.4	217	60.3	65	34.4	67	98.5
Symptom types above threshold for participants with psychosis								
Delusions	302	90.1	235	87.7	75	77.3	67	100.0
Conceptual disorganization	144	43.0	100	37.3	25	25.8	44	65.7
Hallucinatory behavior	248	74.0	186	69.4	59	60.8	62	92.5
Suspiciousness/Persecution	131	39.1	82	30.6	22	22.7	49	73.1
Unusual thought content	157	46.9	100	37.3	16	16.5	57	85.1
Exclusively monosymptomatic [a]	64	19.1	63	23.5	39	40.2	1	1.5
Polysymptomatic [b]	271	80.9	205	76.5	58	59.8	66	98.5

[a] – Participants with psychosis experiencing only one symptom type above threshold over one year.

[b] – Participants with psychosis experiencing more than one symptom type above threshold over one year, and/or they experienced more than one symptom type above threshold concurrently.

4.3.2 Incidence of new episodes of psychosis

AR group participants without psychosis at baseline (n=189) were included in the incident episode analyses (IE group) (Figure 4.2), described in Table 4.2. Available information at baseline indicated 121 (64.0%) of these participants did not report experiences consistent with any pre-existing psychotic disorder diagnosis. By one year of follow-up, 97 (51.3%) participants endorsed psychotic symptoms above the severity threshold for psychosis. The Kaplan-Meier estimate of the proportion of participants endorsing psychosis by six months was 35.6% (95% CI: 28.2 - 42.2%) and by twelve months was 55.2% (95% CI: 47.1 - 62.1%). The new episode psychosis incidence rate was 833 cases per 1,000 person-years at risk (97 cases per 1398 person-months).

4.3.3 Key symptoms characterizing psychosis

Among all participants, 335 (78.3%) endorsed psychotic symptoms at least once during the year (Table 4.2). Only one SSA group participant was psychosis-free for the year. Compared with the AR group, psychosis in the SSA group was characterized by multiple rather than single symptoms above the severity thresholds (p<0.001). For monosymptomatic participants, delusions were the most common symptom (Figure 4.3). Delusions and hallucinations were the most frequent symptom combination overall (134, 31.3% participants), appearing concurrently in 709 of 4,288 (16.5%) observations. Persistent psychosis, defined as having symptoms above threshold at every visit over the year, was more frequent in the SSA group (34, 50.0%) than the AR group (38, 10.6%) (p<0.001). Thus, risk factors for the presence or absence of psychosis over time were examined in the AR and SSA groups separately.

Figure 4.3 Prevalence of cardinal symptoms of psychosis for the SSA and AR groups.

A. Schizophrenia/Schizoaffective Disorder (SSA) Group (N=68)

B. At-Risk (AR) Group (N=369)

■ Monosymptomatic   ■ Polysymptomatic
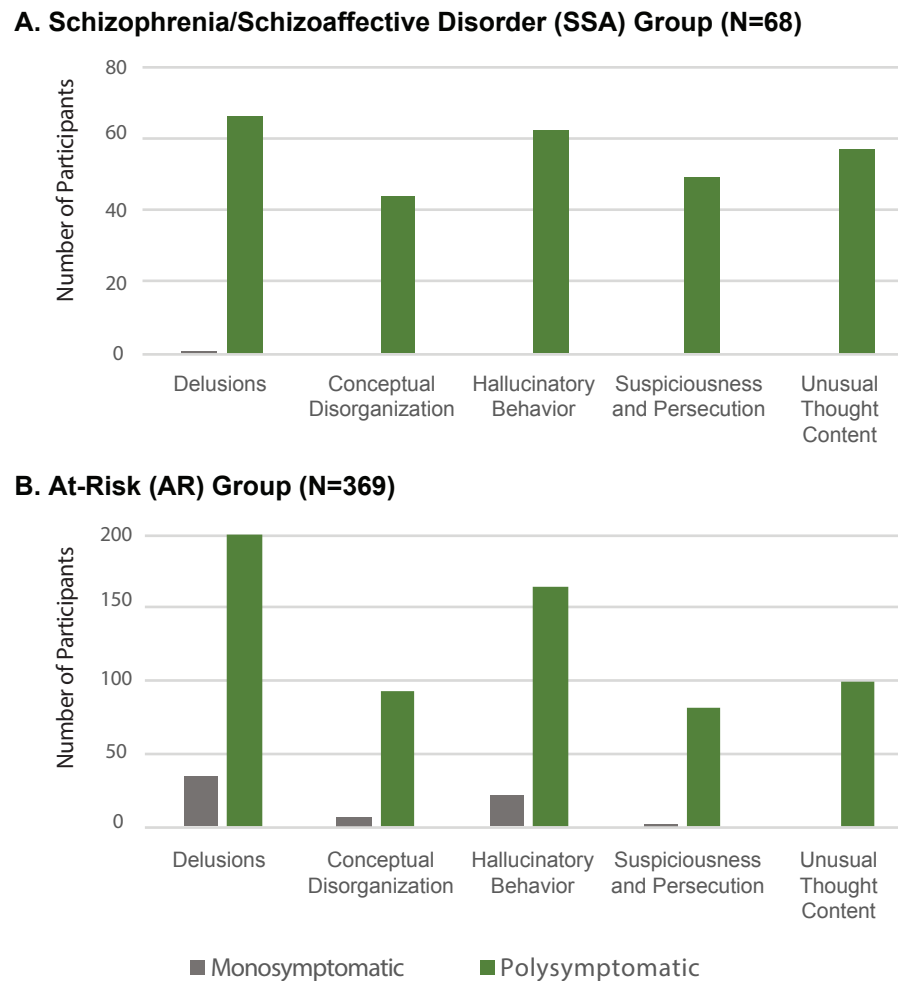
Bar charts depict prevalence of key psychotic symptoms in the (A) SSA group (N=68) and the (B) AR group (N=369). Coloured bars indicate the number of participants endorsing one symptom type exclusively (mono-symptomatic; grey bars) or a symptom type in combination with other symptoms (poly-symptomatic; green bars) in one year of follow-up.

4.3.4   Psychosis risk factor prevalence

Table 4.3 describes the prevalence of time-invariant and time-varying psychosis risk factors in the AR and SSA groups. Among all enrolled individuals, early-life traumatic events were reported by 331 (81.0%). All types of traumatic events in childhood and

adolescence were endorsed, with mean 2.9 (SD = 2.6) types of events. Persistent sequelae of past TBI were noted in 43 (9.9%) participants. During the year, exposure to substances ranged from 163 (37.4%) for powder cocaine to 390 (89.2%) for daily tobacco. Frequency of substance use varied from once to daily, with mean 2.4 (SD = 1.2) substances used per week. Traumatic events were experienced by 353 (85.7%) participants over the year. These most frequently involved death or serious injury of a loved one or witnessing someone's injury or death. Similar patterns of risk factors were seen in both AR and SSA groups.

Table 4.2 Time-invariant and time-varying psychosis risk factors in AR and SSA groups

	AR Group (N=369)		SSA Group (N=68)	
Time-invariant factors	N	%	N	%
Persistent clinical or MRI evidence of past TBI	41	11.2	2	2.9
Traumatic events by age 18				
Any event (THQ score ≥1) [a]	285	79.8	46	71.9
Sexual abuse	121	33.9	15	23.4
Physical abuse	120	33.6	20	31.3
Crime-related	118	33.1	18	28.1
Disaster-related	238	66.7	41	64.1
Attack to self/loved one	172	48.2	34	53.1
Witnessed injury/murder	112	31.4	22	34.4
Lost/Injured loved one	78	21.8	15	23.4
	Mean	SD	Mean	SD
THQ items endorsed by age 18 – no.	2.9	2.6	2.8	2.8
Time-varying factors	N	%	N	%
Homeless ≥1 time over 1-year	38	10.3	10	14.7
Traumatic events over 1-year				
Any event (THQ score ≥1) [b]	300	86.7	53	80.3
Sexual abuse	24	6.9	6	9.1
Physical abuse	92	26.6	20	30.3
Crime-related	145	41.9	26	39.4
Disaster-related	254	73.4	46	69.7
Attack to self/loved one	149	43.1	26	39.4
Witnessed injury/murder	116	33.5	28	42.4
Lost/Injured loved one	154	44.5	19	28.8
Any non-prescribed substance use over 1-year				
Tobacco (any daily use)	331	89.7	59	86.8
Alcohol	275	74.5	57	83.8
Methamphetamine	158	42.8	41	60.3
Cannabis	249	67.7	62	91.2
Powder cocaine	143	38.9	20	29.4
Crack cocaine	243	66.0	41	60.3
Opioids	197	53.5	24	35.5
Any prescribed substance use over 1-year				
Methadone maintenance therapy	155	42.0	11	16.2
Adequate antipsychotic treatment	49	13.3	52	76.5

	AR Group (N=369)		SSA Group (N=68)	
	Mean	SD	Mean	SD
Types of non-prescribed substances used in past week – no.	2.4	1.2	2.3	1.3
Alcohol use – days in past week	3.1	2.3	2.3	1.9
Methamphetamine use – days in past week	3.8	2.4	3.0	2.0
Cannabis use – days in past week	4.9	2.5	4.7	2.4
Powder cocaine use – days in past week	4.1	2.5	4.0	2.4
Crack cocaine use – days in past week	4.4	2.5	3.7	2.4
Opioid use – days in past week	4.9	2.5	4.6	2.5

[a] – Trauma History Questionnaire of retrospective traumatic events prior to age 18 (THQ18)

[b] – Trauma History Questionnaire of prospective traumatic events in the month prior to each monthly assessment (rTHQ)

4.3.5   Associations between risk factors and psychosis

Effects of time-invariant and time-varying psychosis risk factors in the AR group are summarized in Table 4.4. In both unadjusted and adjusted models, odds of experiencing psychosis were greatest among males, those with past TBI, and greater THQ18. The final adjusted model indicated independent, linear, dose-dependent effects of the number of days of methamphetamine, powder cocaine, alcohol, and cannabis use on odds of concurrent psychosis. The effect of cocaine was specific to powder cocaine; days of crack cocaine use was not associated with psychosis nor did it modify the effect of powder cocaine. The frequency of use both forms of cocaine was similar (mean 4 days). All participants reporting powder cocaine use had injected cocaine in the year, and 94.4% of observations of reported powder cocaine use were injected. Also, greater rTHQ was associated with increased odds of psychosis. Additionally, psychosis was associated with receiving adequate antipsychotic treatment in the past month. These effects did not change over time and there was no evidence of multiplicative interactions. Periods of homelessness, daily tobacco use, non-

prescribed opioid use, or prescribed methadone were not associated with psychosis. Time itself did not change psychosis risk. Unstandardized and standardized fixed effects coefficients were very similar (r = 0.902, p<0.001) (Appendix Table A.7 – A.8). By comparing the standardized effect coefficients, we observe that of the acute, time-varying factors, days of methamphetamine use has the greatest impact on odds of psychosis, followed by rTHQ then days of cannabis use and powder cocaine use. In contrast to the AR group, these time-invariant and time-varying risk factors were not associated with psychosis in the SSA group (Table 4.5). In the latter chronically ill group, odds of psychosis increased over time.

Table 4.3 Concurrent effects of time-invariant and time-varying risk factors for psychosis over one Year for the At-Risk group (N=340, 2994 observations)

	Unadjusted [a]		Adjusted [b]	
	OR	95% CI	OR	95% CI
Covariates				
Time	0.95*	0.90, 1.00	0.97	0.92, 1.01
Age	0.99	0.96, 1.02	—	—
Male	2.14*	1.06, 4.36	2.03*	1.05, 3.95
Time-invariant factors				
Persistent sequelae of TBI [c]	3.13*	1.26, 7.79	2.84*	1.22, 6.64
THQ score by age 18	1.19**	1.06, 1.33	1.14*	1.03, 1.28
Time-varying factors				
Concurrent week				
Daily tobacco use	1.71	0.98, 2.98	1.67	0.97, 2.87
Days using alcohol	1.12*	1.02, 1.23	1.10*	1.01, 1.21
Days using methamphetamine	1.18**	1.07, 1.30	1.18***	1.07, 1.29
Days using cannabis	1.10**	1.03, 1.17	1.08*	1.02, 1.15
Days using powder cocaine	1.13*	1.03, 1.25	1.13*	1.02, 1.24
Days using crack cocaine	1.00	0.94, 1.07	—	—
Days using non-prescribed opioid	1.06	0.99, 1.14	—	—
Past month				
THQ score [d]	1.61**	1.20, 2.17	1.61**	1.20, 2.16
Homeless	1.24	0.47, 3.28	—	—
Adequate antipsychotic treatment	2.36*	1.10, 5.04	2.26*	1.07, 4.79
Adequate methadone therapy	0.87	0.56, 1.34	—	—
Random effect (SD): Subject	2.425		2.430	
Random effect (SD): Time	0.236		0.221	
AIC	2935.0		2887.9	

[a] – Adjusted for time only.

[b] – Adjusted for all time-invariant, time-varying factors, and covariates included.

[c] – Data from participants with MRI evidence (n=21) or clinical evidence (n= 12) of previous traumatic brain injury (loss of consciousness ≥5 minutes or confusion ≥1 day) and persistent symptoms attributed to TBI.

d – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥2) in the past month are reported. Quadratic effects were not significant (p>0.10).

*p<0.05; **p<0.01; ***p<0.001

Table 4.4 Concurrent effects of time-invariant and time-varying risk factors for psychosis over one year for SSA group (N=61, 452 observations)

	Unadjusted [a]		Adjusted [b]	
	OR	95% CI	OR	95% CI
Covariates				
Time	1.27*	1.03, 1.57	1.33*	1.05, 1.68
Age	1.02	0.97, 1.07	—	—
Male	1.11	0.21, 6.00	—	—
Time-invariant Factors				
Persistent sequelae of traumatic brain injury	—	—	—	—
THQ score prior to age 18	1.00	0.82, 1.24	—	—
Time-Varying Factors				
Concurrent week				
Daily tobacco use	1.33	0.50, 3.55	—	—
Days using alcohol	0.90	0.70, 1.15	—	—
Days using methamphetamine	1.11	0.86, 1.44	—	—
Days using cannabis	1.03	0.90, 1.18	—	—
Days using powder cocaine	1.29	0.96, 1.74	1.31	0.97, 1.79
Days using crack cocaine	1.05	0.88, 1.24	—	—
Days using non-prescribed opioid	1.04	0.82, 1.32	—	—
Past Month				
THQ score [d]	1.16	0.53, 2.50		
Adequate antipsychotic treatment	0.64	0.28, 1.44	0.61	0.27, 1.38
Adequate methadone therapy	3.34	0.59, 18.86	—	—
Random effect (SD): Subject	0.847		0.757	
Random effect (SD): Time	0.250		0.305	
AIC	370.4		369.5	

[a] – Adjusted for time only.

[b] – Adjusted for all time-invariant, time-varying, and covariates included.

[c] – Prevalence in group (n=2/68) was too low for analysis. Data from participants with MRI evidence (n=2) or clinical evidence (n=2) of previous traumatic brain injury (loss of consciousness ≥5 minutes or confusion ≥1 day) and persistent symptoms attributed to TBI.

[d] – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥2) in the past month are reported. Quadratic effects were not significant (p>0.10).

*p<0.05

4.3.6   Combined effects of time-invariant and time-varying factors

Figure 4.4 depicts the predicted probability of experiencing psychosis for men in the AR group with exposure to significant risk factors. In the absence of all risk factors, the probability of experiencing psychosis was 9.3% for men and 4.8% for women (weighted average 7.9%). Recent polysubstance use and trauma added risk. For example, individuals using methamphetamine, on average, were also using daily tobacco, three days of cannabis, and one day of alcohol in one week. For a man using daily methamphetamine (Figure 4.4, blue), adding this average polysubstance pattern increased the probability of psychosis five-fold to 42.7%. Further step-wise increases in probability of psychosis occur in the presence of a recent traumatic event, the mean experience of past traumatic events, or persistent TBI sequelae.

Figure 4.4 Predicted probability of psychosis by time-invariant and time-varying risk factors for AR group (N=340).
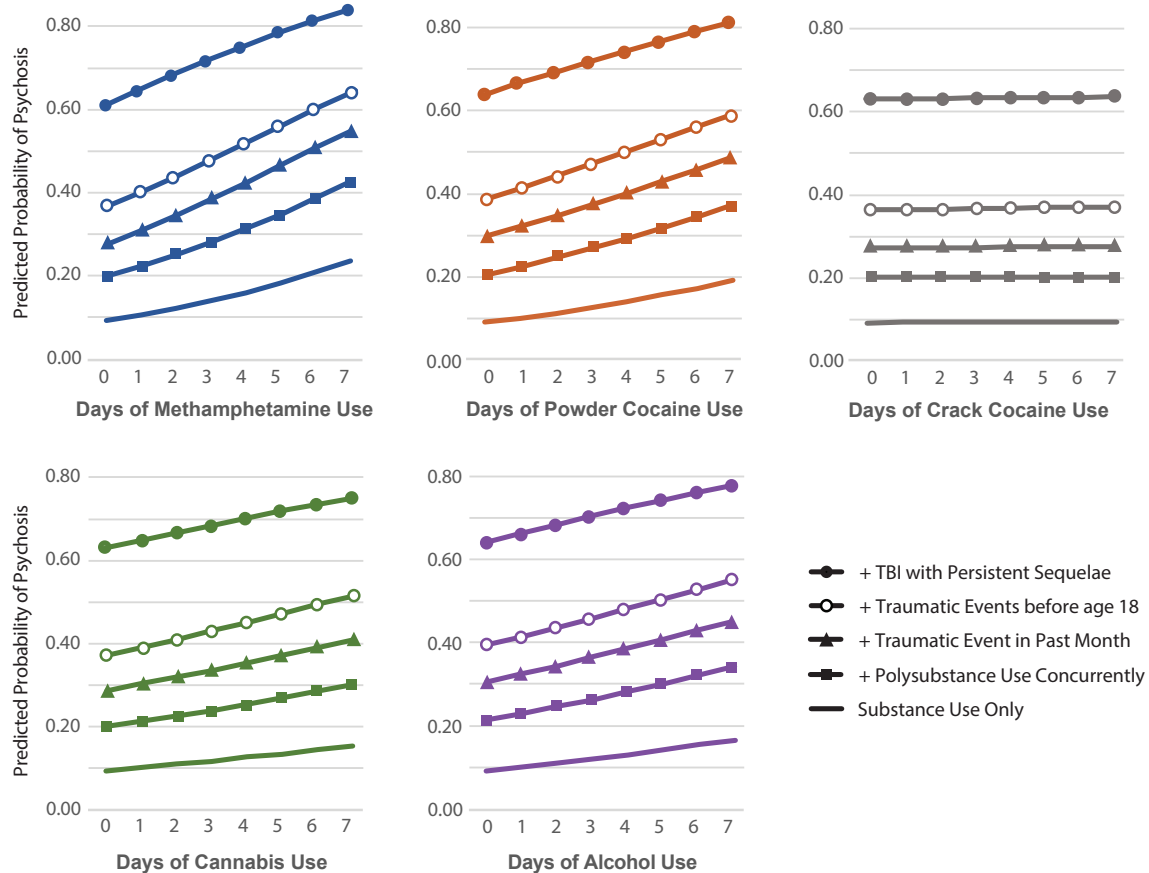
The predicted probability values assume all other model covariates are unchanged over time and equal to the reference category (e.g., male) or mean value for continuous variables. Risk factors were ordered by temporal proximity to psychosis assessment. The dose-dependent effects of days of methamphetamine (blue), powder cocaine (orange), crack cocaine (grey), cannabis (green), and alcohol (purple) use on psychosis are depicted. Markers indicate the cumulative effects of substance use and additional risk factors: squares represent the effect of the average polysubstance use pattern for each substance; triangles represent the effect of experiencing one recent traumatic event; open circles represent the effect of experiencing (the mean) three types of traumatic events prior to age 18; and closed circles represent the total effect of past TBI with persistent sequelae as well as all other risk factors. The average polysubstance use pattern for participants using methamphetamine included three days of cannabis, one day of alcohol, and daily tobacco use. Among those using powder cocaine, the average use included two days of cannabis, one day of alcohol, and daily tobacco use. Among participants

using crack cocaine, two days of cannabis, one day of powder cocaine, one day of alcohol, and daily tobacco were reported on average. Among participants using cannabis, average use included one day of methamphetamine, one day of powder cocaine, one day of alcohol, and daily tobacco use. Among those using alcohol, average use also included one day of methamphetamine, one day of powder cocaine, two days of cannabis, and daily tobacco use.

4.3.7   Directionality of effects and potential reverse causation

To test the possibility of reverse causality (psychosis leading to increased substance use), four models estimated the effect of psychosis on days of alcohol, methamphetamine, cannabis, and powder cocaine use in the subsequent week (Table 4.5). After controlling for covariates, psychosis was not associated with subsequent substance use frequency. Psychosis was associated with increased likelihood of experiencing a traumatic event in the subsequent month, adjusting for covariates. Reverse causality was also tested for non-significant risk factors (Appendix A.9).

Additionally, the previous week (time-lagged) days of methamphetamine, powder cocaine, and cannabis use significantly predicted subsequent psychosis, adjusting for covariates (Table 4.6). In contrast to the effects of alcohol use in the concurrent week, alcohol use in the previous week did not predict psychosis.

Table 4.5 Relationship between psychosis and subsequent substance use and traumatic events for the AR group (N=328, 2697 observations)

	Days of Alcohol Use		Days of Methamphetamine Use		Days of Cannabis Use		Days of Powder Cocaine Use		Any Traumatic Event [a]	
	B	SD	B	SD	B	SD	B	SD	OR	95% CI
Psychosis										
Without covariates	0.131	0.114	0.037	0.054	0.089	0.085	-0.015	0.059	1.49**	1.19, 1.85
With covariates [b]	0.120	0.114	0.029	0.054	0.075	0.084	-0.030	0.058	1.40*	1.12, 1.74

[a] – THQ score for the subsequent month was dichotomized as experiencing any type of traumatic event.

[b] – Covariates included time, age, sex, persistent sequelae of past traumatic brain injury, number of types of traumatic events before age 18, days of other non-prescription substance use in the subsequent week, and, in the subsequent month, adequate antipsychotic treatment, adequate methadone therapy, and any type of traumatic event.

*p<0.01; **p<0.001

Table 4.6 Relationship between time-lagged substance use frequency and psychosis over

one year for AR group (N=340, 2992 observations)

	Unadjusted [a]		Adjusted [b]	
	OR	95% CI	OR	95% CI
Covariates				
Time (months)	0.95*	0.90, 1.00	0.97	0.92, 1.02
Age (years)	0.99	0.96, 1.02	—	—
Male	2.14*	1.06, 4.36	2.03*	1.05, 3.95
Time-Invariant Factors				
Persistent Sequelae of TBI [c]	2.99*	1.19, 7.48	3.07**	1.32, 7.13
THQ score prior to age 18	1.19*	1.06, 1.33	1.15*	1.03, 1.28
Time-Varying Factors				
Past Month				
THQ score [d]	1.62*	1.21, 2.18	1.64**	1.22, 2.19
Adequate Antipsychotic Treatment [e]	2.37*	1.11, 5.07	2.21*	1.04, 4.68
Adequate Methadone Therapy [e]	0.89	0.58, 1.38	—	—
Time-Lagged Factors [f]				
Past Week				
Daily Tobacco Use	1.66	0.95, 2.90	1.63	0.95, 2.79
Days Using Alcohol	1.07	0.97, 1.17	—	—
Days Using Methamphetamine	1.19*	1.08, 1.31	1.18***	1.07, 1.29
Days Using Cannabis	1.12*	1.06, 1.19	1.09**	1.02, 1.15
Days Using Powder Cocaine	1.09	0.99, 1.20	1.10*	1.00, 1.21
Days Using Crack Cocaine	1.02	0.96, 1.09	—	—
Days Using Non-Prescribed Opioid	1.04	0.97, 1.12	—	—
Random Effect (SD): Subject	2.432		2.459	
Random Effect (SD): Time	0.238		0.224	
AIC	2929.		2891.4	

[a] – Adjusted for time only.

[b] – Adjusted for all time-invariant, time-varying, and covariates included.

[c] – Data from participants with MRI evidence (n=21) or clinical evidence (n= 12) of previous traumatic brain injury (loss of consciousness ≥5 minutes or confusion ≥1 day) and persistent symptoms attributed to TBI.

[d] – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥2) in the past month are reported. Quadratic effects were not significant (p>0.10).

[e] – Adequate antipsychotic or methadone treatment in the month prior to psychosis assessment.

[f] – Number of days of substance use in the week prior to week of psychosis assessment.

*p<0.05; **p<0.01; ***p<0.001

4.3.8   Sensitivity analyses

Effects of substance use in the concurrent week were similar when modeled by urine drug screen results instead of self-report (Table 4.7). Urine detection of cocaine metabolites was not associated with concurrent psychosis, but powder and crack cocaine could not be differentiated. When individuals with psychosis not otherwise specified or mood disorder with psychosis diagnoses (according to DSM-IV-TR criteria) were removed from the AR group, the effects were similar (TBI, early-life and recent traumatic events, and days of methamphetamine, powder cocaine, and cannabis were significant risk factors), except alcohol use, antipsychotic treatment, and sex were no longer significant predictors (p>0.05) (Appendix Table A.10). Sensitivity analyses revealed no evidence of systematic bias (Appendix Table A.1 − A.5). Participants included in longitudinal analyses did not differ from excluded individuals, except they were older (included: mean, SD = 42.0, 10.7 years of age; excluded: 36.0, 12.3 years of age; χ^2 (1) = 6.67, p = 0.010) (see Appendix Table A.6). Removal of all (5) outlier observations did not change findings (analyses not shown). Multiple imputation of missing values was performed to obtain ten completed datasets. Results were pooled to yield fixed effects estimates that were similar to the complete case findings (r = 0.956, p<0.001) (Appendix Table A.11).

Table 4.7 Relationship between psychosis and urine drug screen results in AR group (N=325, 2427 observations)

	Unadjusted [a]		Adjusted [b]	
	OR	95% CI	OR	95% CI
Time-Invariant Factors				
Time	0.94*	0.89, 1.00	0.96	0.91, 1.01
Age	1.00	0.97, 1.03	—	—
Male	1.47	0.76, 2.84	—	—
Persistent Sequelae of TBI	4.09**	1.63, 10.26	3.81**	1.63, 8.95
THQ score prior to age 18	1.19**	1.06, 1.33	1.14*	1.02, 1.27
Time-Varying Factors				
Past Month				
Methamphetamine Positive UDS	2.45**	1.65, 3.65	2.35***	1.58, 3.48
Cannabis Positive UDS	1.69**	1.16, 2.46	1.60*	1.11, 2.33
Cocaine Positive UDS	0.91	0.61, 1.35	—	—
Opioid Positive UDS	1.35	0.95, 1.94	—	—
Methadone Positive UDS	0.60*	0.39, 0.93	0.65*	0.43, 1.00
THQ score	1.57**	1.14, 2.16	1.51*	1.09, 2.08
Adequate Antipsychotic Treatment	2.13	0.90, 5.06	1.94	0.83, 4.52
Random Effect (SD): Subject	2.301		2.304	
Random Effect (SD): Time	0.231		0.223	
AIC	2480.1		2438.4	

[a] – Adjusted for time only.

[b] – Adjusted for all time-invariant, time-varying, and covariates included.

*p<0.05; **p<0.01; ***p<0.001

4.4   Discussion

4.4.1   Summary of findings

We observed a high one-year prevalence of psychosis as well as early-life and recent risk factors among adults living in urban marginal housing. Most participants reported multiple types of psychotic symptoms, either concurrently or over time. Risk factors demonstrated dose-response effects among adults at risk for psychosis (AR group), but not in the SSA group. In particular, psychosis was most common during periods of frequent

methamphetamine, powder cocaine, cannabis, or alcohol use, without evidence of interaction or reverse causality.

4.4.2   High prevalence and incidence of poly-symptomatic psychosis

Over 75% of adults endorsed psychosis in at least one monthly visit over one year — greater than three-times the rate observed in a study of primary care patients who also lived on low incomes (20.9% in the primary care study versus 78.3% in this study) (Olfson et al., 2002). Between studies, the rates of baseline psychotic disorder (7.1% versus 15.6% in this study) and risk factors differed: the primary care sample included fewer males (25.0% versus 77.3% in this study) and lower rates of substance use disorders (8.0% versus 94.5% in this study). Similarly, the incidence rate of new psychotic episodes was substantially higher than rates reported in a recent US general population-based medical record study of 46 per 100 000 people aged 30 to 59 (Simon et al., 2017). The observed rate of new episodes and the frequent combination of delusions and hallucinations were more comparable to characteristics of psychosis relapse seen in patients with first-episode psychotic disorders (Bebbington et al., 2006; Chen et al., 2010; Schennach-Wolff et al., 2011). While the AR group experienced psychosis intermittently, those in the SSA group were more likely to experience persistent psychosis characterized by multiple symptoms. Similar phenomena have been observed in patients with first-episode psychosis who experienced persistent delusions and disorganization and were unresponsive to antipsychotic treatment (Schennach-Wolff et al., 2011). Emerging work describing psychiatric illness as a complex dynamic system suggests the interactions between symptoms may relate to the persistence of illness (Borsboom, 2017; Kendler et al., 2011).

4.4.3   Independent, dose-related effects of psychosis risk factors

Understanding the complexity of psychosis requires consideration of context. Our results extend previous studies (McKetin et al., 2013; Willi et al., 2016) by demonstrating in addition to methamphetamine, that frequency of powder cocaine, cannabis, and alcohol all exert independent, dose-related effects on psychosis risk in adults without schizophrenia or schizoaffective disorder. These findings are particularly timely as a growing number of regions legalize and regulate cannabis. Importantly, these effects only occurred in one direction: experiencing psychosis did not increase subsequent substance use. Effects may differ by route of drug administration: powder cocaine (typically injected in this study) but not crack cocaine (typically smoked in this study), conferred dose-related increases in psychosis risk. Heightened vulnerability with intravenous administration may be attributed to higher dose-related serum concentrations, as well as greater intake due to slower onset and reduced subjective effects (Evans, Cone, & Henningfield, 1996; Volkow et al., 2000). Additionally, both early-life and recent traumatic exposures exhibited independent dose-response associations with psychosis, similar to recent studies (Lataster et al., 2012; Mansueto & Faravelli, 2017). However, evidence of reverse causality suggests individuals endorsing psychosis may be prone to subsequent trauma, perhaps due to victimization or reduced social support (Lukoff, Snyder, Ventura, & Nuechterlein, 1984). TBI, which frequently co-occurs with these risk factors (Schmitt et al., 2017), was independently associated with psychosis. Conversely, for adults with schizophrenia or schizoaffective disorder, psychosis risk was unchanged in the presence or absence of risk or protective factors, including antipsychotic treatment, and in fact gradually increased over time. Our data demonstrate a distinct course of psychosis over one year, differences in clinical profile, and a

restricted influence of risk factors on the emergence of psychosis in the SSA group compared

to the AR group. These observations suggest more precise preventive and therapeutic

strategies may need to be developed according to psychotic disorder diagnosis.

4.4.4   Study strengths and limitations

This study had several limitations. The community sample was recruited in a

neighborhood where non-prescribed substance use is widespread and universal health care is

available. In other contexts, drivers for psychosis, including migration, may differ and affect

generalizability. Since the likelihood of psychosis was similar during periods of marginal

housing or homelessness, these results may also apply to people at risk of homelessness.

Similar to other longitudinal studies, missed visits may affect precision of the results, though

no evidence of systematic bias was identified. Further, the SSA sample size may have limited

our ability to detect true risk factor effects and future study may require longer follow-up.

Also, since the binary outcome was common (>10%), additive interactions could not be

accurately estimated in this study (Vanderweele & Knol, 2014). Among the risk factors

examined, the definition of TBI was conservative, but was supported by both clinical and

imaging evidence. Further study of remote or mild TBI, particularly with diffuse brain injury,

may reveal lasting implications for psychopathology (Sachdev et al., 2001). The other risk

factors were examined as continuous or ordinal variables, and the estimated dose-related

effects, in addition to analysis of potential reverse causality, advances the field beyond the

categorical assessment of risk factors.

These findings underscore the value of assessing psychosis risk factors

independently, even among those without psychotic illness. Adults using non-prescribed

substances and experiencing ongoing trauma may have incremental but relevant increases in

psychosis risk, regardless of their history of trauma or psychiatric diagnoses. TBI screening

may also be useful for psychosis risk stratification. Overall, the risk of psychosis among

marginally housed adults is considerable. Our results emphasize the need for innovative

treatment strategies that mitigate the impact of these biopsychosocial factors for adults at-risk

for psychosis.

Chapter 5: Longitudinal characterization of psychotic symptom dynamics among marginally housed adults

5.1 Brief introduction

As described in Chapter 1, emerging research examines psychopathology as a network of symptoms that can interact and influence each other over time. To continue to build our understanding of the evolution of psychosis, we sought to investigate the interdependencies among symptoms themselves using a dynamic network approach that considers the within-individual dynamics in the context of group-level associations. We expected psychotic symptoms to co-occur and mutually reinforce one another, particularly in individuals with psychotic disorder.

5.2 Brief methods

5.2.1 Measures

Detailed description of recruitment and study design are outlined in Chapter 2. The evaluation of psychotic symptoms occurred monthly over five years. Five cardinal symptoms of psychosis were assessed by trained interviewers using the PANSS: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness and persecution, and unusual thought content. The time interval between assessments was mean (SD) 30.8 (6.1) days.

Three psychosis risk groups were delineated according to psychotic disorder and presence of psychosis at study entry. Individuals who met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder were included in the Schizophrenia/Schizoaffective Disorder (SSA) group. The remaining individuals were included in the Endorsing Psychosis (EP) group if they endorsed at least one of five psychotic symptoms above threshold at

baseline assessment (see Table 2.1), or in the Not Endorsing Psychosis (NP) group if they did not meet criteria for psychosis at study entry.

5.2.2   Statistical analysis

As described in Chapter 2, the Person-Mean, Contemporaneous, and Dynamic Networks were estimated by a two-step multilevel VAR(1) modeling approach. In the first step, the Person-Mean and Dynamic Networks were estimated and the residuals were used in the second step to estimate the Contemporaneous Network. First, the Person-Mean Network is an undirected network that represents the average tendency for symptoms to co-exist in a population or group, and thus represents the between-individual differences in the population. The Person-Mean Network was derived from the L_1-regularized partial correlation matrix of person-specific stationary mean symptom severity (i.e., severity scores averaged over five years). Conversely, the Contemporaneous and Dynamic Networks represent the within-individual relationships. Second, the Contemporaneous Network represents the co-occurrence of symptoms within an individual at a given time. This network is derived from the L_1-regularized partial correlation matrix of the residuals from the multilevel VAR(1) model. Third, the Dynamic Network was a directed network derived from a matrix of regression coefficients indicating the extent to which change in past-month symptom severity predicts change in next-month symptom severity (i.e., within-person fluctuations around the person-specific mean), controlling for all other symptoms. In these networks, edges represent potentially Granger-causal relations between symptoms, and the absence of an edge is interpreted as conditional independence, whereby two nodes are unrelated given the other nodes in the system (Granger, 1969; Pearl, 2000). To reduce false positive error, in the undirected Person-Mean and Contemporaneous Networks, edges that

were not significant by bootstrap analysis were removed. In the directed Dynamic Network, edges that were not significant by False Discovery Rate of 5% were removed. Of the 14,622 monthly visits made (63.9% of possible 22,875 months), PANSS assessments were missing in 2.4%. Psychosis assessments were missing in 2.1% of 373 baseline visits. Multiple imputation was performed and estimates were pooled across ten completed datasets and compared to the complete-case Dynamic Network. The networks were also estimated by the automated *mlVAR* package (Epskamp, Deserno, et al., 2017).

Strength, closeness, and betweenness centrality measures were calculated for all symptoms in each network. Strength (CS index = 0.75) and closeness (CS index = 0.75) centrality of the Person-Mean and Contemporaneous Networks exhibited adequate stability (Epskamp & Fried, 2016). However, betweenness centrality estimates became less stable with reduced sample sizes (CS index = 0.52). Thus, for this analysis, betweenness centrality measures may be less reliable, and interpreted with caution, while strength and closeness centrality may be interpreted with more confidence.

In post-hoc analyses, the autoregressive effects (self-loops) were extracted for each individual participant by calculating the sum of the fixed effects and random effects estimates from the Dynamic Network. The individual-specific autoregressive effects were regressed on the stationary mean value of the symptom, (mean-centered) age, and sex using multiple linear regression.

To assess the relationship between these psychotic symptom inter-dependencies and psychosis risk, the three complementary networks were constructed for each of the SSA, EP, and NP groups. Person-Mean and Contemporaneous Networks for each group were compared using the Network Comparison Test (van Borkulo et al., 2015), and Dynamic

Networks were compared by constructing an omnibus model with group-by-lagged symptom interaction terms and by permutation testing (Klippel et al., 2017).

5.3 Results

5.3.1 Participant characteristics

Of the 375 participants enrolled at least five years before the time of analysis (October 21, 2017), 251 (67.0%) participants remained engaged with the study at five years. Table 5.1 is a summary of participant characteristics. Additional participant characteristics are summarized in Appendix Table A.12.

Table 5.1 Baseline and psychosis characteristics of adults living in marginal housing

	All Enrolled (N=375)	
Sample Characteristic	N	%
Sex		
Male	293	78.1
Female	82	21.9
Ethnicity/Race		
White	227	60.5
Indigenous	100	26.7
Other	48	12.8
Completed high school or equivalent	164	43.7
Any formal employment	45	12.0
Past homelessness	268	72.6
Lifetime psychiatric diagnosis		
Schizophrenia or schizoaffective	49	13.1
Mood disorder with psychosis	12	3.2
Substance-induced psychosis	64	17.1
Psychosis not otherwise specified	48	12.8
Participant Characteristic	Mean	SD
Follow up duration (months)	49.3	19.8
Monthly visits – no.	39.1	19.4
Monthly PANSS assessments– no.	38.7	18.7
Age (years)	43.4	9.4
SOFAS score	39.6	10.8
PANSS item score over five years		
Delusions	2.3	1.3
Conceptual disorganization	1.9	0.9
Hallucinatory behaviour	1.8	1.0
Suspiciousness and persecution	2.3	1.1
Unusual thought content	2.0	1.0

5.3.2 Person-mean psychosis symptom network

First, we examined the polysymptomatic patterns across the community-based sample by constructing the Person-Mean Network. The networks estimated with and without L_1-regularization or by the automated *mlVAR* package were very similar (all $\rho > 0.96$, p<0.001). Significant edges were identified using the bootstrapped 95% confidence intervals (Appendix Figure A.1) and were visualized in the network.

Figure 5.2 depicts the Person-Mean Network for the whole community-based sample. Individuals with severe delusions tended to have severe unusual thought content, suspiciousness, and hallucinations. Likewise, individuals with severe unusual thought content tended to also have severe hallucinations and conceptual disorganization. While unusual thought content and delusions were highly correlated symptoms, the absence of structural equivalence (i.e., identical edges) of these symptoms suggests they are separate, non-equivalent symptoms. Additionally, the associations linking delusions with unusual thought content or suspiciousness were conditionally independent, as indicated by the absence of a significant edge between unusual thought content and suspiciousness. Thus, individuals experiencing delusions were likely to have one of these two symptoms, but not both (i.e., unusual thought content or suspiciousness). This is also the case for delusions with suspiciousness or hallucinations. While the majority of these associations linked two symptoms, there was also a tendency for the occurrence of a symptom triad in this sample: individuals with severe delusions tended to have both severe unusual thought content and hallucinations.

Conceptual disorganization exhibited a unique pattern. Similar to individuals with severe delusions, individuals with severe conceptual disorganization tended to have severe unusual thought content or severe suspiciousness, but not both (i.e., unusual thought content or suspiciousness), as unusual thought content and suspiciousness were found to be conditionally independent. However, unlike the patterns seen with delusions, these individuals were much less likely to experience hallucinations. Conceptual disorganization and delusions were found to be conditionally independent.

Overall, delusions and unusual thought content had the greatest strength (i.e., sum of each node's edge weights) in the network (1.47 and 1.20, respectively), compared to the other symptoms (conceptual disorganization: 0.65, hallucinatory behavior: 0.63, and suspiciousness: 0.62) (all p>0.05, see Appendix Figure A.2). These two symptoms also had the greatest closeness centrality in the network (0.08 and 0.07, respectively), compared to the other symptoms (suspiciousness: 0.06, hallucinatory behavior: 0.05, and conceptual disorganization: 0.05) (all p>0.05). Centrality measure stability is depicted in Appendix Figure A.3.

Figure 5.2 Person-Mean psychotic symptom network.
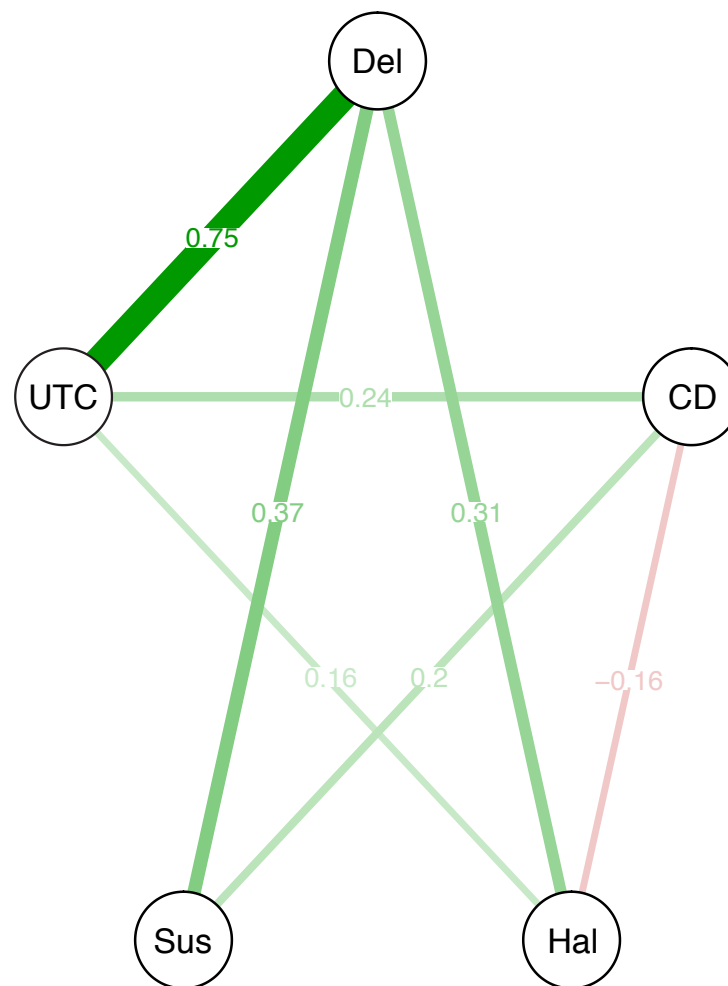
	Strength	Closeness	Betweenness
Del	1.471	0.078	6
CD	0.649	0.048	0
Hal	0.631	0.050	0
Sus	0.619	0.056	0
UTC	1.201	0.071	2

Undirected network of psychotic symptoms averaged over five years across the sample (n=369). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Green = positive edges; Red = negative edges. Saturation and thickness indicates edge weight.

5.3.3 Contemporaneous psychosis symptom network

Figure 5.3 depicts the average pattern of psychotic symptom co-occurrence as the Contemporaneous Network within an individual at a given assessment. Based on this analysis, when one psychotic symptom was severe, it was likely that the other four cardinal psychotic symptoms were also more severe. Particularly, we observed that, at a given moment cross-sectionally, delusions, unusual thought content, and suspiciousness or hallucinations tend to co-occur. The Contemporaneous Networks estimated with or without L_1-regularization or by the automated *mlVAR* package were very similar (all $\rho > 0.98$, $p<0.001$). The 95% confidence interval of edges were estimated by the bootstrap procedure (Appendix Figure A.4) and significant edges were incorporated into the network.

Similar to the Person-Mean Network, delusions and unusual thought content had the most central role in the Contemporaneous Network (strength: 0.90 and 0.83, respectively) (Appendix A.5). Conceptual disorganization had the lowest strength and closeness centrality in the network (strength: 0.38, closeness: 0.03). Centrality measure stability is depicted in Appendix Figure A.6.

Figure 5.3 Contemporaneous psychotic symptom network.
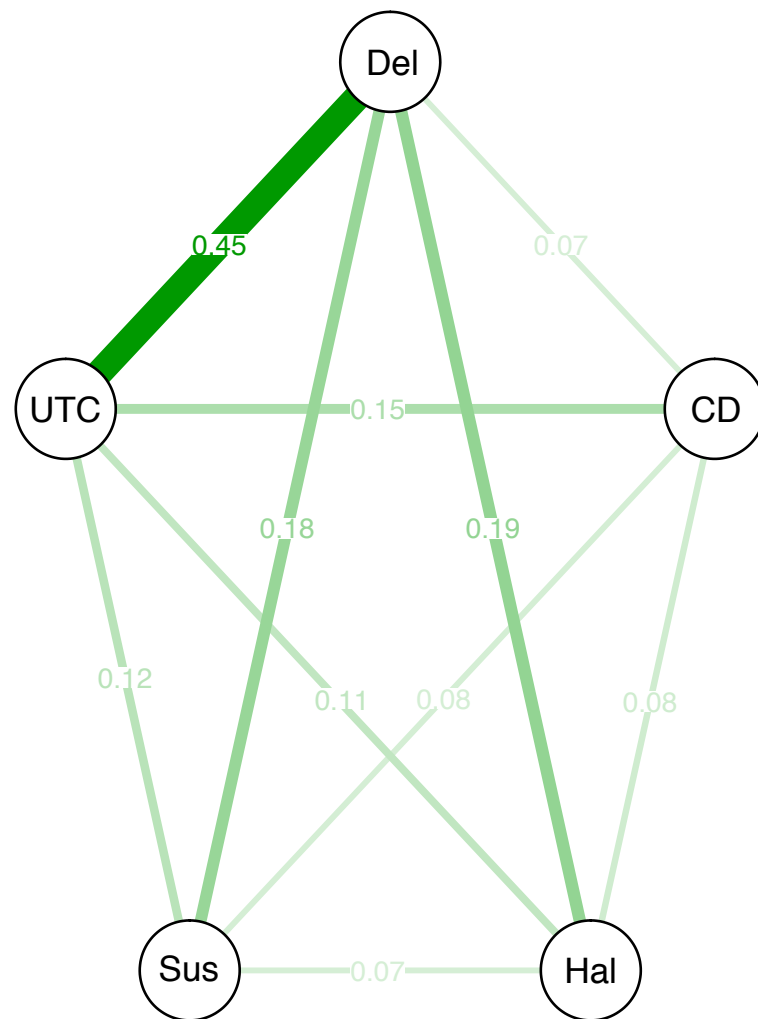
	Strength	Closeness	Betweenness
Del	0.895	0.045	6
CD	0.381	0.025	0
Hal	0.458	0.028	0
Sus	0.454	0.027	0
UTC	0.827	0.041	2

Undirected network of psychotic symptoms within an individual at the same time point (n=294, 10,420 observations). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Green = positive edges. Saturation and thickness indicate edge weight.

5.3.4   Dynamic psychotic symptom network

Figure 5.4 is the Dynamic Network for the entire sample (n=294) and illustrates how psychotic symptoms may predict change in other psychotic symptom severity in the next month. Each edge represents the corresponding within-person standardized effect coefficient from the multilevel VAR(1) analysis. Thus, the nodes represent the deviation from the individual's mean symptom severity, and the edges represent how a deviation from the mean (i.e., period of exacerbation or amelioration) in a symptom is predicted by past-month changes in symptom severity, conditioning on past-month severity of other symptoms. The coefficients of the within-person standardized network were highly correlated with the unstandardized network ($\rho = 0.859$, p<0.001). This network was also very similar to the networks estimated by the *mlVAR* package ($\rho = 0.981$, p<0.001) or from complete datasets generated from the multiple imputation procedure ($\rho = 0.968$, p<0.001). Thus, the estimated network does not seem to be affected by the computation method or the presence of missing data.

Notably, all directed edges were positive, indicating that symptom severity was positively associated with subsequent emergence of other psychotic symptoms. Most potently, psychotic symptoms exhibited positive self-loops. The strongest edges in the network were the autoregressive edges, which indicates the degree of inertia, or resistance to change, of the symptom. Greater positive autoregressive effects suggests persistence of symptom exacerbations or ameliorations. Greater negative autoregressive effects suggest rapid cycling above and below the mean severity. Thus, exacerbations of all psychotic symptoms, particularly delusions, tended to persist over time. Autoregressive effects

accounted for the majority of the total network density (58.9%, 0.850/1.444). Thus, once activated, symptoms may continue to persist at least one month later.

Many of the cross-regressive edges between symptoms were bidirectional, in some cases, with differing edge weights. For example, delusions were more likely to precede unusual thought content ($\beta = 0.081$, SE $= 0.015$, 95% CI $= 0.051 - 0.110$) than the reverse ($\beta = 0.028$, SE $= 0.014$, 95% CI $= 0.001 - 0.055$), but both paths were possible. Further, several effects occurred in only one direction: suspiciousness predicted later hallucinations or unusual thought content, and conceptual disorganization predicted later hallucinations. Interestingly, as in the Person-Mean Network, conceptual disorganization and delusions were conditionally independent. In contrast, in the Dynamic Network, conceptual disorganization was also conditionally independent from unusual thought content.

Overall, delusions and suspiciousness had the greatest direct influence on subsequent symptom severity (out-strength: 0.22 and 0.17, respectively) and exhibited the greatest efficiency in the spread of their influence (closeness: 0.01 and 0.01, respectively). Conversely, unusual thought content and hallucinations were more likely to be influenced downstream (in-strength: 0.15 and 0.14, respectively).

Figure 5.4 Dynamic psychotic symptom network.
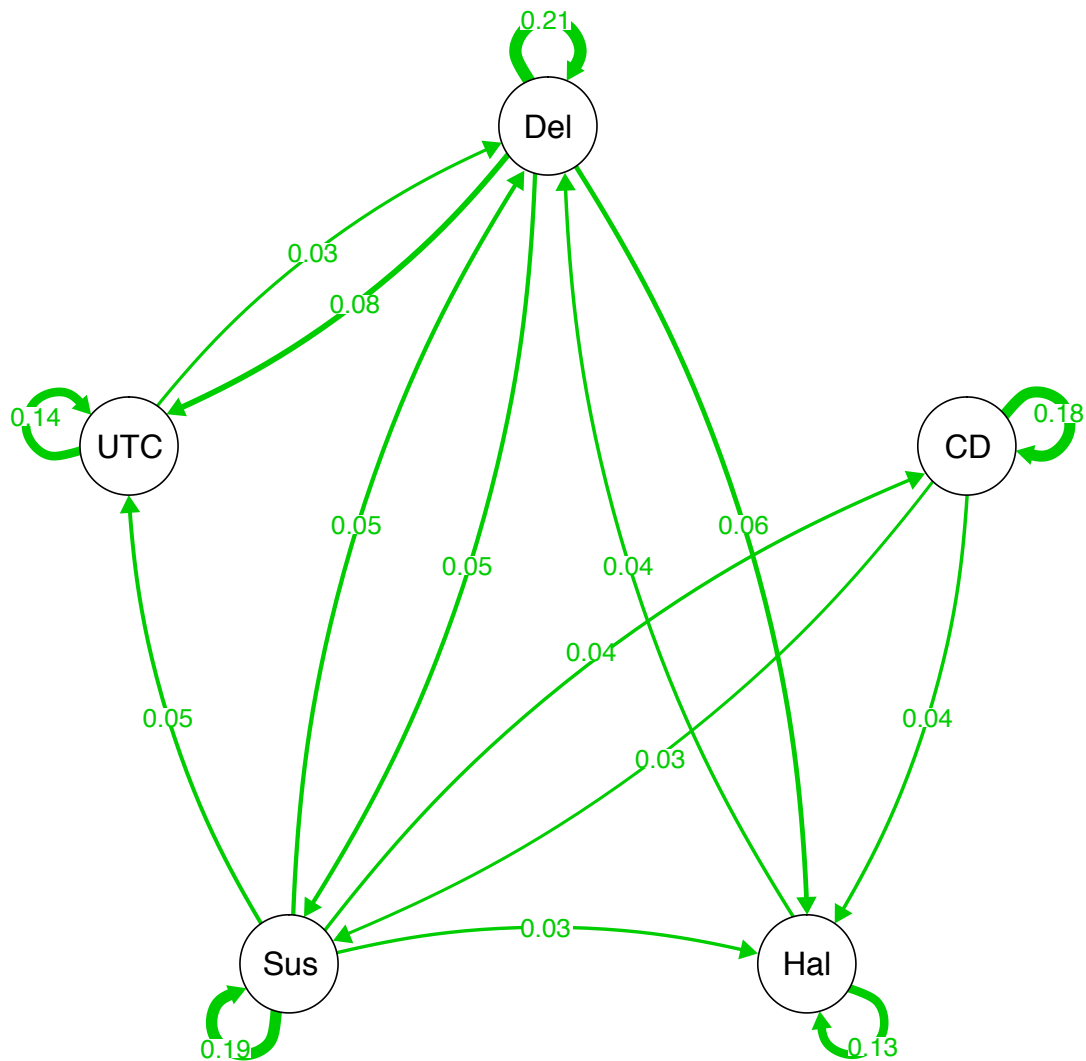
	Out-Strength	No. of Sig. Out-Edges	In-Strength	No. of Sig. In-Edges	Closeness	Betweenness
Del	0.220	3	0.118	3	0.012	5
CD	0.067	2	0.093	1	0.006	0
Hal	0.081	1	0.138	3	0.005	0
Sus	0.166	4	0.097	2	0.010	2
UTC	0.059	1	0.148	2	0.005	0

Directed network of psychotic symptoms predicting other symptoms in the next month (lag-1) within an individual (n=294, 10,420 observations). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Out-Edges = outgoing edges; In-Edges = incoming edges. Green indicates positive edges. Thickness indicates edge weights.

5.3.5   Individual-specific symptom inertia

Table 5.2 summarizes the person-specific autoregressive effects in the whole

community-based sample, and the relationships between these effects and the person-specific

stationary mean severity, age, and sex determined. The purpose of this analysis was to

evaluate the relationship between symptom persistence (i.e., autoregression or inertia) and

severity. This analysis was also used to test for evidence of a "floor" effect, whereby limited

change secondary to lower scores was underlying the autoregressive estimates (negative

relationship between autoregressive effects and mean symptom severity). The range of

autoregressive effects observed were similar across symptoms and included a distribution of

both positive and negative autoregressive effects. The linear regression analysis revealed that

individuals with higher mean severity of conceptual disorganization, hallucinatory behavior,

suspiciousness, and unusual thought content exhibited greater persistence and slower

recovery from exacerbations for that symptom. The relationship between severity and

persistence of hallucinatory behavior was observed to be particularly strong among older

participants. The persistence of delusions, however, was unrelated to the severity of the

delusions. These findings support that the conjecture that persistence of psychotic symptoms

is related to greater symptom severity, and not just the consistent absence of symptoms.

Further, the persistence of unusual thought content was associated with the

persistence of delusions, and suspiciousness, and hallucinations across individuals (Table

5.3). The persistence of suspiciousness was associated with the persistence of delusions and

conceptual disorganization. Notably, the degree of persistence of delusions and

hallucinations were not correlated ($r = 0.052$, $p > 0.05$).

Table 5.2 Relationships between symptom autoregression and stationary mean severity

	Delusions		Conceptual Disorganization		Hallucinatory Behavior		Suspiciousness/ Persecution		Unusual Thought Content	
Autoregressive Effects										
Mean, SD	0.21	0.12	0.18	0.09	0.13	0.11	0.19	0.10	0.14	0.09
Min, Max	-0.07	0.47	-0.08	0.46	-0.15	0.49	-0.03	0.45	-0.16	0.33
	β	SE_β	β	SE_β	β	SE_β	β	SE_β	β	SE_β
Age	0.010	0.007	0.008	0.005	-0.007	0.006	0.021***	0.006	-0.002	0.005
Sex	-0.001	0.017	-0.017	0.014	-0.010	0.016	-0.023	0.014	-0.017	0.013
Stationary Mean	0.013	0.007	0.021***	0.005	0.033***	0.006	0.015**	0.006	0.015**	0.005
Stationary Mean* Age	—	—	—	—	0.024***	0.007	—	—	—	—

Table 5.3 Relationships between symptom autoregressive effects [a]

	Delusions	Conceptual Disorganization	Hallucinatory Behavior	Suspiciousness/ Persecution	Unusual Thought Content
Delusions	—	0.156	0.052	0.247**	0.220**
Conceptual Disorganization	—	—	0.063	0.208**	0.066
Hallucinatory Behavior	—	—	—	0.122	0.177*
Suspiciousness/ Persecution	—	—	—	—	0.204**
Unusual Thought Content	—	—	—	—	—

* p<0.005, ** p<0.001

[a] - Pearson correlation of autoregressive effects derived from dynamic network. Bonferroni correction applied.

5.3.6 Psychotic symptom networks by psychosis risk groups

To enhance the understanding of how psychotic symptoms may interact differently over time accounting for psychosis risk, psychotic symptom networks were estimated for the SSA, EP, and NP groups. Group characteristics are described in Table 5.4. Compared to the

SSA and NP groups, the EP group exhibited intermediate psychotic symptom severity, likelihood for lifetime diagnosis of substance-induced psychosis or psychosis not otherwise specified, and social and occupational functioning. Individuals in the SSA group had the most severe psychotic symptoms, with similar variability (SD) in severity over time. Groups were similar in sociodemographic variables and follow-up duration. Additional participant characteristics are summarized in Appendix Table A.12.

Table 5.4 Baseline and psychosis characteristics of psychosis risk groups

Sample Characteristic	NP Group [a] (N=169) N	%	EP Group [a] (N=147) N	%	SSA Group [a] (N=49) N	%	Group Comparison Groups	p
Sex							—	NS
Male	131	77.5	111	75.5	42	85.7		
Female	38	22.5	36	24.5	7	14.3		
Ethnicity/Race							—	NS
White	102	60.4	85	57.8	36	73.5		
Aboriginal	46	27.2	41	27.9	9	18.4		
Other	21	12.4	21	14.3	4	8.2		
Completed high school or equivalent	81	48.2	60	41.1	20	41.7	—	NS
Any formal employment	21	12.4	14	9.5	10	20.4	—	NS
Past homelessness	120	71.4	110	76.4	30	62.5	—	NS
Lifetime psychiatric diagnosis								
Schizophrenia or schizoaffective	0	0.0	0	0.0	49	100.0	—	—
Substance-induced psychosis	14	8.3	48	32.7	0	0.0	NP<EP	<0.001
Psychosis not otherwise specified	9	5.3	38	25.9	0	0.0	NP<EP	<0.001

Participant Characteristic	Mean	SD	Mean	SD	Mean	SD	Groups	p
Follow up duration (months)	50.0	19.5	50.0	18.9	50.2	18.3	—	NS
Monthly assessment visits – no.	40.0	19.1	38.9	18.7	35.6	17.5	—	NS
Age (years)	44.8	9.2	43.1	9.5	40.3	9.6	SSA<NP	0.004
SOFAS score	43.0	10.8	37.8	9.7	33.8	10.0	SSA<EP<NP	<0.05
PANSS item score								
Delusions	1.5	0.6	2.6	1.0	4.3	1.1	NP<EP<SSA	<0.001
Conceptual disorganization	1.4	0.5	2.0	1.0	2.8	1.0	NP<EP<SSA	<0.001
Hallucinatory behaviour	1.3	0.4	1.8	0.8	3.4	1.0	NP<EP<SSA	<0.001
Suspiciousness and persecution	1.8	0.7	2.4	1.0	3.7	1.1	NP<EP<SSA	<0.001
Unusual thought content	1.4	0.5	2.2	0.8	3.6	0.9	NP<EP<SSA	<0.001

[a] – NP group: no schizophrenia or schizoaffective disorder diagnosis and not endorsing psychosis at study entry; EP group: no schizophrenia or schizoaffective disorder diagnosis and endorsing psychosis at study entry; SSA group: schizophrenia or schizoaffective disorder diagnosis.

Figure 5.5 displays the Person-Mean Networks of the SSA, EP, and NP groups. Only significant edges were included (see Appendix Figure A.7 – A.9 for 95% CI estimates). Observed centrality estimates suggest that unusual thought content and delusions were the most central symptoms across groups (Table 5.5). The Network Comparison Test revealed

that the Person-Mean Networks were similar across groups in terms of global network connectivity (all $p>0.05$) and the strength of individual edges (all $p>0.05$ accounting for Bonferroni correction). Notably, the triad of symptoms associated in the whole-sample Person-Mean Network (delusions, hallucinations, and unusual thought content), was not present in these subgroup analyses. By combining both whole-sample and subgroup analysis, we could determine that this finding was likely only present due to the aggregation of the three psychosis risk groups.

Figure 5.5 Person-Mean psychotic symptom networks by psychosis risk group.

Undirected network of psychotic symptoms partial correlations across individuals (A) Not Endorsing Psychosis at Baseline (NP) group (n = 169), (B) Endorsing Psychosis at Baseline (EP) group (n = 147), or (C) Schizophrenia or Schizoaffective (SSA) group (n = 49). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Green = positive edges. Thickness indicates edge weight. Opaque edges are significant by 95% CI permutation test, and translucent edges are significant by L_1-regularization estimation only.

Table 5.5 Person-Mean Network centrality measures across psychosis risk groups [a]

	NP Group				EP Group				SSA Group			
	Sig. Edges	Strength	Closeness	Betweenness	Sig. Edges	Strength	Closeness	Betweenness	Sig. Edges	Strength	Closeness	Betweenness
Del	3	1.584	0.068	8	3	1.488	0.770	6	2	1.181	0.076	6
CD	0	0.456	0.029	0	2	0.732	0.053	0	1	0.542	0.050	0
Hal	1	0.545	0.047	0	1	0.578	0.052	0	1	0.751	0.050	0
Sus	1	0.411	0.040	0	2	0.914	0.064	0	1	0.552	0.049	0
UTC	1	0.933	0.062	4	2	1.219	0.070	2	3	1/294	0.086	8

[a] – NP group: no schizophrenia or schizoaffective disorder diagnosis and not endorsing psychosis at study entry, EP group: no schizophrenia or schizoaffective disorder diagnosis and endorsing psychosis at study entry; SSA group: schizophrenia or schizoaffective disorder diagnosis.

Likewise, the Contemporaneous Networks were similar across the three psychosis risk groups (Figure 5.6). Individuals in these groups exhibited a connected network, where an increase in severity of one symptom was positively associated with an increase in severity of all symptoms at that time. See Appendix Figure A.10 – A.12 for the 95% confidence interval estimates for the edges. Since these networks were estimated using the residuals from the multilevel VAR analysis, only participants who exhibited change in psychotic symptom severity were included (NP group = 114/169, 67.5%; EP group = 129/147, 87.8%; SSA group = 47/49; 95.9%).

Unusual thought content and delusions were the most central symptoms in the network across groups (Table 5.6). The Network Comparison Test identified that individuals in the SSA group had more densely connected Contemporaneous Network than individuals who endorsed psychosis at baseline (SSA: 1.590, EP: 1.472, p=0.026). However, this difference was not significant after considering multiple comparisons by Bonferroni correction (p<0.05/3 = 0.017).

Figure 5.6 Contemporaneous psychotic symptom networks by psychosis risk group.
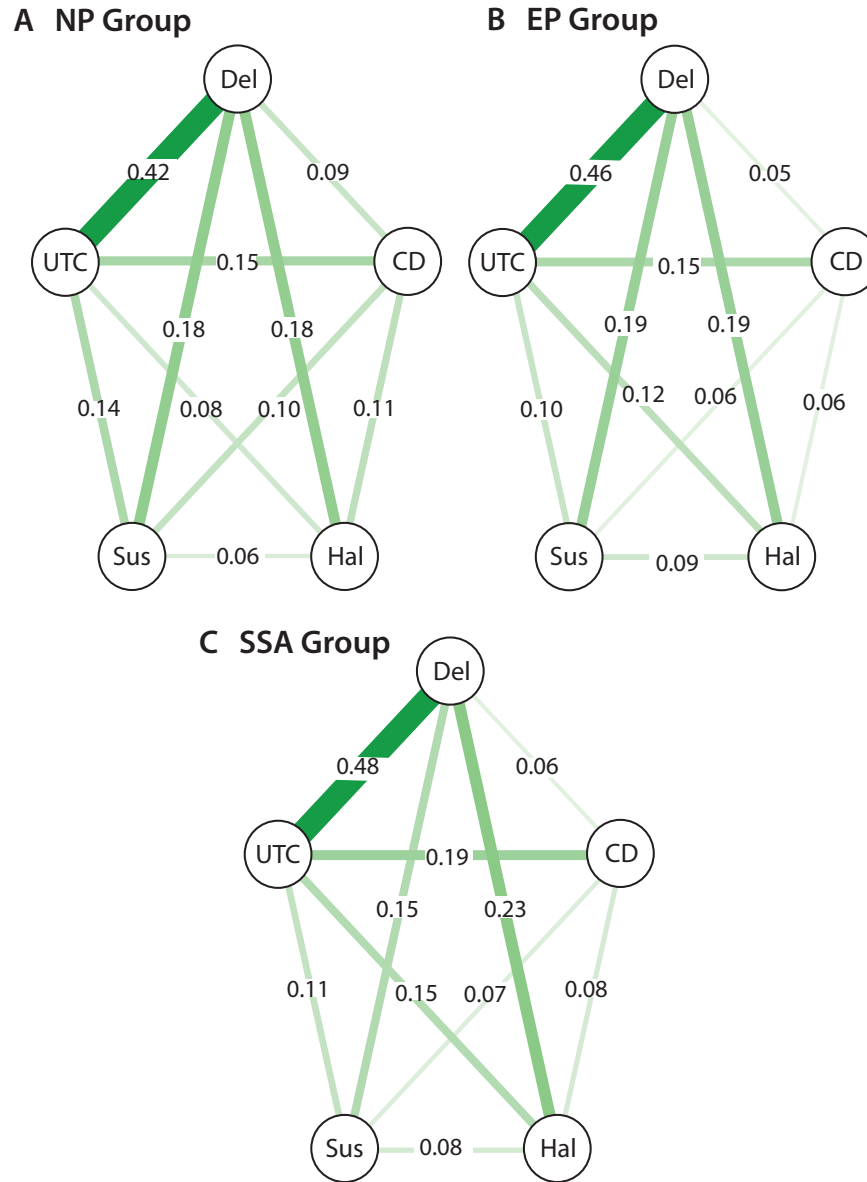
Undirected network of psychotic symptoms within-person co-occurrence. (A) Not endorsing psychosis at baseline (NP) Group (n=114, 4418 observations), (B) endorsing psychosis (EP) Group (n=129, 4532 observations), or (C) schizophrenia or schizoaffective disorder diagnosis (SSA) Group (n=47, 1383 observations). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Green = positive edges. Thickness indicates edge weight. Opaque edges are significant by 95% CI permutation test, and translucent edges are significant by L_1-regularization estimation only.

Table 5.6 Contemporaneous Network centrality measures across psychosis risk groups [a]

	NP Group			EP Group			SSA Group		
	Strength	Closeness	Betweenness	Strength	Closeness	Betweenness	Strength	Closeness	Betweenness
Del	0.875	0.044	4	0.891	0.047	10	0.916	0.049	6
CD	0.449	0.028	0	0.318	0.023	0	0.386	0.026	0
Hal	0.428	0.029	0	0.458	0.027	0	0.536	0.030	0
Sus	0.479	0.030	0	0.435	0.027	0	0.414	0.025	0
UTC	0.780	0.041	2	0.841	0.042	6	0.929	0.044	6

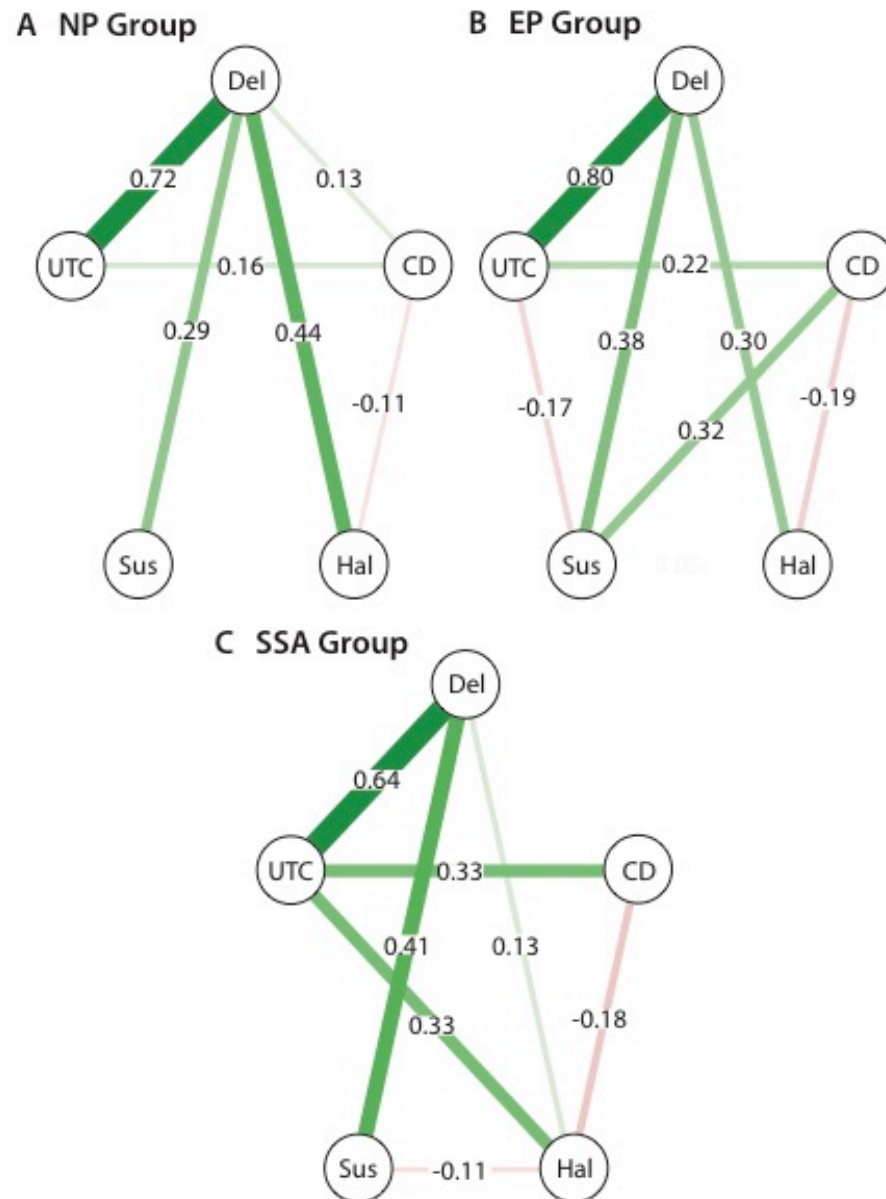[a] – NP Group: no schizophrenia or schizoaffective disorder diagnosis and not endorsing psychosis at study entry, EP Group: no schizophrenia or schizoaffective disorder diagnosis and endorsing psychosis at study entry; SSA Group: schizophrenia or schizoaffective disorder diagnosis.

Figure 5.7 depicts the Dynamic Networks of each psychosis risk group. The networks were similar whether estimated manually or with *mlVAR* package ($\rho = 0.965 - 0.989$, all p<0.001). All groups exhibited moderate autoregressive effects for all symptoms. While there were fewer number of significant edges in the SSA group (SSA: 7, EP: 12, NP: 10), permutation analysis revealed that network connectivity differed between groups, whereby the NP group was significantly less densely connected than the SSA and EP groups (SSA vs EP: difference = 0.015, p = 0.217; SSA vs NP: difference = 0.032, p = 0.002; EP vs NP: difference = 0.016, p = 0.004). These differences were driven by differences in average autoregressive connectivity (SSA vs EP: difference = 0.078, p = 0.001; SSA vs NP: difference = 0.196, p < 0.001; EP vs NP: difference = 0.118, p < 0.001) rather than cross-regressive connectivity (SSA vs EP: difference = -0.004, p = 0.345; SSA vs NP: difference = -0.010, p = 0.026; EP vs NP: difference = -0.009, p = 0.083).

Across groups, suspiciousness exhibited one of the highest descriptive out-strength centrality measures, while hallucinations exhibited the highest in-strength (Figure 5.8). Thus, in the cascade of psychosis evolution, the suspiciousness symptom exerted the most influence on other symptoms and if activated first would have the most consequences. Hallucinations, on the other hand, were observed to occur later in the cascade and would have less impact on the other symptoms if activated. Between groups, delusions exhibited higher out-strength in the NP and EP groups, but higher in-strength in the SSA group. Unusual thought content, however, exhibited higher in-strength in the NP and EP groups and higher out-strength in the SSA group. While primarily descriptive, these findings may suggest that, in the SSA group, worsening unusual thought content predicts subsequent worsening of delusions and hallucinations, while in the NP and EP groups, worsening

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delusions tended to precede worsening unusual thought content and hallucinations. Interestingly, conceptual disorganization may play different roles in the symptom network across groups: change in conceptual disorganization severity was not related to the other symptoms in the SSA group, but lay on the path from delusions to hallucinations in the EP group.

Figure 5.7 Dynamic psychotic symptom networks by psychosis risk group.
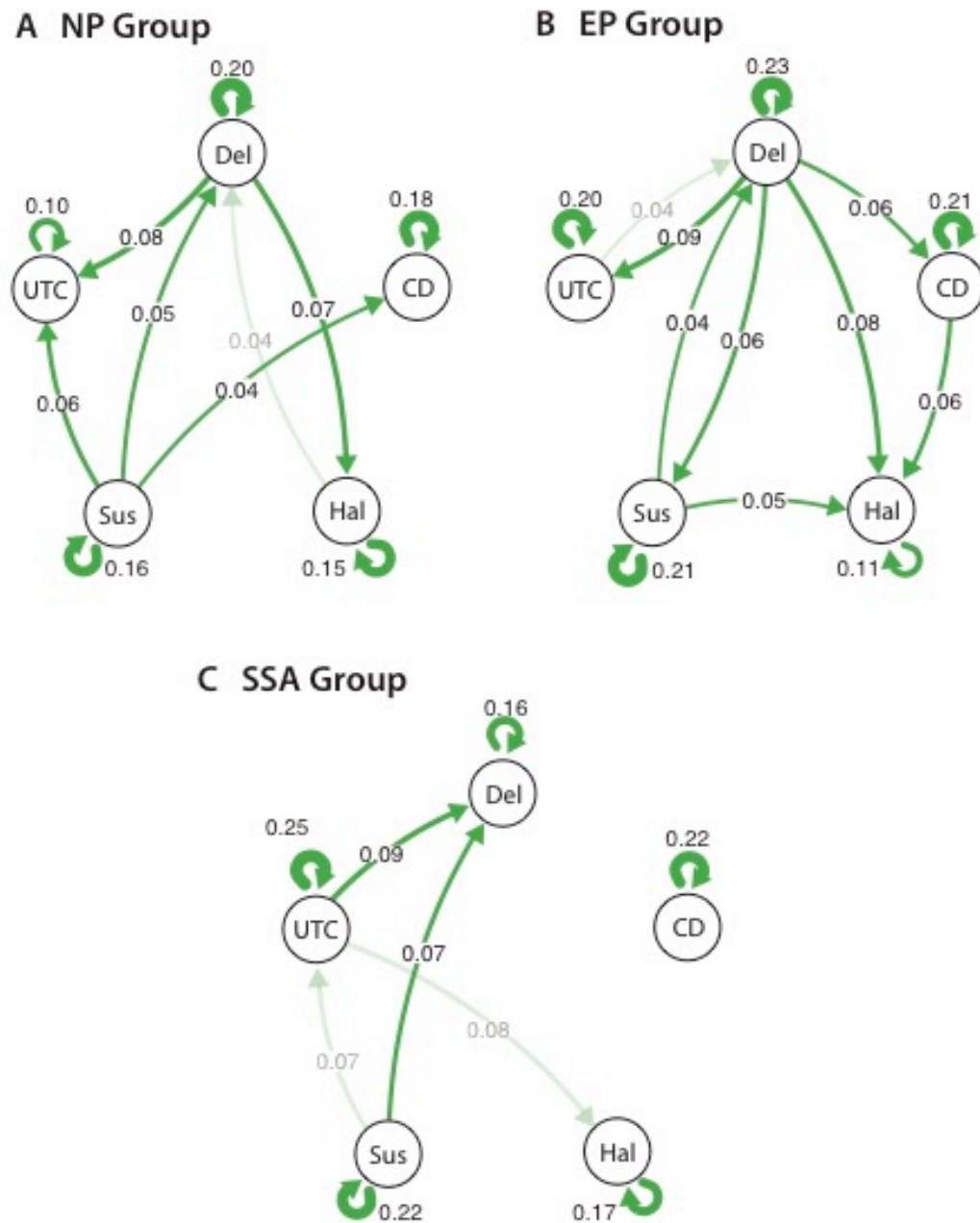
Directed network of psychotic symptoms predicting other symptoms in the next month (lag-1) within an individual in (A) NP Group (n=114, 4418 observations), (B) EP Group (n=129, 4532 observations), or (C) SSA Group (n=47, 1383 observations). Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; Green = positive edges. Thickness indicates edge weight. Opaque edges are significant by FDR 5%, and translucent edges are p<0.05.

Figure 5.8 Dynamic Network centrality measures across psychosis risk groups.
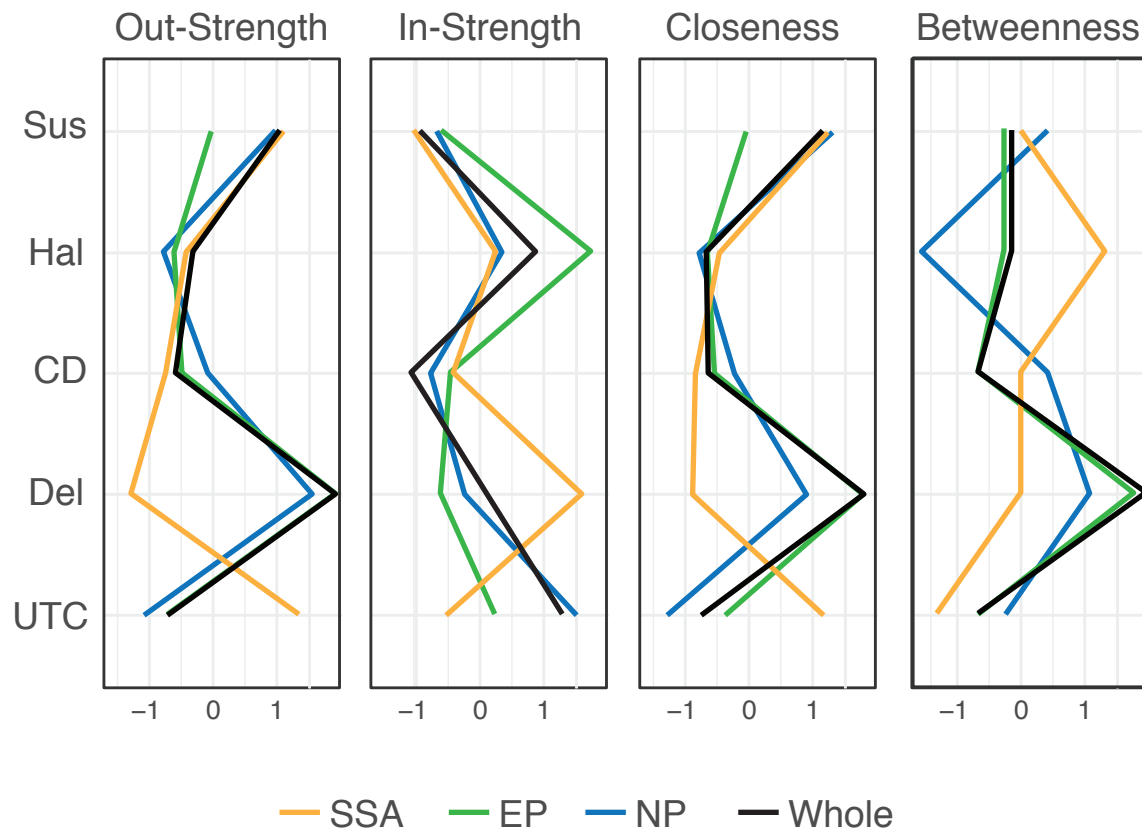
Standardized out-strength, in-strength, closeness, and betweenness centrality measures for the five psychotic symptoms across NP, EP, and SSA groups and the whole sample. Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content. SSA: schizophrenia or schizoaffective disorder diagnosis; EP: endorsing psychosis at baseline, NP: not endorsing psychosis at baseline.

For further comparison, an omnibus model that included interaction terms of psychosis risk group-by-lagged symptom variables (fixed effects) was estimated, and yielded equivalent networks for each group when compared to the subgroup analyses described above ($\rho = 0.988 - 0.998$, all $p<0.001$). The interaction terms in this model represent the group differences in edge weights, and were used to empirically test group differences

beyond descriptive comparison. Figure 5.9 depicts the differences visually, where the edges

depict the interaction terms (Dynamic Difference Network). First, while the autoregressive

effects of unusual thought content were significant in the SSA group, the NP group was less

likely to have persistent unusual thoughts (interaction term: β = -0.156, SE_β = 0.049, p =

0.001). In the EP group, this effect may be intermediary between the two other groups (EP

versus SSA interaction term: β = -0.088, SE_β = 0.049, p=0.070). Permutation analysis

confirmed that the NP group was less likely to have persistent unusual thought content than

the other groups (SSA versus EP: difference = 0.078, p = 0.144; SSA versus NP: difference =

0.196, p < 0.001; EP versus NP: difference = 0.118, p < 0.001). Second, compared to the

SSA group (reference), the EP group (interaction term: β = 0.129, SE_β = 0.038, p<0.001) —

and the NP group (interaction term: β = 0.102, SE_β = 0.039, p=0.009) though not significant

in subgroup analyses described — were more likely to have changes in conceptual

disorganization predict subsequent changes in hallucinations. This finding converged with

results from the permutation analysis (SSA versus EP: difference = -0.117, p = 0.006; SSA

versus NP: difference = -0.094, p = 0.021; EP versus NP: difference = 0.024, p = 0.414),

suggesting the SSA group was significantly less likely to have a connection from conceptual

disorganization to hallucinations (Appendix Table A.13). In addition, there were several

trend differences (significant p<0.05, converged with permutation analysis, but not

significant after accounting for false discovery rate of 5%): the relationship between unusual

thought content and delusions was less likely in the NP group, intermediary in the EP group,

and greatest in the SSA group, (converged with permutation analysis findings) and the

relationship between delusions predicting conceptual disorganization was more likely in the

EP group than either other group.

Figure 5.9 Differences in psychotic symptom dynamics by psychosis risk group.
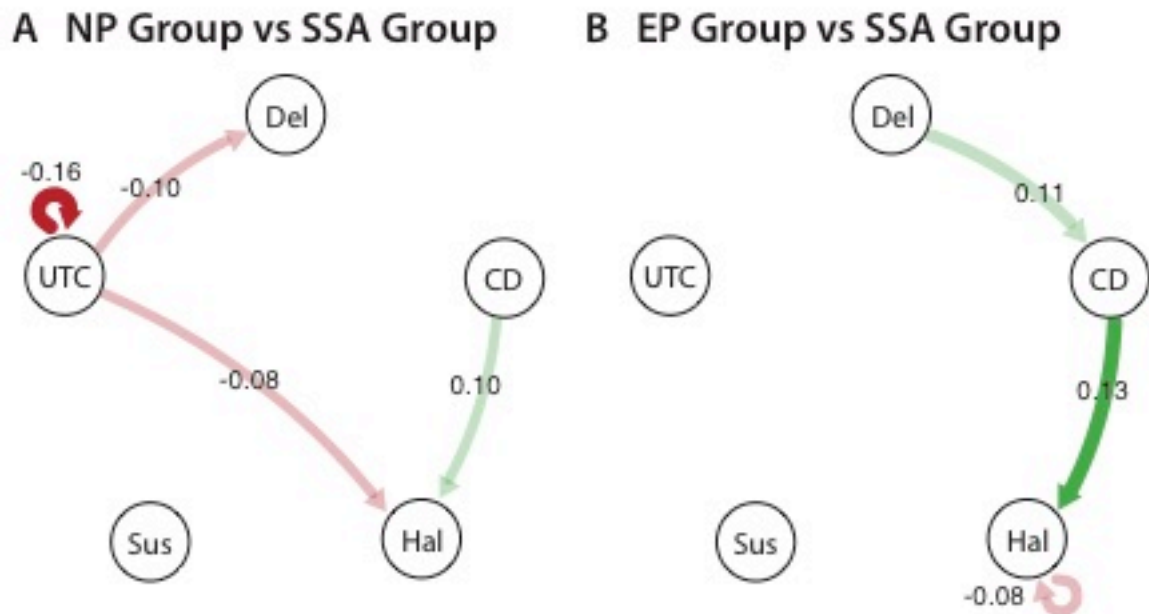
Directed networks of significant differences in psychotic dynamics between groups. Networks of interaction parameter estimates between lagged symptom effects and (A) NP group (as compared to reference SSA group), or (B) EP group (as compared to reference SSA group) membership. Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content; SSA = schizophrenia or schizoaffective disorder diagnosis; EP = endorsing psychosis at baseline; NP = not endorsing psychosis at baseline. Green = positive edge (interaction term); Red = negative edge (interaction term). Thickness indicates group difference in edge weight in reference to the SSA Group. Opaque edges are significant by false discovery rate of 5%, and translucent edges are p<0.05.

5.4 Discussion

This is the first dynamic network study of psychotic symptoms. This study examined the interplay among psychotic symptoms that may underlie the evolution of psychosis over time among a community-based sample of adults who experienced high rates of psychosis. By assessing symptoms monthly and applying a multilevel dynamic network analytic

approach, we separated these complex inter-relationships across time and participants. The within-individual temporal dynamics of psychotic symptoms were disentangled from the individual cross-sectional profile and the aggregated between-person differences that are stable across time. This was critical for distinguishing the temporality and scale of the effects between symptoms. Across these levels of causal hierarchy, psychotic symptoms exhibited distinct co-occurrence patterns and positively reinforced each other over time. To orient these novel findings in the context of the existing literature, we synthesized the three levels of networks with a focus on symptom pairs, then we examined the overall cascade of psychotic symptom dynamics.

5.4.1   Delusions as a central psychotic symptom

Delusions had a central role in the symptom network, at the between-individual, the within-individual levels, and across psychosis risk groups. Delusions were strongly associated with several other psychotic symptoms, and over time the delusion exacerbations exerted influence and were also affected by other symptom changes. Further, the persistence (autoregressive effects) of delusions was independent of delusion severity and had a similar distribution to other symptoms. These findings suggest that no matter the extent of crystallization or systematization of the delusions, the beliefs tended to persist month-to-month. The implications of this may be that delusions are the most difficult to modify with treatment. This aligns with recent findings that delusions were the most persistent psychotic symptom among individuals with schizophrenia spectrum disorder who did not achieve remission status (Johansson, Hjärthag, & Helldin, 2017).

5.4.2 Delusions and hallucinations: Hallmark symptoms of psychosis

Delusions and hallucinations are considered cardinal symptoms of psychosis and psychotic disorder (Kendler, 2016). Unsurprisingly, our analysis demonstrated a strong connection and mutually reinforcing phenomena between delusions and hallucinations over time. Specifically, delusions and hallucinations co-occurred across psychosis risk groups from a cross-sectional perspective (Contemporaneous Network). This finding is consistent with cross-sectional studies of the early emergence of psychosis in adolescents (Smeets et al., 2012) and adults with psychotic disorder (Shinn, Heckers, & Öngür, 2013) and their families (Smeets et al., 2015), as well as longitudinal studies of adults with first episode psychosis (Evensen et al., 2011) or schizophrenia (Harrow & Jobe, 2010).

The co-occurrence of these symptoms is associated with persistence of psychopathology and decreased functioning (Evensen et al., 2011; Smeets et al., 2012). However, our study found that, when examined over five years, the mean and the fluctuations in these symptoms were related in the NP and EP groups only. In the SSA group, who had poorer functioning at study entry, the relationship between delusions and hallucinations was strictly mediated through unusual thought content. Additionally, the degree of persistence of these two symptoms was not correlated across individuals. This indicates unique and potentially independent, month-to-month dynamics of these two hallmark symptoms. Indeed, findings from previous research in people with schizophrenia who had auditory hallucinations and delusions observed that it was the distress associated with these symptoms, but not the other symptom attributes that were correlated (Woodward et al., 2014). Together, our findings in the context of previous research highlight the initial existence of multiple pathways (e.g. delusions to hallucinations via increasing distress or via

bizarre thoughts) that may lead to the progression of psychosis — an individualized psychopathology cascade.

5.4.3   Delusions and unusual thought: Independent from delusions and suspiciousness

Similarly, delusions were also associated with unusual thought content or suspiciousness: individuals with more severe delusions on average tended to have more unusual thought content or worse suspiciousness, but not both. The three psychosis risk groups shared this pattern. This finding aligns with phenomenological descriptions that consistently distinguish bizarre delusions from persecutory delusions or paranoia (Cermolacce et al., 2010; Kendler, 2017). The key distinction is in the content of the beliefs — whether it is considered outside the logical framework of the patient's culture and history, or within. Unusual content versus increased suspiciousness may be driven by independent cognitive mechanisms: unusual thoughts may be generated by impaired self-monitoring that removes agency from one's actions (Langdon, Ward, & Coltheart, 2010), whereas suspiciousness may be driven by attributional bias and aberrant salience events (Kapur, 2003) or impaired theory of mind (Corcoran, Mercer, & Frith, 1995), whereby the thoughts and behaviours of others are misinterpreted.

While individuals with schizophrenia may endorse either type of belief, bizarre content, such as Schneiderian first rank symptoms of thought insertion or thought broadcasting, are thought to be relatively more specific to schizophrenia (Cermolacce et al., 2010). More recent study has demonstrated that in fact bizarre thoughts may be strongly predictive of schizophrenia (Soares-Weiser et al., 2015). Our findings support this assertion. The persistence (autoregression) of unusual thought content differentiated the psychosis risk groups. The SSA group was most likely to exhibit persistence of unusual thought content,

and the NP group, the least likely. Considering the high centrality of unusual thought content across groups, the bizarre quality of the beliefs and delusions may be an important target for future interventions.

In addition, the Dynamic Network revealed an acute effect of suspiciousness on subsequent unusual thought content unique to the NP group, who had the lowest risk for psychosis. This is consistent with a recent networks study of psychotic-like experiences in the general population (Murphy et al., 2017). Based on a cross-sectional network structure, Murphy et al. (2017) postulated two possible causal pathways: affective predicting suspicious predicting unusual thought content symptoms, or the reverse. Our study provides evidence for the first: in individuals with low risk for psychosis, suspiciousness may predict subsequent unusual thoughts, directly or mediated through delusional beliefs.

5.4.4   Delusions independent from conceptual disorganization

Interestingly, delusions were not directly associated with conceptual disorganization across individuals, nor as part of temporal pathways. This is in line with previous studies, including Liddle's original identification of three syndromes (Liddle, 1987) as well as more recent factor analysis work. Consistently, in symptom factor studies, conceptual disorganization tends to load onto a different (disorganized) factor from the other four psychotic symptoms (positive factor) (Anderson et al., 2015; Emsley et al., 2003; Wallwork et al., 2012). Additionally, in a 20-year longitudinal study of people with schizophrenia, delusions did not co-occur with thought disorder (Harrow & Jobe, 2010).

Building on these findings, we observed that not only do conceptual disorganization and delusions tend to not co-occur, they also do not predict each other over time, with two exceptions. First, within individuals in the NP group, delusions indirectly exacerbated

disorganization through enhanced suspiciousness. Indeed, tangentiality may be more common among people with schizophrenia experiencing paranoia (Mazumdar, Chaturvedi, & Gopinath, 1991). In recent years, the suspiciousness/persecution item has often been excluded from factor analysis studies due to considerable cross-loading and worse model fit (Anderson et al., 2015; Emsley et al., 2003; Wallwork et al., 2012). The present alternative network approach suggests the suspiciousness/persecution item may in fact act as a bridge between several clinical presentations and should not be ignored.

Second, delusions may directly exacerbate conceptual disorganization in people who present with psychosis at study entry but did not have schizophrenia. This effect may be embedded within previously observed moderate (0.424) cross-factor correlation between the positive and disorganized factors (Wallwork et al., 2012) and moderate cross-loading (0.337) of conceptual disorganization with the other psychotic symptoms (Mohr et al., 2004), which have received limited attention to date. Indeed, when disentangled from the between-person and temporal relationships, the Contemporaneous Network suggests that all five psychotic symptoms may relate at a given moment. Whether this relationship is due to shared underlying pathology such as an acute hyperdopaminergic state is currently unknown; however, this network approach allows us to explore these inter-relationships that are missed by other analytic approaches.

5.4.5 Conceptual disorganization and hallucinations: Simpson's paradox

An example of Simpson's paradox was evident when interpreting the three network levels: while disorganization and hallucinations were negatively associated in the whole sample, these symptoms were positively associated in the within-individual Contemporaneous Network and the Dynamic Network of the NP group, specifically. We

applied Pearl's theory of inferred causation (Pearl, 2000) to interpret the Person-Mean

Network. This theory posits that a negative relationship between two nodes that are both

positively related to a third node is indicative of the presence of a common effect (i.e.,

collider) causal relation (Pearl, 2000). In our research, a negative association between

conceptual disorganization and hallucinations, conditioning on unusual thought content,

suggests that both conceptual disorganization and hallucinations may potentially cause

unusual thought content, and not the other way around. However, we observed that this

effect was not specific to a psychosis risk group and did not remain significant in subgroup

analyses. Further, the Dynamic Network findings indicated that conceptual disorganization

may drive a portion of the observed fluctuations in hallucination severity, particularly in

participants without schizophrenia. We observed that this effect was significantly different in

the EP and NP groups compared to the SSA group. Further mechanistic inference is limited

given the group-level nature of the Person-Mean Network findings. Our findings suggest the

existence of nuanced and complex dynamics in psychosis symptomology and demonstrate

the importance of separating the effects by time and within- versus between-person levels.

Perhaps, the Person-Mean effects represent dynamic effects from earlier development that

are shared across at-risk individuals and solidified over time. Further investigation over the

developmental trajectory of psychosis is required to disentangle these complex mechanisms.

5.4.6   Psychotic symptom cascade

In our Dynamic Network analyses, we observed a cascade of psychosis: perturbations

in one symptom may lead to the eventual exacerbation of all other symptoms over the course

of months (Figure 5.10). In this cascade, suspiciousness was found to be upstream, mutually

reinforced by delusions and conceptual disorganization through independent mechanisms.

This finding was consistent across psychosis risk groups. Indeed, suspiciousness, along with sleep disturbances and dysphoria, were reported in the days preceding the onset of hallucinations and delusions in people with schizophrenia or a transient psychosis presentation (Marneros, Pillmann, Haring, Balzuweit, & Blöink, 2005). These findings also align with a recent symptom network study that observed associations between childhood trauma and suspiciousness or unusual thought content severity, followed by effects on delusions and hallucinations (Isvoranu et al., 2017). Interestingly, though SSA had fewer number of edges, this group exhibited a more densely connected dynamic network, driven by stronger autoregressive effects. This observation is in line with the assertion that network density may relate to severity and progression of illness (Borsboom, 2017; van Borkulo et al., 2015).

Figure 5.10 Schematic of Dynamic Networks of psychosis risk groups
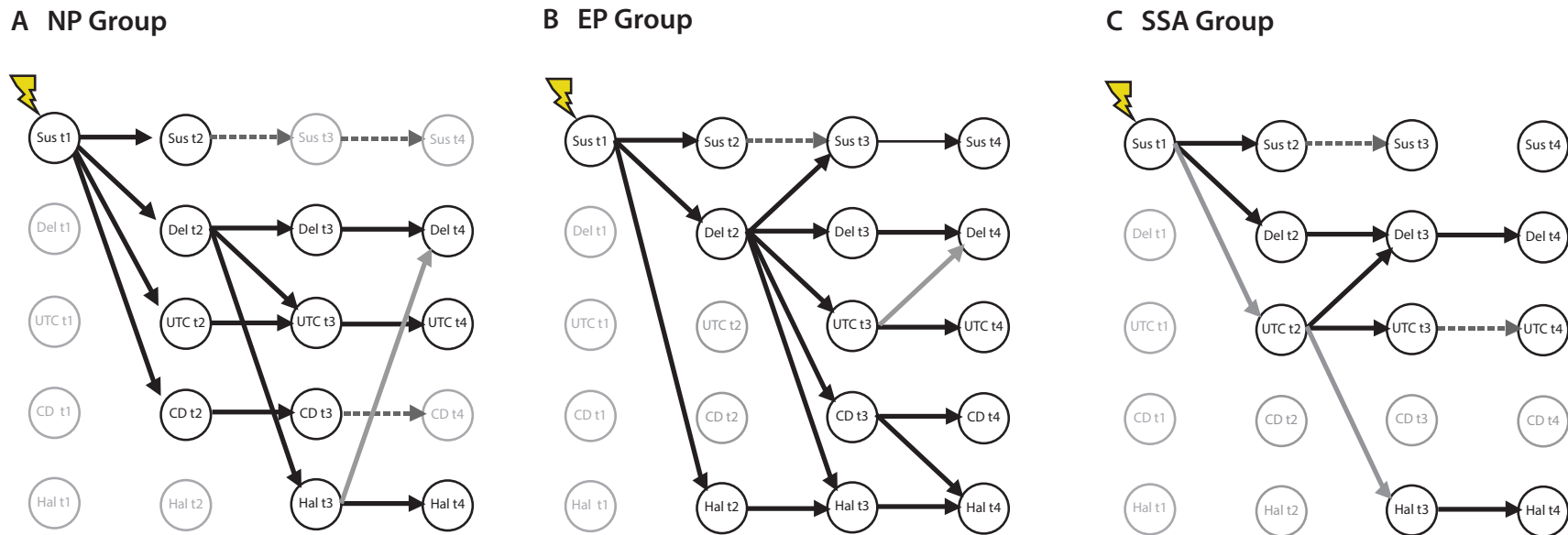
The symptom activation cascade as estimated by the Dynamic Networks of the (A) NP group, (B) EP group, and (C) SSA group. Given a hypothetical event that triggers the activation of suspiciousness, there are different possible downstream consequences – and opportunities for prevention or therapy – between each group. Black arrows represent estimated effects from Dynamic Network accounting for False Discovery Rate of 5%. Grey arrows represent estimated effects significant to p<0.05 only. Dashed lines represent the unknown persistent effects given that the multilevel VAR(1) model tests only 1-month lag. Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness/persecution; UTC = unusual thought content; SSA = schizophrenia or schizoaffective disorder diagnosis; NP = not endorsing psychosis at baseline; EP = endorsing psychosis at baseline; lightning bolt represents a triggering event.

In the present study, hallucinations, however, appeared to be activated more downstream in the cascade in all psychosis risk groups. Indeed, individuals with first episode psychosis were reported to rarely experience hallucinations alone; hallucinations were experienced concomitantly with delusions, or at least one month before or after the onset of delusions (Compton et al., 2012). Moreover, a recent qualitative study on the evolution of psychosis from the patient perspective identified a similar symptom progression that aligns with our findings (Cheng et al., 2017). In this study, individuals with schizophrenia described progressive stages of symptoms that began with unusual thoughts and delusions (accompanied by difficulty sleeping and attentional disturbances) followed by distorted perceptions and difficulty communicating (Cheng et al., 2017). Patients described the eventual sense of "losing control" and fear. While the course of psychosis is heterogeneous, our findings suggests that characterizing the within-individual cascade my help to inform future prevention strategies.

5.4.7 Study limitations

There are four key limitations to the findings of this study. First, in contrast to dynamic network studies using experience sampling method, the time interval for observations in this study was one month; thus, the Dynamic Network effects may be underestimated, with the finer effects embedded in the Contemporaneous Network (Epskamp, van Borkulo, et al., 2017). However, the significant effects demonstrated at this time scale suggest that the dynamic processes for psychotic symptoms may occur slower than other phenomena, such as emotional states, which require more frequent observations to capture change (Wichers, 2014). Additionally, the magnitude of the dynamic effects observed in the present study were similar to those seen in experience sampling method

studies with time intervals of 90 minutes (Klippel et al., 2017; Wigman et al., 2015). Second, the dynamic network examined only one lag and thus the effects cannot be extrapolated to the effect of a symptom change on another multiple months later. Third, while standardization is considered best practice for dynamic network modeling, this approach may underestimate autoregressive effects (Bulteel et al., 2016). Last, to most accurately capture the system of psychosis, other psychopathological and biopsychosocial factors should be included (Borsboom, 2017; Kendler et al., 2011), such as mood and negative symptoms, treatment, substance use, trauma, and/or brain injury. These factors may contribute to the risk and resilience to psychotic symptoms and shape their course over time. Communities, including the present sample, endure many factors that contribute to their risk for psychosis. While current dynamic network analysis approaches permit only a limited number of variables (Epskamp, Waldorp, et al., 2016), future analytic tools may allow us to examine these complex systems and potentially mitigate risk for onset or progression of psychosis.

Chapter 6: Discussion

6.1   Overview of findings

This dissertation examined the longitudinal consequences, risk factors, and dynamics of psychosis in adults living in marginalized housing in Vancouver, Canada. These longitudinal studies further our understanding of psychosis and provide a foundation for future research to ultimately inform clinical practice. We identified that psychotic disorders and hepatic fibrosis were significant risk factors for premature death in adults younger than 55 years of age. Individuals with schizophrenia or schizoaffective disorder were more likely to experience persistent psychosis characterized by multiple symptoms and limited associations with environmental risk factors. Among individuals without these disorders, the number of days of methamphetamine, powder cocaine, cannabis, or alcohol use predicted dose-related increases in the odds of psychosis, without evidence of interaction or reverse causation. Additionally, recent traumatic events, and histories of early-life trauma or brain injury were independently associated with psychosis. Psychotic symptoms were positively reinforcing over time in distinct patterns, as revealed by dynamic network analysis. Delusions had a central role in the symptom network, at both the between-individual and within-individual levels. Delusions were associated with severe unusual thought content or suspiciousness, but not conceptual disorganization. While delusions played an influencing role with suspiciousness on symptom dynamics in people without schizophrenia or schizoaffective disorder, delusions and hallucinations were more downstream in the psychotic symptom cascade in people with these psychotic disorders. Overall, these completed studies identified multiple risk factors and psychopathological processes that may

contribute to the longitudinal characteristics of psychosis and suggest potential targets for treatment strategies and therapeutic interventions among adults at-risk for psychosis.

6.2   Implications for future research

6.2.1   Investigations of potential causal relationships between risk factors and psychotic symptom networks

Ultimately, psychiatric epidemiology and related scientific fields seek to identify factors that may cause the phenomena observed in a population. As discussed in Chapter 1, the Bradford Hill viewpoints can be used as guiding principles in the consideration of associations as potentially causal effects (Hill, 1965) (Table 1.1). However, in the age of rapid technological advancement, global collaboration, and interdisciplinary integration, these principles require adaptation to guide how we seek causal explanations in contemporary research. A recent article (Fedak, Bernal, Capshaw, & Gross, 2015) provided suggestions to update the Bradford Hill viewpoints (Hill, 1965), which are summarized in Table 6.1. These updated principles highlight the advancements in rigorous statistical and biological methods that deepen our understanding of the complex, interacting effects that exposures may have on even distal outcomes. It is postulated that biopsychosocial factors may accumulate in their effects through additive, synergistic, or antagonistic mechanisms (Vanderweele & Knol, 2014). For now, many of these mechanisms remain in a "black box," but could be revealed with further structured inquiry and intentional interdisciplinary collaboration.

Table 6.1 Updated Bradford Hill viewpoints (based on Fedak et al., 2015)

Criteria	Definition
Strength	Statistical significance (considering underlying methodology)
Consistency	Consistent causal story across disciplines and levels of inquiry
Specificity	Exposure has effect on refined aspects of the outcome
Temporality	The factor precedes the outcome, with many complex processes possible (e.g., transgenerational), given other factors in the system
Biological gradient	Dose-response effect, with non-linear, threshold, and cumulative synergistic/antagonistic/additive interaction effects possible
Plausibility	The effect aligns with current interdisciplinary understanding
Coherence	The effect does not conflict with current interdisciplinary knowledge and/or may explain incoherent knowledge areas
Experiment	Intervention on the factor changes outcomes at steps in the pathway towards the outcome
Analogy	Only helpful for proposing future areas of inquiry

6.2.2 Proposed integrative model

Aligned with these updated recommendations, Table 6.2 and Figure 6.1 summarize the assessment of the findings from the present studies and propose hypothetical mechanisms for future study based on existing interdisciplinary knowledge. In particular, Chapter 3 examined aspects of the strength, temporality, plausibility, coherence, and consistency of the relationship between psychotic disorders and premature mortality. In Chapter 4, we examined the biological gradient, strength, temporality, plausibility, coherence, and consistency of several biopsychosocial effects on psychosis (Table 6.2). As depicted in Table 6.2, biological gradient was determined by the presence of a dose-related effect on psychosis in the present study, strength was determined if the effect was statistically significant, and temporality was determined according the reverse causality analysis described in Chapter 4. The viewpoints of plausibility, coherence, and consistency places the findings from Chapter 4 in the context of the existing literature reviewed in Chapter 1 that has informed our

understanding of psychosis risk factors to date. Last, in Chapter 5, we sought to further refine

the outcome itself by considering psychosis as a dynamic system to address the "specificity"

principle. Indeed, we distinguished the "trait" (Person-Mean Network), "state"

(Contemporaneous Network), and "dynamic" (Dynamic Network) aspects of the psychosis

outcome. While some aspects of this system appear self-perpetuating, there may be

underlying mechanisms, with even more refined temporal and spatial resolution, steering

these phenomena. Thus, we propose that biopsychosocial risk factors should be examined for

their impact on these refined aspects of the psychotic symptom network. Applying existing

knowledge from the field, we hypothesize the biopsychosocial risk factors could have both

specific and broad impacts on the psychotic symptom network, through their actions on

neuronal activity (Figure 6.1). Future examination of these potential causal effects may also

be guided by these adapted principles.

Table 6.2 Evaluation of the present findings using updated Bradford Hill viewpoints

Factors	Present Study Findings for Adults At Risk for Psychosis [a]			Relation to Existing Interdisciplinary Knowledge	
	Strength	Biological Gradient	Temporality	Plausibility/ Coherence	Consistency
Age	✖	✖[b]	—	✖	✖
Male sex	✔	◯	—	✔	✔
Homelessness vs Marginal Housing	✖	◯	✖[c]	◯	◯
Methamphetamine	✔	✔	✔	✔	✔
Powder Cocaine	✔	✔	✔	✔	✔
Crack Cocaine	✖	✖	✖	✖	✖
Cannabis	✔	✔	✔	✔	✔
Tobacco	✖	◯	✖[c]	~	~
Alcohol	✔	✔	✔	✔	✔
Opioid	✖	✖	✖	✔	✔
Early Life Trauma	✔	✔	✔[d]	✔	✔
Recent Trauma	✔	✔	✖	✔	✔
TBI	✔	◯	✔[d]	✔	✔
Antipsychotic	~[e]	◯	✖	✖	✖

✔ demonstrated to be present in the current study, or consistent with existing knowledge and causal framework

✖ demonstrated to be absent in the current study, or inconsistent with existing knowledge and causal framework

~ mixed findings in current study, or existing knowledge is inconsistent and framework is unclear

◯ not tested in current study, or currently untested in the literature

[a] – These findings are limited to adults without schizophrenia or schizoaffective disorder. These effects were not related to psychosis among individuals with schizophrenia and schizoaffective disorder in this study.

[b] – Detection of age effects may be limited by age range and further study should include adolescents.

[c] – The prevalence was too low to generate reliable findings on the reverse temporality analyses. Future study will require a greater number of observations and participants.

[d] – Both early life trauma and TBI occurred prior to all psychosis assessments, thus meeting the criteria for temporality. However, we are inherently unable to test the other possible direction of effect. Further study including prospective assessment of TBI could elucidate the temporality of this effect.

e – The effects of specific types, doses, or routes of administration of antipsychotic medication were not examined due to low rates. The positive effect in the AR group was likely associated with presence of psychotic disorder as this effect was absent when individuals with other psychotic disorder were removed. Importantly, antipsychotic treatment was not associated with reduced odds of psychosis in participants with schizophrenia, schizoaffective disorder, psychosis not otherwise specified, or mood disorder with psychosis.

Figure 6.1 Hypothesized model of the effects of biopsychosocial factors on the refined aspects of psychosis outcome (psychotic symptom network) and downstream impacts on mortality.
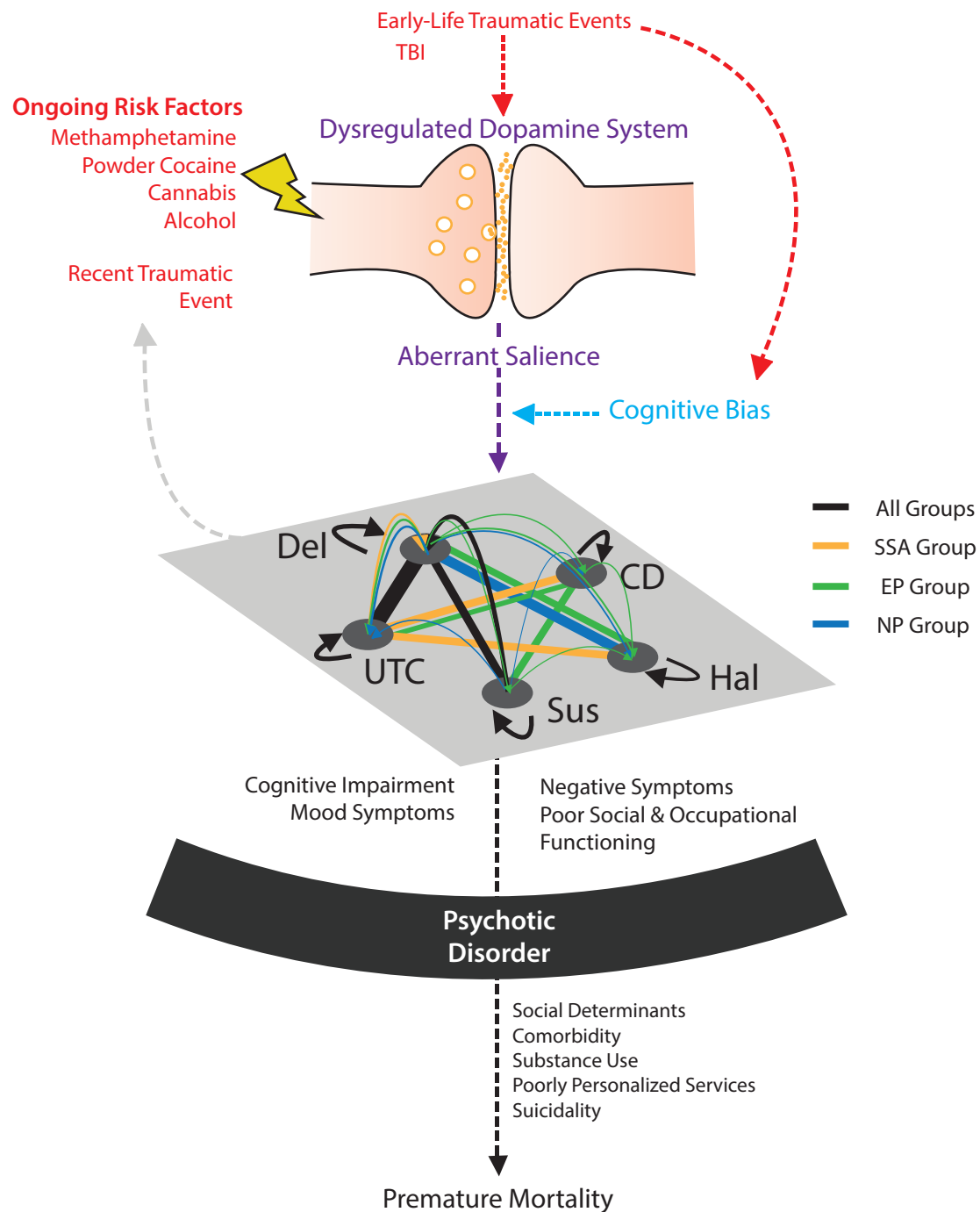
Exposure to early-life traumatic events may modulate neural and cognitive processes, specifically contributing to dysregulated dopamine systems and cognitive bias (e.g., attributional bias). In adulthood, ongoing risk factors (TBI, substance use, traumatic events) may lead to activation of dopamine system, either through

reduced frontal inhibition, activation of the dopamine systems directly, or another unknown mechanism. This dysregulation may underlie aberrant salience attribution to stimuli and, combined with cognitive bias, may underlie the development of a positively reinforcing psychotic symptom network. Activation of the psychotic symptom network may lead to a cascade of worsening symptom severity, as well as subsequent traumatic events. Further, individuals may develop additional symptoms, behaviours, and functional and cognitive impairment associated with a diagnosis of psychotic disorder. Additional vulnerabilities, including social determinants (e.g., housing, poverty, isolation) and inadequately personalized services and poor service engagement, may contribute to premature mortality observed in people with psychotic disorders. SSA = schizophrenia or schizoaffective disorder diagnosis; EP = endorsing psychosis at baseline; NP = not endorsing psychosis at baseline; Red = biopsychosocial factors; Purple = neuronal mechanisms; Lightning bolt = activation of dopamine systems; Cyan = cognitive mechanisms; Grey square = psychotic symptom network; Grey dashed arrow = psychosis effect on subsequent traumatic events (bi-directional relationship); Grey circles = psychotic symptoms; Flat, undirected edges = Person-Mean Network; Raised, directed edges = Dynamic Network; Black edges = exhibited in all psychosis risk groups; Orange edges = SSA group only; Green edges = EP group only; Blue edges = NP group only. Model informed by Howes and Murray, 2014.

Howes and Murray (2014) proposed a sociodevelopmental-cognitive model of schizophrenia that integrates the hypothesized roles of dopamine, cognitive biases, and developmental course. In this model, genetic and early-life environmental factors interact to dysregulate the dopaminergic system, and adversity modulates cognitive schema to "see the world as threatening" (Howes & Murray, 2014). According to this model, there is altered striatal dopaminergic transmission with ongoing stressors and exposures, leading to misattribution of salience due to the hyperdopaminergic state and paranoid interpretations due to cognitive biases.

We apply and extend this model to the present studies. To begin with, suspiciousness was located upstream in the symptom cascade, whereby change in suspiciousness had downstream consequences on the other symptoms. Across psychosis risk groups, exacerbations in suspiciousness persisted over time and predicted subsequent delusional severity. In individuals without schizophrenia or schizoaffective disorder, suspiciousness predicted subsequent hallucinations, or subsequent disorganization and unusual thought content. Other researchers propose that overlapping causal mechanisms may give rise to psychopathological phenomena (Kendler, 2008; Kendler et al., 2011). If we conceptualize the network edges as having underlying neurobiological and psychological mechanisms, we then hypothesize that a sensitized striatal dopamine system and cognitive biases may contribute to the downstream effects of suspiciousness. Specifically, several studies have demonstrated that the jumping-to-conclusions or data gathering biases (McLean, Mattiske, & Balzan, 2017) may lead to delusion formation. After initial suspiciousness exacerbation, this bias may lead to formation of a delusional thought that is sustained by a bias against disconfirmatory evidence (Woodward, Moritz, Cuttler, & Whitman, 2006). In addition, an attributional bias may underlie the suspiciousness exacerbation (e.g., negative interpretation of a social cue) and subsequent hallucinations (e.g., misinterpretation of sensory stimuli) and unusual thought content (e.g., misinterpretation of stimuli in the environment).The fact that suspiciousness precedes these other phenomena, may lie in the greater degree of uncertainty and complexity of social interactions, and hence increased susceptibility to misattribution.

While this model may explain a portion of these phenomena, the explanation is far from complete. A complementary model proposes that an imbalance in the excitatory and inhibitory regulation in the system (Keshavan, Nasrallah, & Tandon, 2011) leads to "circular

belief propagation" (Jardri & Denève, 2013). In this model, abnormalities in top-down regulation may lead to over reliance on prior experience causing misinterpretation of sensory stimuli, whereas bottom-up regulation abnormalities may lead to increased salience of the stimuli and less integration with past experience (Jardri & Denève, 2013). These feedback mechanisms are proposed to be governed by long-range excitatory (i.e., glutamatergic) transmission and short-range inhibitory (i.e., GABA-ergic) transmission. In a recent study, individuals with schizophrenia were found to have a bottom-up regulation abnormality (Jardri, Duverne, Litvinova, & Denève, 2017), in line with the aberrant salience hypothesis (Kapur, 2003), as well as behavioral evidence of sensory disturbances (Adcock et al., 2009; Vercammen, De Haan, & Aleman, 2008). Under this model, misinterpretation of perceived stimuli (e.g., sensory or social) may lead to experiences of hallucinations or suspiciousness that, due to imbalanced system controls, may perpetuate as delusions.

The findings of our research are in alignment with this model. When integrating the findings from the Person-Mean and Dynamic Networks, the SSA group demonstrated a trend pathway from hallucinations to unusual thought content, then, on a month-to-month time scale, exacerbations in unusual thought content predicted subsequent increases in severity of delusions. Perhaps, the Person-Mean effects represent once tenuous or dynamic relationships that solidified during development due to biopsychosocial influences. Based on this interpretation, imbalanced regulation may contribute to the misinterpretation of stimuli and later manifest as unusual thoughts and delusions. The greater persistence of unusual thought content in this group compared to the others may suggest a key role for this symptom in the perpetuation of psychopathology in individuals with psychotic disorder. This pathway may be unique to the SSA group. Individuals in the EP and NP groups did not share these Person-

Mean effects (i.e., hallucinations associated with unusual thought content), and perhaps have a distinct developmental course, whereby top-down or alternative controls were altered over the life course trajectory.

6.2.3 Specific steps for psychotic symptom network development and validation

Additional steps are required to test and validate the psychotic symptom networks. First, the accuracy of the system improves when all components of the system are included in the analysis (Borsboom, 2017; Kendler et al., 2011). Network studies demonstrate a high degree of overlapping symptoms in different disorders. It may be necessary to examine a wider range of psychopathology to determine the true architecture that channels the symptom cascade. Specifically, grandiosity, somatic concern, preoccupation, stereotyped thinking, excitement, and difficulty in abstract thinking have strong connections with psychotic symptoms (Isvoranu et al., 2017; van Rooijen, Isvoranu, Kruijt, et al., 2017) and could be considered in further study. Further, phenomenological decomposition of symptom variables may be necessary to understand the nuances of how symptoms evolve and interact (e.g., auditory versus visual hallucinations). Indeed, one study identified that the level of distress associated with hallucinations was highly related to the distress associated with delusions (Woodward et al., 2014). Hallucinations and delusions may be related by modality (van Rooijen, Isvoranu, Meijer, et al., 2017). Exploring the direction of this potential pathways could shed light on how symptoms are reinforcing over time.

Second, replication with a greater number of participants and time points may improve the accuracy of the parameter estimates. While psychotic disorders are prevalent in this community-based study, future research may need to over-sample individuals with psychotic disorder in order to be able to test whether the disorder is related to specific aspects

of network structure. In particular, there is ongoing debate and conflicting evidence as to whether individuals with psychiatric disorder have more densely connected symptom networks (Bos & Wanders, 2016; van Borkulo et al., 2015). In the present study, in addition to having significantly more severe psychotic symptoms, individuals with schizophrenia or schizoaffective disorder demonstrated more densely connected Contemporaneous and Dynamic Networks but a similar Person-Mean Network density than those without the disorder. However, the interpretation of these findings is limited by the unequal and small group sizes. Further study with larger samples is needed to conclusively address this issue.

Third, our analytic approach assessing the influence of biopsychosocial factors on the psychosis system could be improved. Exploration of the additive, synergistic, or antagonistic effects among exposures would help to strengthen our understanding of these complex effects, some of which may be embedded in the shared effects not depicted in the current approach to network modeling (Bulteel et al., 2016). Additionally, current findings assume linear change. While our study found linear dose-dependent effects of several substances on psychosis risk, when considering their impact on network dynamics, change may instead occur in a discontinuous, non-linear fashion (Hayes et al., 2007).

While this proposed integrated model extends our current knowledge by specifying the psychosis outcome, it still preserves the "black box" between the biopsychosocial factors and the symptoms themselves. We propose how to explore some of these mechanisms using a multilayer network approach.

6.2.4 Multilayer networks

If psychopathological phenomena may be conceptualized as a network of interacting elements, perhaps the entities that underlie these phenomena are also networks. Indeed,

others have proposed that the brain-mind-environment system may be better understood as multiple layers of networks that influence one another over time and space (Braun et al., 2018; Looijestijn, Blom, Aleman, Hoek, & Goekoop, 2015). As mentioned in the previous section, exploration of this psychosis network model will require collaboration across disciplines of research including, but not limited to, health (medicine and allied health professions), neuroscience, psychology, physics, computer science, mathematics, sociology, and public policy. Indeed, network structures are found to explain the interrelationships at all levels – from genes to neurons, from individual to society. These structures help explain the flow of information or activation between its nodes, and may also dictate flow between these levels (Figure 6.2). In this multilayered network model, an individual's symptoms emerge from dynamic, interdependent systems, embedded in a larger social network, undoubtedly influenced by the norms and policies of society. This framework was proposed by Kivelä et al. (2014) and summarizes decades of work in the fields of sociology, engineering, physics, mathematics, computer science, and systems science. This framework has only recently been proposed for application in psychiatric disorders (Braun et al., 2018).

Indeed, the formation and modification of psychotic symptoms and the relationships among these symptoms, may be driven by underlying networks at the genetic, cellular, and regional networks of the brain. It is conceivable that the proximal (and perhaps most directly influential) level to psychopathology is at the level of neural circuitry. This level integrates inputs from external and internal stimuli to generate outputs observed as thoughts and behaviours. Schizophrenia has been described as a disorder of widespread structural and functional disconnectivity of brain networks (Uhlhaas & Singer, 2010; White & Hilgetag, 2011). Across development, genetic and environmental factors may impair processes such as

neuronal migration and maturation resulting in patterns of diffuse changes in structure, such as gyrification (White & Hilgetag, 2011). Functionally, coordinated systems of synaptic transmission may also be altered by acute and chronic exposure to environmental risk factors (Kohno, Morales, Ghahremani, Hellemann, & London, 2014). These structural and functional networks can be examined as regions that are physically linked by white matter tracts, or that share similar morphology, or engage in synchronous activity (Braun et al., 2018; Seidlitz et al., 2018).

Dynamic multilayer network techniques have advanced in the last several years and have been used to describe the dynamic processes of learning (Bassett, Yang, Wymbs, & Grafton, 2015) and working memory (Braun et al., 2015). Longitudinal study examining life course risk factors on neuronal, brain, and symptom networks may provide targets for treatment development. Further, non-invasive neurotherapeutic interventions such as transcranial magnetic stimulation (TMS) may be helpful tools to test hypothetical network structures and explore potential causal dynamic mechanisms and treatment targets. For example, several studies demonstrated that repetitive TMS (rTMS) at the left temporoparietal area is effective in reducing auditory verbal hallucinations (Slotema et al., 2014). However, this treatment does not provide significant benefit for psychotic symptoms overall (Slotema et al., 2014). Applying the findings from the present studies, due to the downstream position of hallucinations in the psychotic symptom cascade, we would not expect improvement in this symptom to be associated with improvement in other psychotic symptoms. Instead, treatments that target underlying causes for symptoms positioned more upstream, and therefore with greater influence on other symptoms, may demonstrate broader improvement.

These innovative pursuits are imperative given the urgency and severity of the

consequences of psychosis and psychotic illness on quality of life and years lost. Leveraging both existing, proven therapies and advancements in treatment, coupled with a multilayer network approach to psychiatric illness, may expedite treatment development as well as our understanding of these complex phenomena.

Figure 6.2 Proposed schematic of multilayer networks of psychosis
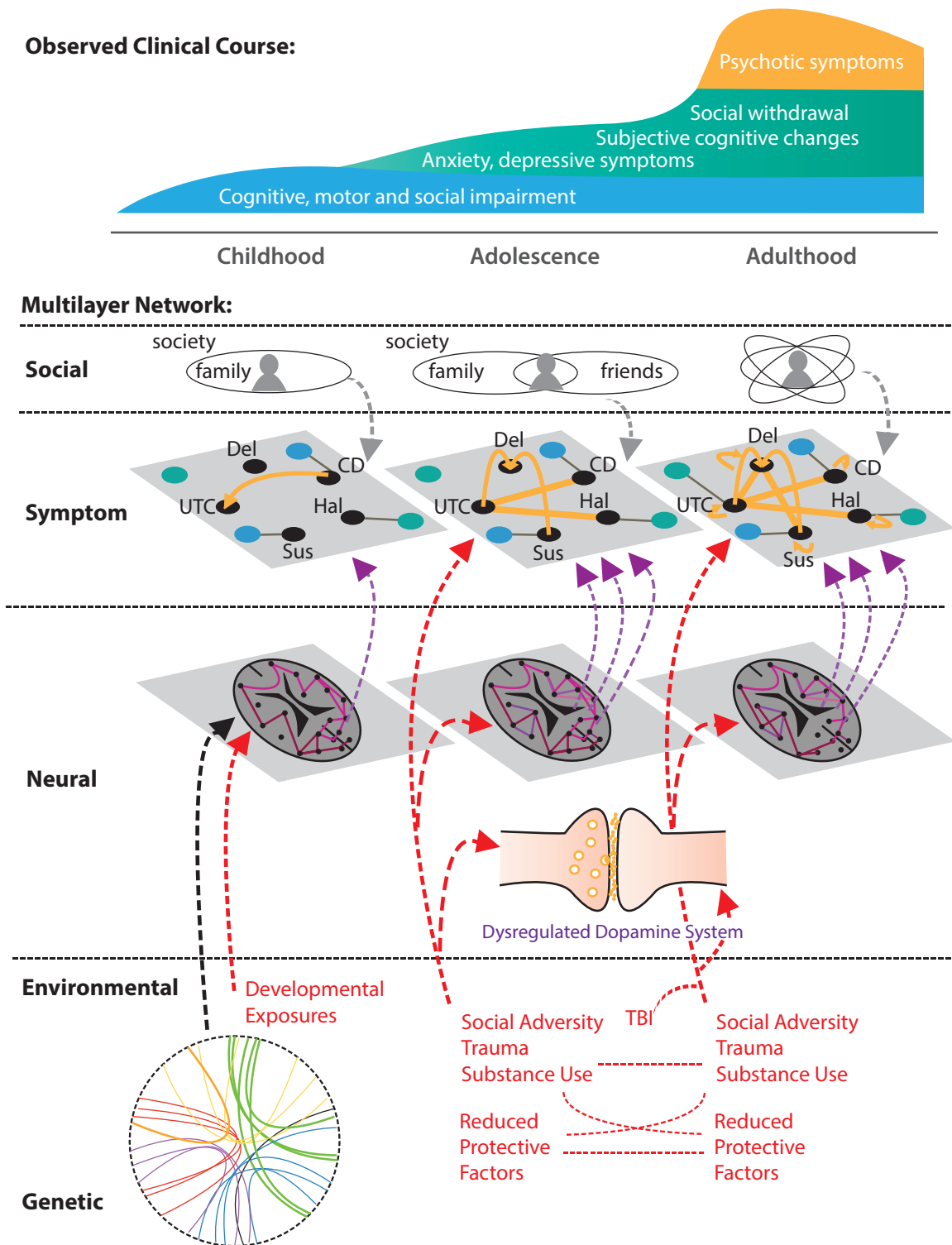
Proposed structure for developmental multilayer networks underlying the observed clinical course of

schizophrenia, including nested social, symptom, neural, environmental, and genetic networks. In childhood,

underlying brain networks (e.g., excitatory/inhibitory imbalance), shaped by genetic network, developmental exposures, and social environment, may lead to the formation of tenuous, perhaps dynamic, connections between symptoms at the symptom network level. In early-life into adolescence, environmental exposures (e.g., trauma) and/or reduced protective factors (e.g., social isolation) may build on this vulnerability by affecting neural networks (e.g., dopamine system dysregulation), and formation and strengthening of symptom network density. By adulthood, as psychotic symptoms emerge clinically, these environmental factors may continue to accumulate, impacting neural and symptom networks. Acute stressors may cause stimulation of dopamine transmission, misattribution of salience, and may activate a symptom cascade that is channeled by the established and evolving symptom network. Grey dashed arrows = effect of social network on symptom network; Black circles = psychotic symptoms; Green circles = unidentified psychopathological symptoms important in reinforcing psychosis; Blue circles = cognitive biases important in reinforcing psychosis; Orange edges = positive symptom-to-symptom influence; Grey edges = possible edges connecting important unidentified symptoms with psychotic symptoms; Purple = neural networks; Purple arrows = effect of brain networks on symptom networks; Red = environmental exposures; Red arrows = effect of environmental exposures on neural and symptom networks; Multicoloured network = genetic network. Observed clinical course panel is adapted from Howes and Murray, 2014. Model is informed by Looijestijn et al., 2015.

6.3 Clinical and public health implications

Based on the findings from the present studies, there are several potential areas for future inquiry as well as implications for treatment and clinical care (Table 6.3). Improved engagement in treatment for psychotic disorders and HCV infection may be critical to reduce all-cause mortality among marginally housed adults facing compounding barriers to health. Providing timely and multicomponent (i.e., pharmacological and non-pharmacological) treatment that is personalized to the complex, co-occurring needs of individuals at risk for psychosis is critical for improved clinical outcomes (Breitborde, Moe, Ered, Ellman, & Bell, 2017).

Table 6.3 Summary of findings and suggested targets for treatment and future study

Findings	Suggested Treatment Targets	Future Experimental Inquiry
Psychotic disorder and hepatic fibrosis associated with active HCV infection were risk factors for premature mortality in adults younger than 55	Increased treatment engagement for psychotic disorders and HCV infection to reduce mortality risk	Test pharmacological and/or non-pharmacological treatments in their effects on reduction of premature mortality
Early-life traumatic events, past TBI, and ongoing frequent methamphetamine, powder cocaine, cannabis, or alcohol use and traumatic events were associated with dose-related increases in odds of psychosis over time in adults without schizophrenia or schizoaffective disorder	Interventions for substance use, trauma, and TBI to prevent psychosis, particularly in people without chronic psychotic illness who may be at risk for psychosis	Targeted interventions to reduce risk factor exposure, in order to test for subsequent reduction of ongoing psychosis risk in adulthood
In the dynamic psychotic symptom network, upstream symptoms included suspiciousness and unusual thought content in people with schizophrenia or schizoaffective disorder, and suspiciousness and delusions in people without these psychotic disorders	Target upstream psychotic symptoms (i.e., suspiciousness) to prevent emergent and persistent psychotic symptoms	Via targeted intervention, modify severity of unusual thought content and delusions to assess whether there is differential attenuation of emergent psychotic symptoms in persons with and without schizophrenia

Examination of specific symptom structures over time may indicate the progression of an individual's psychopathology. Modifying the underlying mechanisms of this activation cascade is a potential opportunity to halt propagation through the network (i.e., Figure 1.1). At present, psychotherapy methods that modify underlying cognitive processes, coupled with the anti-dopaminergic effects of antipsychotic medication, are effective for treating psychosis (National Collaborating Centre for Mental Health, 2014). For example, cognitive behavioural therapy and metacognitive therapy support individuals' ability to recognize and modify

cognitive biases (Menon, Balzan, Harper, & Kumar, 2017). In the previous section, we proposed that attributional bias may relate to the early downstream effects of suspiciousness activation. Perhaps by targeting the modification of this bias early in the progression of illness, we may be able to prevent the consequences of suspicious symptoms. With further information of the anatomical systems underlying these symptom networks, non-invasive neurostimulation approaches, such as rTMS mentioned above, may also be used to target these network edges and halt the progression of psychosis.

In addition to direct modification of the biological networks underlying the symptom network through therapeutic intervention, the findings from this dissertation suggest that screening for both early-life and ongoing psychosis risk factors is important for reducing psychosis risk. This includes inquiring and providing interventions for individuals who report substance use, traumatic events, head injury, and housing instability. Further, risk stratification based on the significance of these exposures over the course of an individual's life should be considered. Although we do not yet know the specific neural mechanisms by which these factors modify an individual's risk for psychosis, there is enough evidence to suggest that interventions to mitigate exposure to these identified risks should be explored as preventative and ameliorative measures. Future strategies that engage people early (Csillag et al., 2017) and strengthen the social and structural networks in which people are embedded (Valente & Pitts, 2017) may have lasting impacts on the psychosis cascade.

Furthermore, in addition to recognizing these social inequities that continue to jeopardize health and wellness, clinicians and scientists play an important role in advocating for evidence-based practice and policy (Kirmayer, Kronick, & Rousseau, 2017). In fact, it is crucial for insights from clinical or research endeavours to be translated to the policies that

scaffold the environments we live. For example, individuals living with serious mental illness, such as schizophrenia, may face immense barriers to safe and quality housing, which is further compounded by the influence and intersection of poverty and race, class, sexuality, and gender identity (Kidd et al., 2013). In addition, stigma related to misperceptions of violence (Swanson, McGinty, Fazel, & Mays, 2015) may contribute to these barriers, compounded by the actual experience of greater likelihood of victimization (Langeveld et al., 2018; Rosen et al., 2017; Stoklosa, MacGibbon, & Stoklosa, 2017). These circumstances may leave individuals with few options. In considering how to circumvent and deconstruct these physical, social, and policy barriers, we must look to the communities with lived experience, who navigate these complex systems daily (Masuda & Crabtree, 2010). Perhaps it is through the mitigation of these risk environments, the enrichment of our social systems, and the enhancement and expansion of our therapeutic options that we can alter the course of psychotic disorder from one of premature mortality to one of higher quality and longevity.

6.4   Conclusions

Despite more than a century of research dedicated to the phenomenology, neurobiology, and environmental circumstances that drive psychosis, our understanding of the causal mechanisms is limited. In order to truly understand the causes and continuation of the psychosis cascade, the complex systems within and outside of a person must be further elucidated. This dissertation outlines the longitudinal consequences, risk factors, and dynamics of psychosis among adults experiencing extreme barriers to health and wellness, and proposes potential strategies to understand this complexity from a biopsychosocial perspective. The purpose of this research is to ultimately improve the experiences of persons with psychosis and to allow people and communities to thrive.

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Appendix

Table A.1 Factors associated with missingness of PANSS assessments

Factor	β	SEβ	p
Age (years)	-0.034	0.013	0.007*
Sex	-0.235	0.290	0.421
Died (time-varying)	-0.671	0.426	0.115
Psychotic Baseline	0.046	0.226	0.838
Completed High School	0.142	0.274	0.603
SOFAS BL	0.007	0.010	0.517
THQ score by age 18	0.037	0.047	0.432
Schizophrenia/Schizoaffective Disorder	0.374	0.352	0.288
Methamphetamine Dependence	0.087	0.276	0.753
Cannabis Dependence	-0.255	0.261	0.328
Powder Cocaine Dependence	-0.400	0.278	0.150
Alcohol Dependence	0.086	0.312	0.782
Persistent Sequelae of Past TBI	-0.316	0.374	0.397
Ever homeless	0.300	0.266	0.260

PANSS = Positive and Negative Syndrome Scale; SOFAS = Social and Occupational Functioning Assessment Scale; BL = baseline; THQ = Trauma History Questionnaire; TBI = traumatic brain injury; SE = standard error of effect coefficient.

Table A.2 Assessment of reasons for discontinuation

	Whole	Intermittent	Returned from Dropout	Dead	Dropout	Non-Response
Number	6	233	12	39	77	6
Mean (SD) Number of PANSS assessments	61 (0)	48.88 (10.18)	21.67 (11.21)	27.54 (16.41)	14.90 (12.90)	0 (0)
Groups	Returnees	Returnees	Returnees	Lost	Lost	Lost

PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

Table A.3 Comparison of participants who were lost to follow-up versus those who remained in the study

Factor	Value [a]	p-value
Mean (SD) number of assessments	2432.5	<0.001
Positive Subscale PANSS BL	11380	0.874
Psychotic BL	0.429	0.513
Delusions BL	14708	0.776
Unusual Thought Content BL	14561	0.900
Hallucinatory Behaviour BL	13658	0.382
Suspiciousness BL	14367	0.877
Disorganization BL	15818	0.141
Age (years)	14854	0.473
Sex	0.184	0.668
Income	13380	0.131
Completed High School	0	1.000
SOFAS	13042	0.082
THQ>1 by age 18	0.002	0.967
THQ score by age 18	16367	0.039
THQ>1 during 1 year follow up	2.325	0.127
Schizophrenia/Schizoaffective Disorder	0.009	0.923
Methamphetamine Dependence	0	1.000
Cannabis Dependence	0.016	0.900
Powder Cocaine Dependence	0.029	0.866
Crack Cocaine Dependence	2.341	0.126
Alcohol Dependence	0.010	0.921
Persistent Sequelae of Past TBI	0.071	0.790
Ever homeless	0.075	0.784
Homeless during first year of follow up	0	1.000

BL = baseline assessment; SD = standard deviation; PANSS = positive and negative syndrome scale; SOFAS = Social and Occupational Functioning Assessment Scale; THQ = Trauma History Questionnaire; TBI = traumatic brain injury.

[a] – Test score generated by the Chi-squared test used for comparing groups by categorical variables or the Wilcoxon rank-sum test used for comparing continuous variables.

Table A.4 Comparison of participants with more or less than 50 assessments

Factor	Value [a]	p-value
Mean (SD) number of assessments	32810	<0.001
7-item Positive PANSS BL	10315	0.087
Psychotic BL	1.395	0.238
Delusions BL	14944	0.461
Unusual Thought Content BL	14826	0.356
Hallucinatory Behaviour BL	15139	0.658
Suspiciousness BL	15960	0.790
Disorganization BL	15200	0.584
Age	18610	0.033
Sex	0.052	0.819
Income	17558	0.074
Completed High School	2.319	0.128
SOFAS	17556	0.091
THQ>1 by age 18	0.960	0.327
THQ score by age 18	13508	0.044
THQ>1 during 1 year follow up	2.024	0.155
Schizophrenia/Schizoaffective Disorder	3.368	0.066
Methamphetamine Dependence	0.948	0.330
Cannabis Dependence	0.017	0.896
Powder Cocaine Dependence	0.029	0.865
Crack Cocaine Dependence	2.577	0.109
Alcohol Dependence	0.172	0679
Persistent Sequelae of Past TBI	0.062	0.803
Ever homeless	0.059	0.809
Homeless during first year of follow up	3.531	0.060

SD = standard deviation; PANSS = Positive and Negative Syndrome Scale; BL = baseline; SOFAS = Social and Occupational Functioning Assessment Scale; THQ = Trauma History Questionnaire; TBI = traumatic brain injury.

[a] – Test score generated by the Chi-squared test used for comparing groups by categorical variables or the Wilcoxon rank-sum test used for comparing continuous variables.

Table A.5 Comparison of participants who discontinued due to death or other reasons

Factor	Value [a]	p-value
Mean(SD) number of assessments	2228	<0.001
7-item Positive PANSS BL	590	0.065
Psychotic BL	1.246	0.264
Delusions BL	1370	0.367
Unusual Thought Content BL	1426	0.543
Hallucinatory Behaviour BL	1210	0.044
Suspiciousness BL	1322	0.232
Disorganization BL	1255	0.109
Age	2372	<0.001
Sex	0.044	0.834
Completed High School	1.350	0.245
SOFAS	1438	0.558
THQ>1 by age 18	0.251	0.616
THQ score by age 18	1323	0.296
THQ>1 during 1 year follow up	0.867	0.352
Schizophrenia/Schizoaffective Disorder	0.389	0.533
Methamphetamine Dependence	7.650	0.006
Cannabis Dependence	3.979	0.046
Powder Cocaine Dependence	2.094	0.148
Crack Cocaine Dependence	2.153	0.142
Alcohol Dependence	4.515	0.034
Persistent Sequelae of Past TBI	0.102	0.750
Ever homeless	7.883	0.005
Homeless during first year of follow up	0.901	0.343

SD = standard deviation; PANSS = Positive and Negative Syndrome Scale; BL = baseline; SOFAS = Social and Occupational Functioning Assessment Scale; THQ = Trauma History Questionnaire; TBI = traumatic brain injury.

[a] – Test score generated by the Chi-squared test used for comparing groups by categorical variables or the Wilcoxon rank-sum test used for comparing continuous variables.

Table A.6 Comparison of participants who were included in longitudinal analysis of psychosis risk factors

Factor	Value [a]	p-value
Positive Subscale PANSS BL	0.103	0.748
Psychotic BL	0.002	0.968
Delusions BL	1.626	0.202
Unusual Thought Content BL	2.472	0.116
Hallucinatory Behaviour BL	0.269	0.132
Suspiciousness BL	0.540	0.462
Conceptual Disorganization BL	3.587	0.058
Age (years)	6.665	0.010
Sex	0.517	0.472
Income	1.366	0.243
Completed High School	0.011	0.917
SOFAS	0.743	0.389
THQ score by age 18	3.908	0.058
THQ>1 during 1 year follow up	0.726	0.394
Methamphetamine Dependence	1.598	0.206
Cannabis Dependence	0	1.000
Powder Cocaine Dependence	3.824	0.051
Crack Cocaine Dependence	2.118	0.146
Alcohol Dependence	0.281	0.596
Persistent Sequelae of Past TBI	0.831	0.362
Ever homeless	1.111	0.574
Homeless during first year of follow up	0.096	0.757

BL = baseline assessment; SD = standard deviation; PANSS = positive and negative syndrome scale; SOFAS = Social and Occupational Functioning Assessment Scale; THQ = Trauma History Questionnaire; TBI = traumatic brain injury.

[a] – Test score generated by the Chi-squared test used for comparing groups by categorical variables or the Wilcoxon rank-sum test used for comparing continuous variables.

Table A.7 Standardized concurrent effects of time-invariant and time-varying risk factors for psychosis over one Year for the At-Risk group (N=340, 2994 observations)

	Adjusted [a]	
	OR	95% CI
Covariates		
Time	0.77	0.53, 1.10
Age	—	—
Male	2.02*	1.04, 3.93
Time-invariant factors		
Persistent sequelae of traumatic brain injury	2.83*	1.21, 6.61
THQ score by age 18	2.01*	1.14, 3.55
Time-varying factors		
Concurrent week		
Daily tobacco use	1.69	0.98, 2.90
Days using alcohol	1.49*	1.05, 2.13
Days using methamphetamine	1.81***	1.29, 2.54
Days using cannabis	1.57*	1.10, 2.25
Days using powder cocaine	1.52*	1.09, 2.12
Days using crack cocaine	—	—
Days using non-prescribed opioid	—	—
Past month		
THQ score [b]	1.62**	1.21, 2.18
Homeless	—	—
Adequate antipsychotic treatment	2.18*	1.03, 4.61
Adequate methadone therapy	—	—
Random effect (SD): Subject	2.190	
Random effect (SD): Time	1.660	
AIC	2900.6	

[a] – Adjusted for time-invariant, time-varying, and covariates included.

[b] – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥2) in the past month are reported. Quadratic effects were not significant (p>0.10).

*p<0.05, **p<0.01, ***p<0.001

Table A.8 Standardized concurrent effects of time-invariant and time-varying risk factors for psychosis over one Year for the Schizophrenia or Schizoaffective Disorder group (N=61, 452 observations)

	Adjusted [a]	
	OR	95% CI
Covariates		
Time	5.36*	1.58, 18.20
Age	—	—
Male	—	—
Time-invariant Factors		
Persistent sequelae of traumatic brain injury	—	—
THQ score prior to age 18	—	—
Time-Varying Factors		
Concurrent week		
Daily tobacco use	—	—
Days using alcohol	—	—
Days using methamphetamine	—	—
Days using cannabis	—	—
Days using powder cocaine	1.48	0.72, 3.02
Days using crack cocaine	—	—
Days using non-prescribed opioid	—	—
Past Month		
THQ score [b]		
Adequate antipsychotic treatment	0.26	0.26, 1.05
Adequate methadone therapy	—	—
Random effect (SD): Subject	2.363	
Random effect (SD): Time	1.807	
AIC	475.7	

[a] – Adjusted for all time-invariant, time-varying, and covariates included.

[b] – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥ 2) in the past month are reported. Quadratic effects were not significant ($p > 0.10$).

*$p < 0.05$

Table A.9 Relationship between psychosis and subsequent substance use and homelessness for the AR group

	Antipsychotic [a]		Methadone [a]		Days of Crack Cocaine Use [a]		Days of Opioid Use [a]		Homeless [a,b]		Daily Tobacco Use [a,b]	
	OR	95% CI	OR	95% CI	B	SD	B	SD	OR	95% CI	OR	95% CI
Psychosis												
Without covariates	1.47	0.61, 3.52	1.18	0.66, 2.12	-0.001	0.081	0.093	0.071	0.94	0.12, 7.57	2.33	0.73, 7.47
With covariates [c]	0.82	0.22, 3.04	1.33	0.70, 2.51	-0.024	0.086	0.089	0.074	—	—	—	—

[a] – N=328, 2697 observations

[b] – Adjusted model did not converge due to high prevalence of daily tobacco use (82.9%) and low prevalence of homeless episodes (4.4%) in the year of follow-up.

[c] – Covariates included time, age, sex, persistent sequelae of past traumatic brain injury, number of types of traumatic events before age 18, days of other non-prescription substance use in the subsequent week, and, in the subsequent month, adequate treatment, and any type of traumatic event.

Table A.10 Concurrent effects of time-invariant and time-varying risk factors for psychosis over one year for adults with and without psychotic disorder diagnosis [a]

| | At Risk N=278, 2427 observations | | | | Psychotic Disorder N=123, 965 observations | | | |
| | Unadjusted [b] | | Adjusted [c] | | Unadjusted [d] | | Adjusted [e] | |
Factor	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Covariates								
Time	0.94*	0.88, 1.00	0.97	0.92, 1.03	1.04	0.94, 1.16	1.06	0.96, 1.17
Age	1.00	0.97, 1.03	—	—	0.97	0.93, 1.01	—	—
Female Gender	0.69	0.34, 1.39	—	—	0.51	0.14, 1.88	—	—
Time-Invariance Factors								
Persistent Sequelae of Traumatic Brain Injury	2.72*	1.02, 7.26	3.31*	1.30, 8.44	0.56	0.14, 2.24	—	—
THQ score by age 18	1.14*	1.01, 1.29	1.13*	1.00, 1.27	1.04	0.88, 1.22	—	—
Time-Varying Factors								
Concurrent Week								
Daily Tobacco	1.83	0.99, 3.36	—	—	1.38	0.62, 3.07	—	—
Alcohol, Days	1.09	0.98, 1.21	—	—	1.05	0.89, 1.23	—	—
Methamphetamine, Days	1.17**	1.06, 1.29	1.17**	1.06, 1.29	1.31*	1.07, 1.61	1.35**	1.10, 1.66
Cannabis, Days	1.11**	1.03, 1.19	1.11**	1.04, 1.19	1.08	0.98, 1.19	—	—
Powder Cocaine, Days	1.17**	1.05, 1.30	1.17**	1.05, 1.31	1.00	0.86, 1.16	—	—
Crack Cocaine, Days	1.00	0.93, 1.08	—	—	0.97	0.87, 1.08	—	—
Opioids, Days	1.09*	1.01, 1.18	—	—	0.90	0.79, 1.03	0.87*	0.77, 0.99
Past Month								
Homeless	1.54	0.57, 4.20	—	—	4.62	0.45, 47.79	—	—
Adequate Antipsychotic	1.77	0.66, 4.78	—	—	1.23	0.64, 2.35	—	—
Adequate Methadone	0.91	0.57, 1.45	—	—	1.10	0.46, 2.60	—	—
THQ score [f]	1.70**	1.22, 2.38	1.74**	1.25, 2.43	1.09	0.57, 1.43	—	—
Random Effect (SD): Subject	2.131		2.282		1.973		1.669	
Random Effect (SD): Time	0.238		0.215		0.214		0.220	
AIC	2295.4		2261.1		930.6		923.4	

b – Adjusted for time only. Includes only participants without a psychotic disorder.

c – Adjusted for time-invariant, time-varying, and covariates included. Includes only participants without a psychotic disorder.

d – Adjusted for time only. Includes only participants with a psychotic disorder.

e – Adjusted for time-invariant, time-varying, and covariates included. Includes only participants with a psychotic disorder.

f – Linear effects of ordinal THQ scores for the number of traumatic events (0, 1, or ≥2) in the past month are reported. Quadratic effects were not significant (p>0.10).

*p<0.05, **p<0.01

Table A.11 Concurrent effects of time-invariant and time-varying risk factors for psychosis over one year for the AR group by multiple imputation (N=340, 20,740 observations)

	Adjusted	
	OR	95% CI
Covariates		
Time	0.97*	0.94, 1.00
Age	—	—
Male	1.45	0.95, 2.21
Time-invariant factors		
Persistent sequelae of traumatic brain injury [c]	2.55***	1.49, 4.34
THQ score by age 18	1.09*	1.02, 1.16
Time-varying factors		
Concurrent week		
Daily tobacco use	1.32	0.95, 1.83
Days using alcohol	1.08	1.00, 1.14
Days using methamphetamine	1.19***	1.12, 1.25
Days using cannabis	1.08***	1.04, 1.13
Days using powder cocaine	1.08*	1.01, 1.16
Days using crack cocaine	—	—
Days using non-prescribed opioid	—	—
Past month		
THQ score - linear	1.49**	1.17, 1.89
THQ score - quadratic	2.07***	1.52, 2.83
Homeless	—	—
Adequate antipsychotic treatment	2.23**	1.34, 3.69
Adequate methadone therapy	—	—
Random effect (SD): Subject	2.190	
Random effect (SD): Time	1.660	
AIC	2900.6	

*p<0.05, **p<0.01, ***p<0.001

Table A.12 Baseline and psychosis characteristics of adults living in marginal housing

	All Enrolled (N=375)		NP Group (N=169)		EP Group (N=147)		SSA Group (N=49)	
Time-invariant factors	Mean	SD	Mean	SD	Mean	SD	Mean	SD
THQ items endorsed by age 18 – no.	2.8	2.5	2.5	2.4	3.2	2.6	2.5	2.3
	N	%	N	%	N	%	N	%
Any traumatic event by age 18 (THQ18≥1)	292	80.4	121	72.5	113	77.4	25	64.1
Persistent clinical or MRI evidence of past TBI	42	11.2	17	10.1	22	15.0	2	4.1
HIV antibody positive	63	17.6	28	17.2	29	20.3	4	8.3
HCV antibody positive	244	68.4	119	73.0	92	66.2	26	55.3
HCV qPCR positive	180	51.3	92	56.8	68	49.6	19	37.5
Time-varying factors	N	%	N	%	N	%	N	%
Homeless ≥1 time over 1-year	40	10.7	16	9.5	14	9.5	8	16.3
Any traumatic event over 1-year (rTHQ score ≥1)	316	88.0	144	87.3	126	88.7	43	87.7
Non-prescription substance use over 1-year								
Tobacco (any daily use)	339	90.4	150	88.8	136	92.5	43	87.8
Alcohol	282	75.2	129	76.3	111	75.5	39	79.6
Methamphetamine	165	44.0	64	37.9	67	45.6	31	63.3
Cannabis	259	69.1	111	65.7	102	69.4	44	89.8
Powder Cocaine	152	40.5	75	44.4	56	38.1	19	38.8
Crack Cocaine	272	72.5	126	74.6	108	73.5	37	75.5
Opioids	199	53.1	96	56.8	80	54.4	20	40.8
Any prescribed substance use over 1-year								
Methadone maintenance therapy	152	40.5	84	49.7	58	39.5	9	18.4
Adequate antipsychotic treatment	70	18.7	12	7.1	20	13.6	38	77.6
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Types of non-prescribed substances used in past week – no.	2.4	1.2	2.4	1.2	2.5	1.3	2.4	1.4
Alcohol use – days in past week	3.1	2.3	2.8	2.2	3.6	2.4	2.4	2.0
Methamphetamine use – days in past week	3.4	2.3	3.6	2.3	3.3	2.4	3.1	2.0
Cannabis use – days in past week	4.8	2.5	4.8	2.5	4.9	2.4	4.6	2.5
Powder cocaine use – days in past week	4.1	2.5	4.0	2.5	4.4	2.6	4.1	2.3
Crack cocaine use – days in past week	4.3	2.5	4.3	2.5	4.4	2.5	3.9	2.4
Opioid use – days in past week	4.9	2.5	4.7	2.5	5.3	2.3	4.3	2.5

[a] – Participants with psychosis experiencing only one symptom type above threshold over one year.

[b] – Participants with psychosis experiencing more than one symptom type above threshold over one year, and/or they experienced more than one symptom type above threshold concurrently.

Table A.13 Dynamic Network edge weight differences between psychosis risk groups

Symptom		SSA vs. EP		SSA vs. NP		EP vs. NP	
Lagged	Current	Difference	p-value	Difference	p-value	Difference	p-value
Del	Del	-0.0787	0.2004	-0.0496	0.4030	0.0291	0.4972
CD	Del	-0.0419	0.2312	-0.0504	0.1484	-0.0084	0.7316
Hal	Del	0.0332	0.3440	0.0164	0.6012	-0.0167	0.5216
Sus	Del	0.0298	0.4460	0.0244	0.5312	-0.0054	0.8268
UTC	Del	0.0565	0.2308	0.0991	0.0300	0.0425	0.1676
Del	CD	-0.1034	0.0424	-0.0757	0.1264	-0.0103	0.2968
CD	CD	0.0075	0.8064	0.0155	0.6700	0.0278	0.4276
Hal	CD	-0.0444	0.2544	-0.0204	0.6152	0.0080	0.7980
Sus	CD	0.0503	0.1732	0.0165	0.6512	0.0239	0.3356
UTC	CD	0.0222	0.6264	0.0255	0.5968	-0.0337	0.1840
Del	Hal	-0.0755	0.1620	-0.0683	0.2032	0.0072	0.8348
CD	Hal	-0.1174	0.0060	-0.0936	0.0212	0.0238	0.4144
Hal	Hal	0.0596	0.2084	0.0125	0.7356	-0.0471	0.1728
Sus	Hal	-0.0020	0.9856	0.0361	0.3344	0.0381	0.1556
UTC	Hal	0.0783	0.0660	0.0893	0.0300	0.0109	0.6740
Del	Sus	-0.0291	0.5432	0.0006	0.9760	0.0297	0.3436
CD	Sus	-0.0225	0.5752	-0.0286	0.4616	-0.0061	0.8080
Hal	Sus	0.0154	0.6956	0.0163	0.6670	0.0009	0.9848
Sus	Sus	-0.0042	0.9824	0.0683	0.1230	0.0725	0.0200
UTC	Sus	0.0608	0.1712	0.0446	0.3180	-0.0162	0.5568
Del	UTC	-0.0942	0.0620	-0.1000	0.0436	-0.0058	0.8532
CD	UTC	-0.0127	0.7032	-0.0313	0.3740	-0.0186	0.4728
Hal	UTC	0.0178	0.6136	0.0376	0.2856	0.0198	0.4248
Sus	UTC	0.0557	0.1364	0.0206	0.5952	-0.0352	0.1528
UTC	UTC	0.0779	0.1440	0.1955	0.0000	0.1176	0.0000

SSA group = schizophrenia or schizoaffective disorder diagnosis; EP group = expressing psychosis at study entry without schizophrenia or schizoaffective disorder diagnosis; NP = not expressing psychosis at study entry; Del = delusions; CD = conceptual disorganization; Hal = hallucinatory behavior; Sus = suspiciousness or persecution; UTC = unusual thought content.

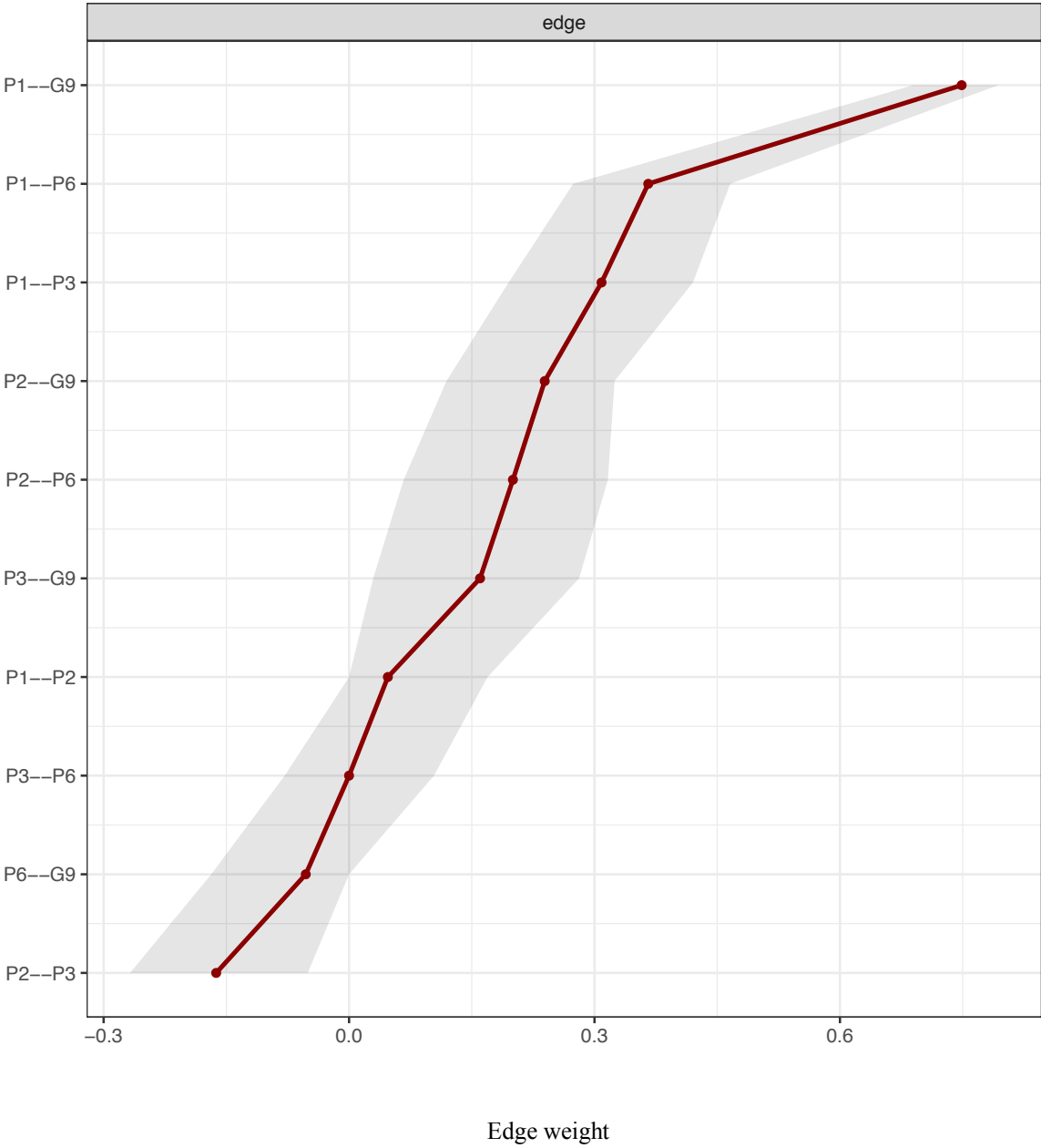**Figure A.1 Person-Mean Network edges 95% confidence interval estimates for entire sample**

Edge weight

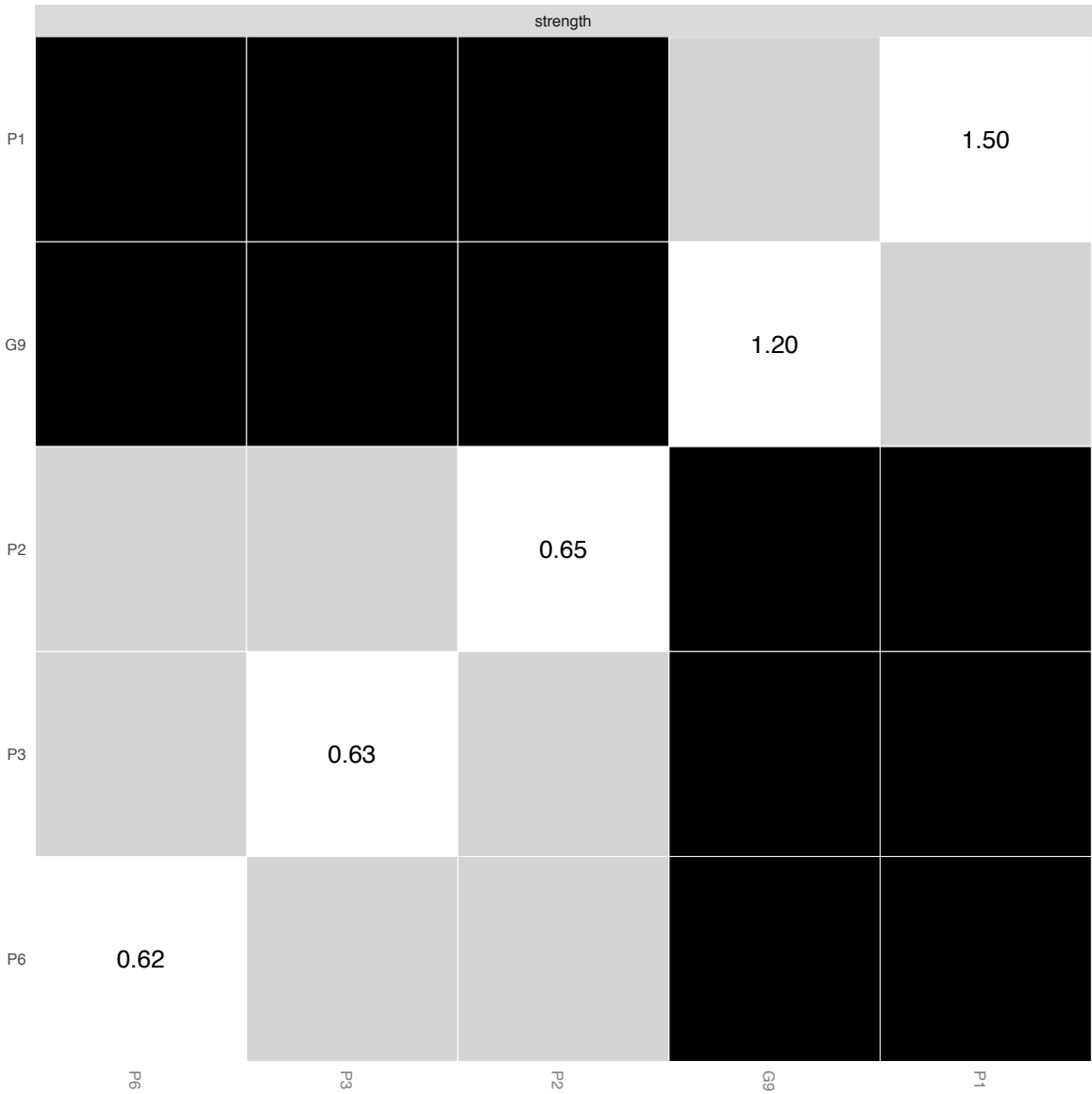**Figure A.2 Comparison of Person-Mean Network symptom centrality measures**

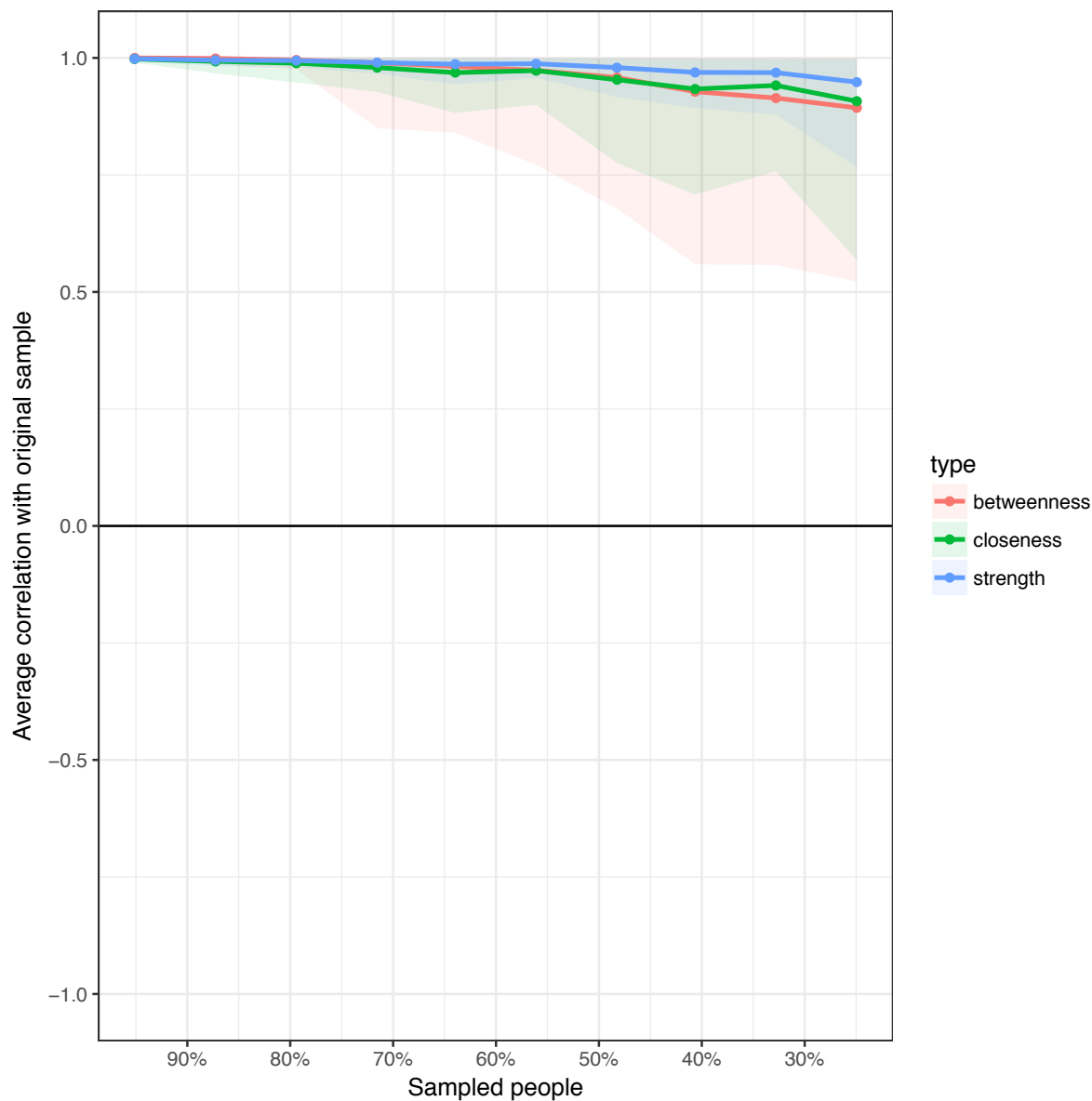**Figure A.3 Person-Mean Network centrality measure stability**

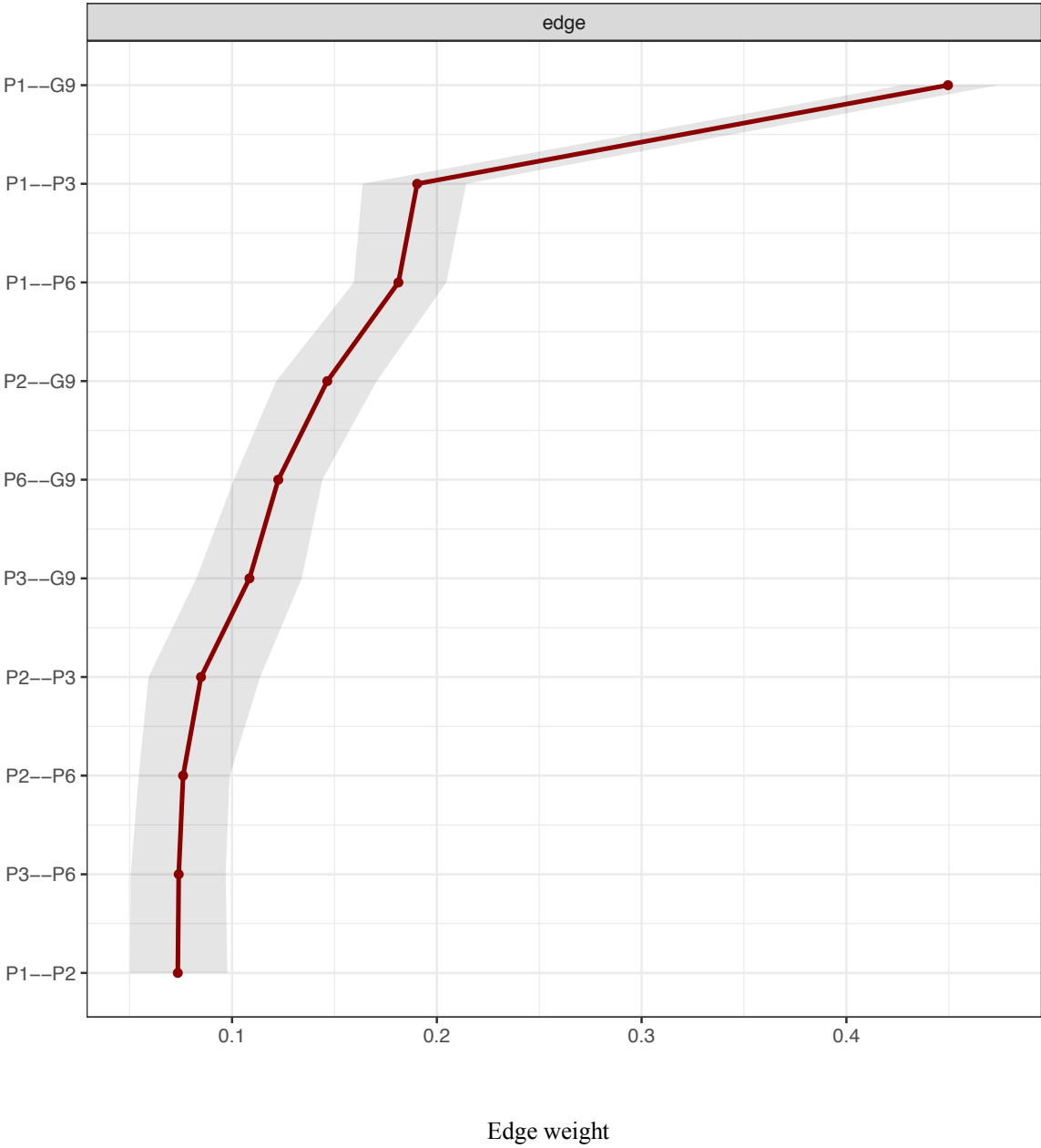**Figure A.4 Contemporaneous Network edge weight estimates for whole sample**

Edge weight

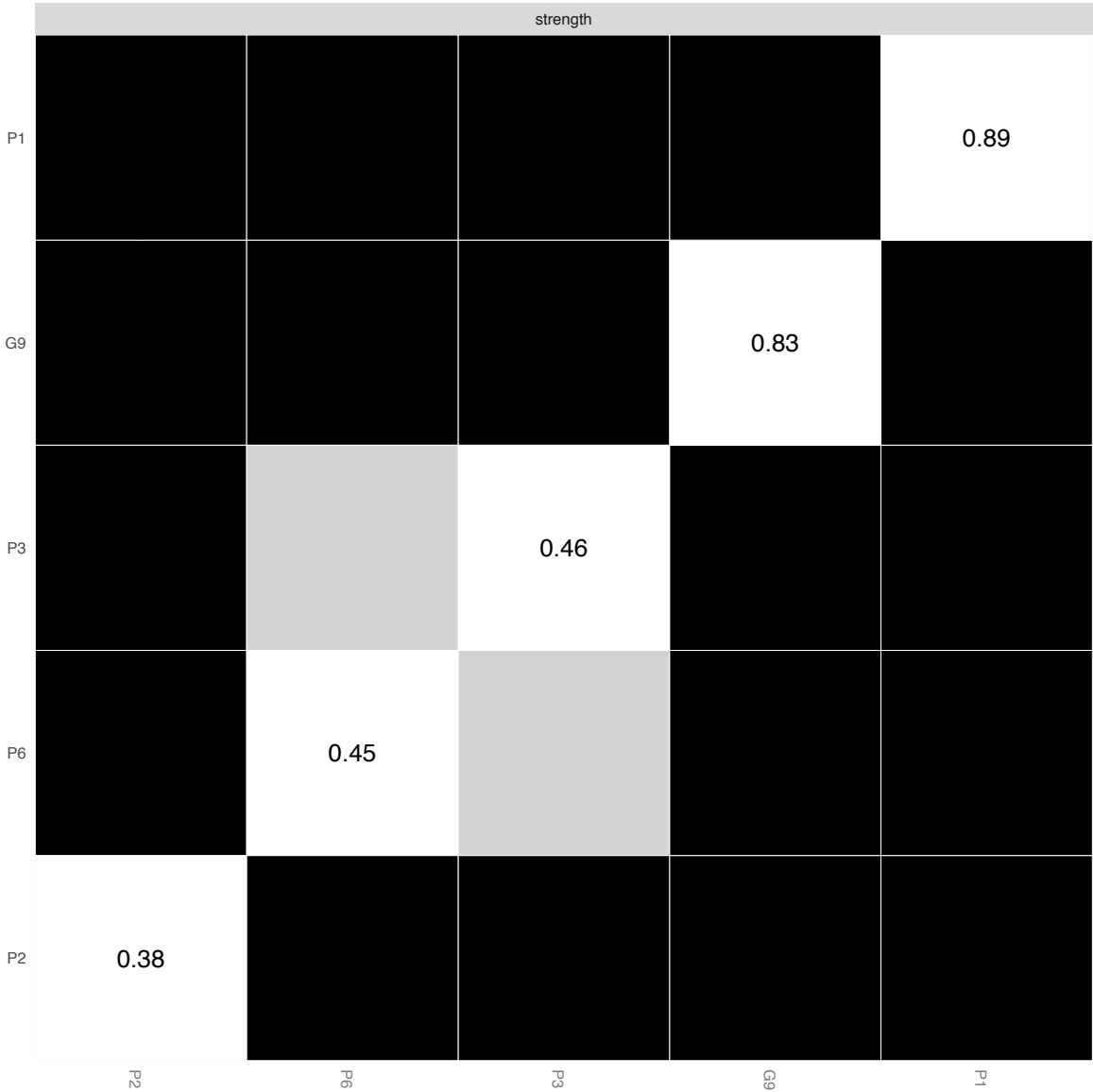**Figure A.5 Contemporaneous Network: comparison of centrality measures for whole sample**
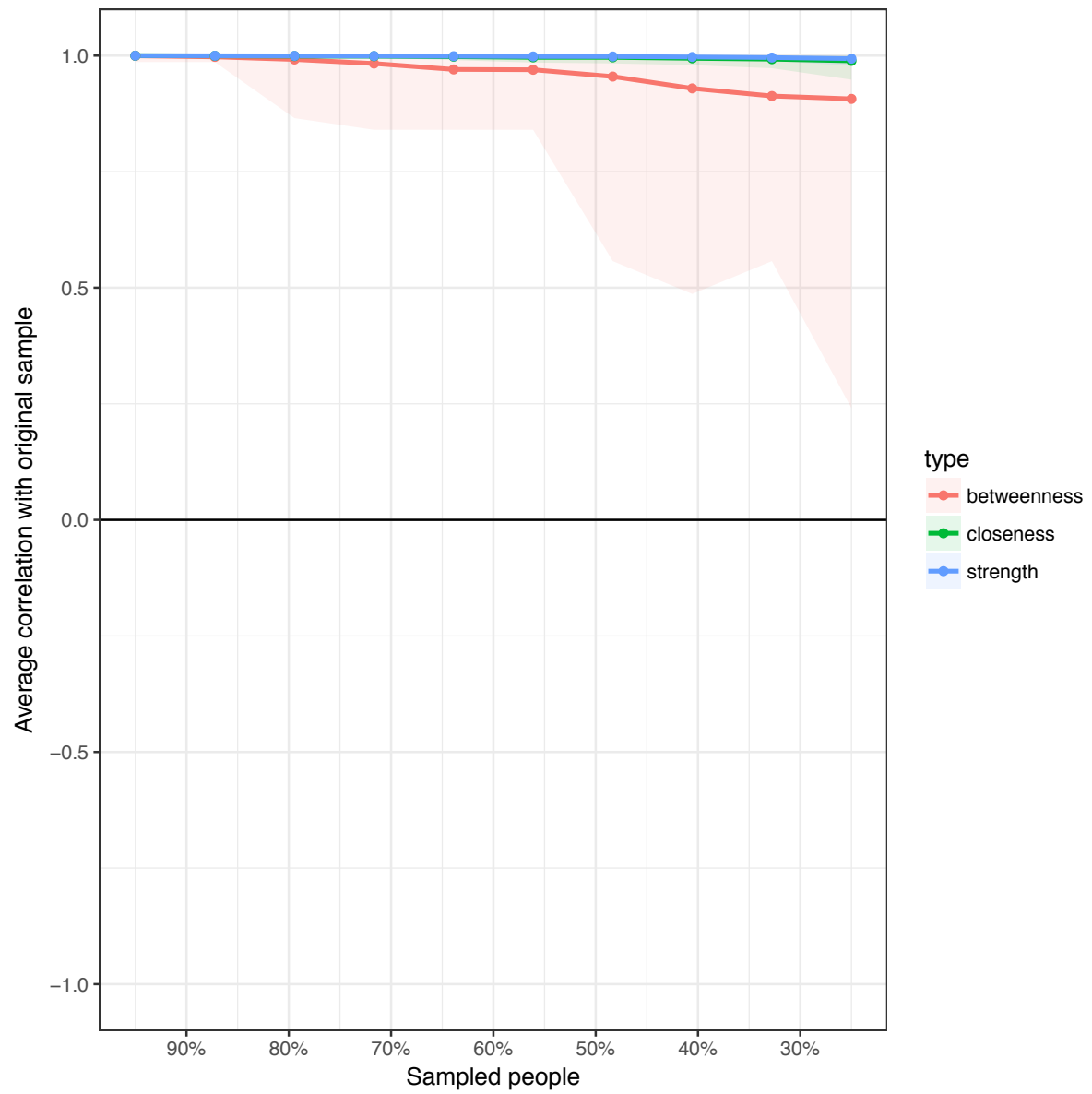
Figure A.6 Contemporaneous Network centrality stability

Figure A.7 Person-Mean Network edge weight estimation for SSA Group
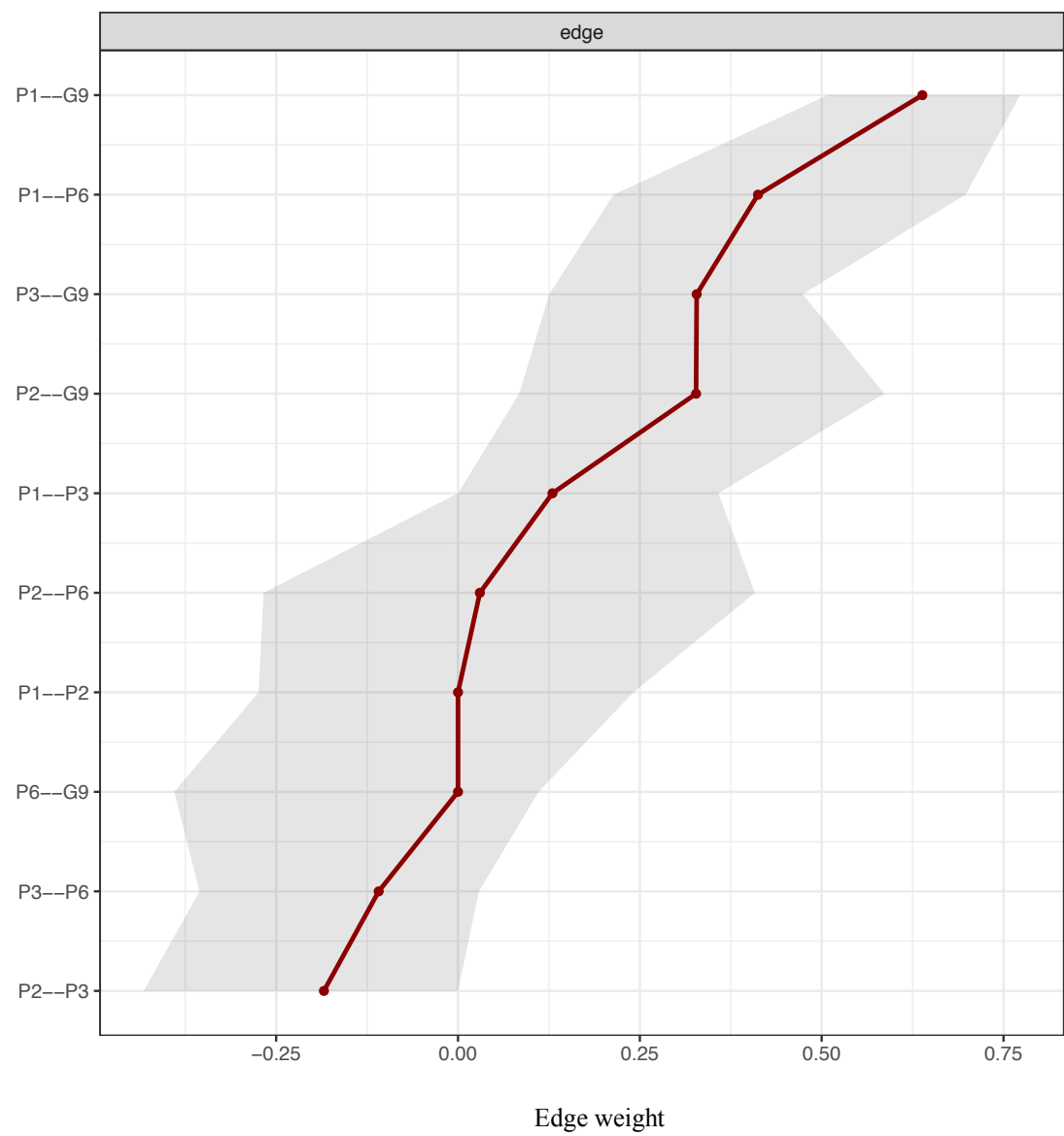
Figure A.8 Person-Mean Network edge weight estimation for EP Group
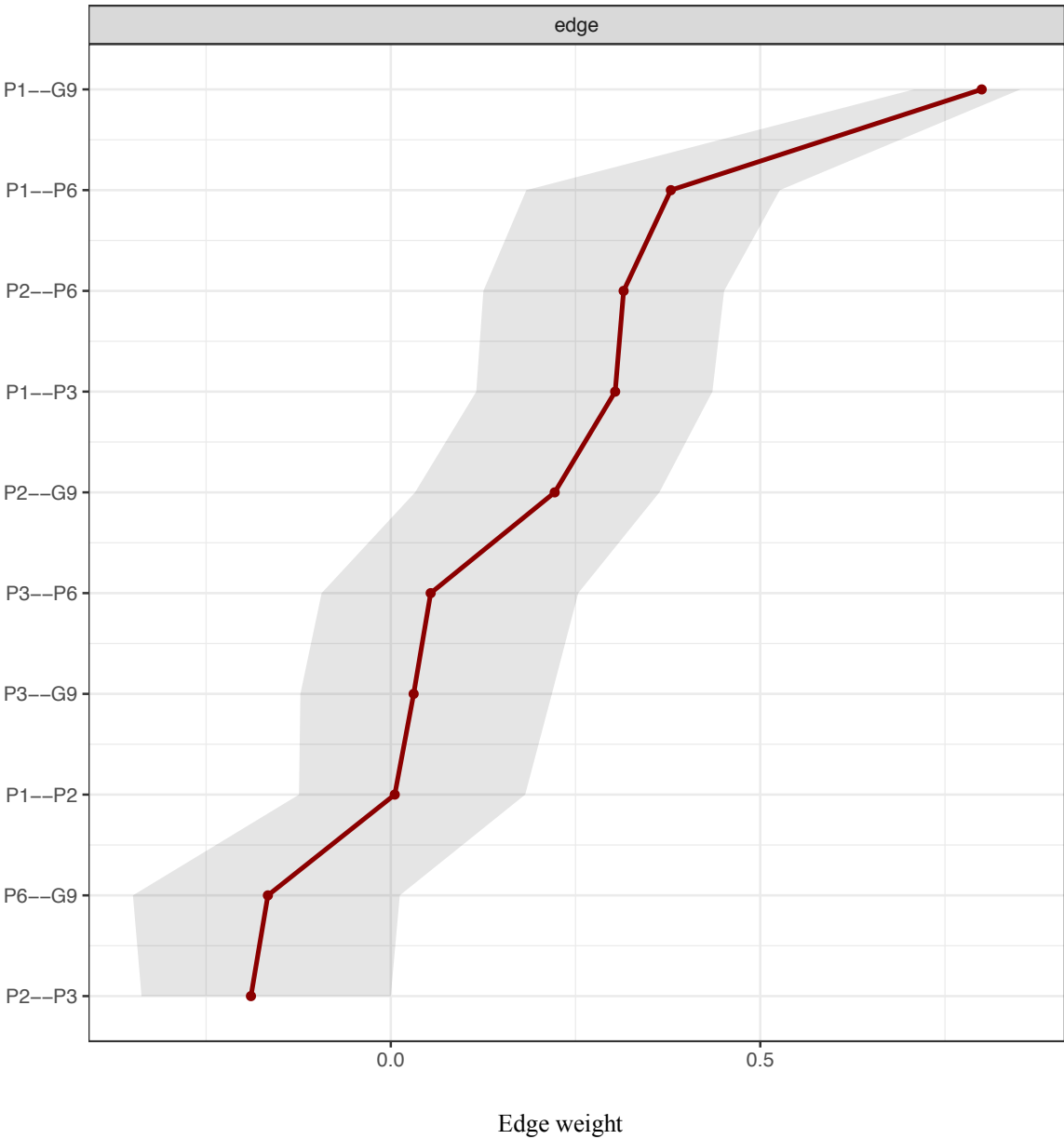
Edge weight

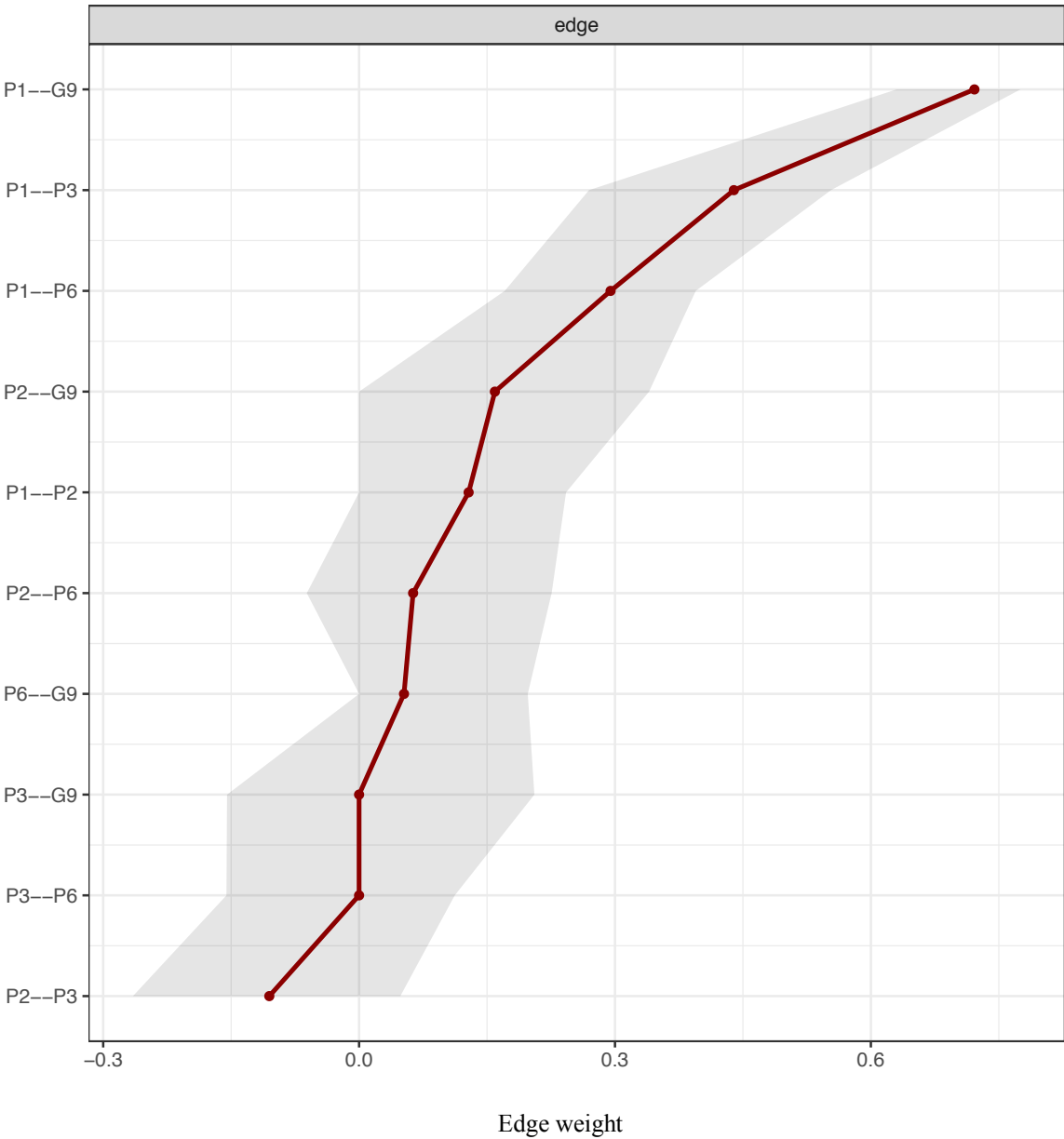**Figure A.9 Person-Mean Network edge weight estimation for NP Group**

Edge weight

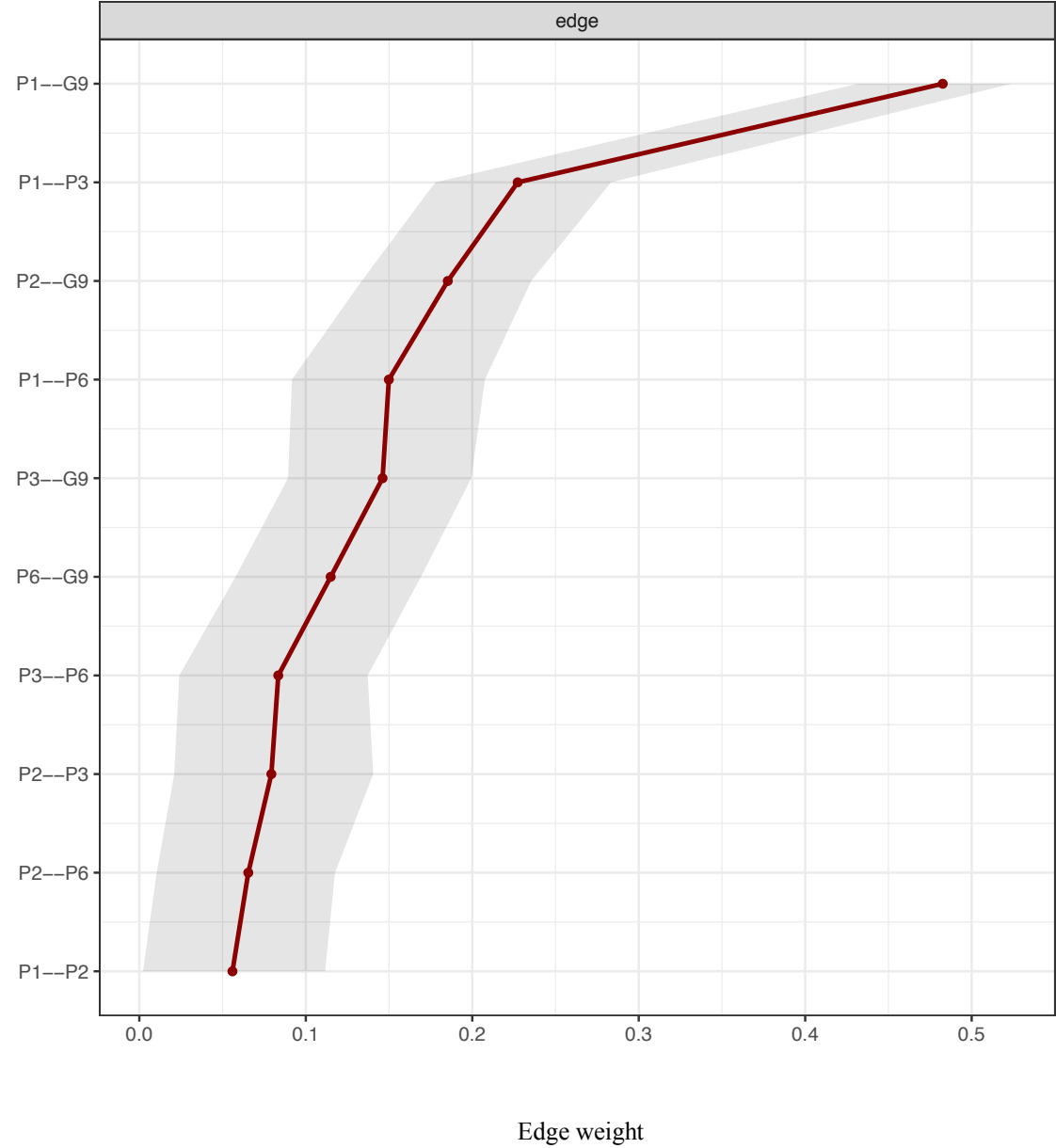**Figure A.10 Contemporaneous Network edge weight estimation for SSA Group**

Edge weight

Figure A.11 Contemporaneous Network edge weight estimation for EP Group
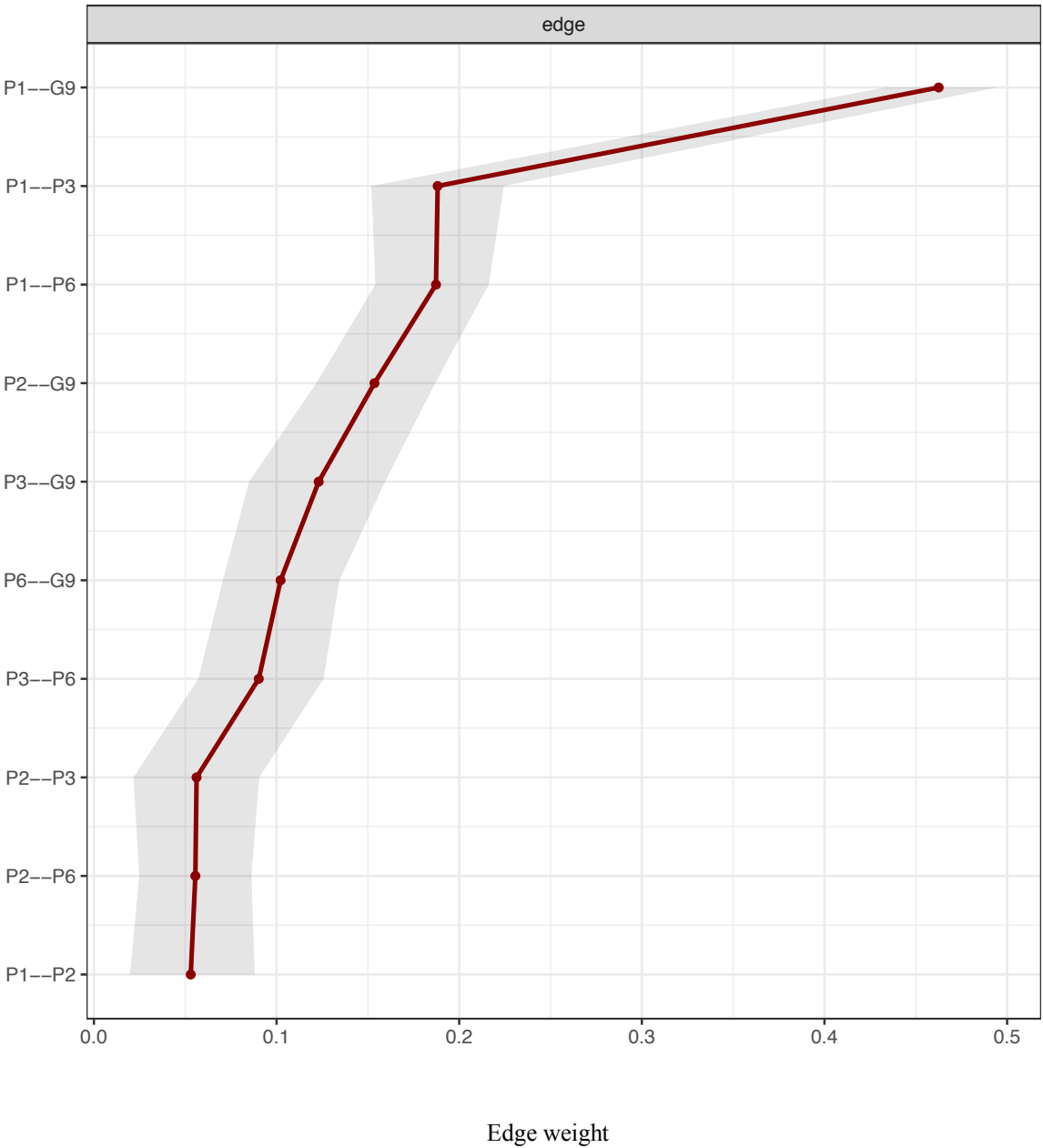

Edge weight

Figure A.12 Contemporaneous Network edge weight estimation for NP Group

Edge weight