6-20-2022 9:00 AM

Sex Differences in the Clinical Presentation of Early Psychosis in a Primary Care Setting

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

Abstract

Psychotic disorders can be variable in clinical presentation, and there may be differences by sex. The objective of this thesis was to explore sex differences in the clinical presentation of early psychosis in the context of primary care. Our systematic review and meta-analysis found that men experienced more negative symptoms and had a higher prevalence of substance use issues, whereas women experienced more depressive symptoms and had higher functioning. Our electronic medical record analysis from primary care found that positive symptoms and substance use were less prevalent in the medical records of women. We also found that visits by women were more likely to be assigned a diagnosis of depression or anxiety, personality disorder, psychological distress, and other mental or behavioural disorders, and less likely to be assigned a diagnosis of substance use. Further research is needed to better understand sex differences in clinical presentation in the primary care context.

Keywords

sex differences, gender differences, first-episode psychosis, primary care, family physicians, electronic medical records

Summary for Lay Audience

Psychotic disorders are a group of severe mental illnesses that vary in clinical presentation, which can include behaviours, symptoms, and course of illness. Psychosis is characterized by impaired cognition or perception, which may present as positive symptoms (i.e., hallucinations, delusions), negative symptoms (i.e., reduction in language, motivation, pleasure), disorganized thoughts and behaviour, and impairments in functioning. It is well-established that early intervention for psychotic disorders can help improve short- and long-term outcomes, and primary care is often the first point of contact for young people experiencing first-episode or early psychosis. Prior research indicates that men and women differ in their clinical presentation of early psychosis, but little is known about these differences as they present to primary care. Given the vital role that family physicians and primary care services play in the recognition of early psychosis, understanding how men and women present differently in these settings is important. The overall aim of this thesis was to explore sex differences in the clinical presentation of early psychosis in the context of primary care. Our first study compiled findings from 35 studies examining sex differences in symptoms of early psychosis, and found that men experienced more negative symptoms and had a higher prevalence of substance use, whereas women experienced more depressive symptoms and had higher functioning. All of the studies included in our review were from specialized mental health services, and none examined sex differences in clinical presentation from a primary care context. Our next study used health administrative data, linked with electronic medical records from primary care in Ontario from 2005-2015. We found that one year preceding the first diagnosis of psychotic disorder, positive symptoms and substance use were less prevalent in the medical records of women. We also found that visits by women were more likely to be assigned a diagnosis of depression or anxiety, personality disorder, psychological distress, and other mental or behavioural disorders, and less likely to be assigned a diagnosis of substance use. Larger studies that incorporate administrative and patient-level data are needed to better understand sex differences in the clinical presentation of early psychosis in the context of primary care.

Co-Authorship Statement

This thesis includes two integrated articles, which have been or will be submitted for publication to a peer-reviewed journal. The co-authorship details for each article are presented below.

Chapter 3: Carter B, Wootten J, Archie S, Terry AL, & Anderson KK. Sex and Gender Differences in Symptoms of Early Psychosis: A Systematic Review and Meta-Analysis. Submitted for publication to an academic journal.

Brooke Carter was involved in the conception and design of the study, in the study screening, in the extraction of data and risk of bias assessment, in the data analysis, interpretation of data, and in writing the first and subsequent drafts of the paper. Jared Wootten was involved in the study screening, in the extraction of data and risk of bias assessment, and in the critical revision of the article. Drs. Suzanne Archie and Amanda L. Terry were involved in critical revision of the article. Dr. Kelly K. Anderson was involved in the conception and design of the study, in the interpretation of data, in writing drafts of the paper, and in the critical revision of the article.

Chapter 4: Carter B, Rodrigues R, Reid J, Archie S, Terry AL, Palaniyappan L, MacDougall A, Voineskos A, Hameed Jan S, Jaakkimainen L, Candido E, Chen B, Sawh N, & Anderson KK. Sex Differences in the Clinical Presentation of Early Psychosis in a Primary Care Setting.

Brooke Carter was involved in the conception and design of the study, in the cleaning, coding and statistical analysis of data, and in writing the first and subsequent drafts of the paper. Rebecca Rodrigues was involved in the conception and design of the study, in the validation of abstraction, and in the critical revision of the article. Jennifer Reid was involved in the conception and design of the study, and in the data cleaning and analysis. Dr. Suzanne Archie was involved in abstraction and in the critical revision of the article. Dr. Amanda L. Terry was involved in the critical revision of the article. Dr. Lena Palaniyappan, Dr. Arlene MacDougall, Dr. Aristotle Voinseskos, Dr. Saadia Hameed Jan, Dr. Liisa Jaakkimainen, Elisa Candido, Branson Chen, and Dr. Neo Sawh were involved in the abstraction process.

Dr. Kelly K. Anderson was involved in the conception and design of the study, in the interpretation of data, in writing drafts of the paper, and in the critical revision of the article.

Acknowledgments

I would first like to thank my amazing supervisor, Dr. Kelly Anderson for her continued support through my time as a graduate student in epidemiology and biostatistics. I cannot express how grateful I am to have worked under your supervision on this project, for the confidence you have helped me gain, and for all the opportunities you have provided me with to grow professionally. Thank you for all your patience, words of encouragement, and guidance through this journey.

I would also like to thank my committee members, Dr. Amanda L. Terry, and Dr. Suzanne Archie for their guidance and feedback on my thesis project. I sincerely appreciate your insightful revisions and am deeply grateful for your support.

I would like to extend my thanks to the staff at ICES for giving me the opportunity to use the data for this project, and to my colleagues in the Department of Epidemiology and Biostatistics for the additional insights and support.

Lastly, I would like to thank my friends and family for their unwavering encouragement through this journey. I am so grateful for the love, support, advice, and laughter you have all given to me over the past two years, and over my whole life, which has enabled me to achieve my goals. I truly could not have done it without you.

I would like to acknowledge the Western Graduate Research Scholarship for funding this thesis project.

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List of Abbreviations

FEP – First-Episode Psychosis

FP – Family Physician

DUP – Duration of Untreated Psychosis

EPI – Early Psychosis Intervention

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

CINAHL – Cumulative Index to Nursing and Allied Health Literature

UHR – Ultra-High Risk

CHR – Clinical High-Risk

SMD – Standardized Mean Difference

CI – Confidence Interval

PR – Prevalence Ratio

RR – Risk Ratio

DSM – Diagnostic and Statistical Manual of Mental Disorders

ICD – International Classification of Diseases

LGBTQ+ – Lesbian, Gay, Bisexual, Transgender, Queer, and Others

SCZ – Schizophrenia

SCZA – Schizoaffective Disorder

NAP – Non-Affective Psychosis

BD – Bipolar Disorder

MDD – Major Depressive Disorder

SFD – Schizophreniform Disorder

BPD – Brief Psychotic Disorder

DD – Delusional Disorder

AP – Affective Psychosis

PDN – Psychotic Disorder Not Otherwise Specified

DIP – Drug-Induced Psychosis

MD – Mood Disorders

AD – Anxiety Disorders

PD – Personality Disorders

FEPM – First-Episode Psychotic Mania

PANSS – Positive and Negative Syndrome Scale

SAPS – Scale for the Assessment of Positive Symptoms

CGI-S – The Clinical Global Impression Severity Scale

BPRS – Brief Psychiatric Rating Scale

SANS – Scale for the Assessment of Negative Symptoms

CDSS – The Calgary Depression Scale

FCQ – Frankfurt Complaint Questionnaire

GAF – Global Assessment of Functioning Scale

SOFAS – Social and Occupational Functioning Assessment Scale

RECORD – REporting of studies Conducted using Observational Routinely-collected health Data

ICES – Institute for Clinical Evaluative Sciences

EMR – Electronic Medical Record

RPDB – Registered Persons Database

OHIP – Ontario Health Insurance Program

NACRS – National Ambulatory Care Reporting System

OMHRS – Ontario Mental Health Reporting System

DAD – Discharge Abstract Database

NOS – Not Otherwise Specified

PPV – Positive Predictive Value

NPV – Negative Predictive Value

EMRPC – Electronic Medical Records Primary Care

PCCL – Early Detection Primary Care Checklist

ADHD – Attention-Deficit/Hyperactivity Disorder

ADG – Aggregated Diagnosis Groups

SD – Standard Deviation

VIF – Variance Inflation Factor

OR – Odds Ratio

Chapter 1

1 Overview of Thesis

Psychotic disorders typically have an onset in adolescence or young-adulthood, and can vary greatly in clinical presentation, including symptom profile and course of illness.[1,2] The sex and gender of the person experiencing early psychosis may play a role in this variability, which may arise from a complex interaction of biological and psychosocial factors.[3]

Although there is evidence that young men and women with early psychosis differ in their clinical presentation, there is limited research on how these differences present outside of specialized settings. Given the important role that primary care and family physicians play in early psychosis recognition and intervention, having a thorough understanding of these sex differences is a clinical imperative.[4]

The overall goal of this thesis was to explore sex differences in the clinical presentation of early psychosis in the context of primary care. Our systematic review and meta-analysis (Chapter 3) synthesized previous literature on sex differences in symptoms of early psychosis and found that men with early psychosis experienced more severe negative symptoms (SMD=-0.15, 95%CI=-0.21, -0.09), whereas women experienced more severe depressive symptoms (SMD=0.21, 95%CI=0.14,0.27) and had higher functioning (SMD=0.16, 95%CI=0.10,0.23). We also found that women with early psychosis had a lower prevalence of substance use issues than men (PR=0.65, 95%CI=0.61,0.69). All of the studies included in our review were from specialized mental health services, and none examined clinical presentation in the context of primary care. We then assessed sex differences in the clinical presentation of early psychosis in a primary care setting using an analysis of electronic medical records (EMR) in Ontario, Canada from 2005 to 2015 (Chapter 4). We found that one year preceding the first diagnosis of psychotic disorder, positive symptoms (PR=0.76, 95%CI:0.58,0.98) and substance use (PR=0.54, 95%CI:0.40,0.72) were less prevalent in the medical records of women. We did not find any other sex differences in symptoms at presentation to primary care. We also found that

visits by women were more likely to be assigned a diagnosis of depression or anxiety (PR=1.18, 95%CI:1.00,1.38), personality disorder (PR=5.49, 95%CI:1.22,24.62), psychological distress (PR=11.29, 95%CI:1.23,103.91) and other mental or behavioural disorders (PR=3.49, 95%CI:1.14,10.66), and less likely to be assigned a diagnosis of substance use, alcohol use, or addiction (PR=0.33, 95%CI:0.13,0.87).

1.1 Role of the Student

In Chapter 2, detailed background information on psychotic disorders, primary care, and sex and gender is provided. Chapter 3 is a systematic review and meta-analysis of prior literature examining sex differences in symptoms of early psychosis. In Chapter 4, we conducted an analysis using EMRs to examine sex differences in the clinical presentation of early psychosis in a primary care setting. Chapter 5 synthesizes findings from the two integrated articles and concludes the thesis.

I collaborated with Dr. Kelly Anderson to identify the research question and objectives for this thesis, which were further refined through consultation with supervisory committee members, Drs. Amanda L. Terry, and Suzanne Archie. I wrote all chapters of this thesis as partial fulfillment of requirements for the Master of Science degree in Epidemiology and Biostatistics. Feedback was incorporated from Drs. Anderson, Terry, and Archie.

I conducted the search for the systematic review, extracted data, and performed and interpreted results of the meta-analysis (Chapter 3). Feedback for this chapter was also sought from Jared Wootten who was a secondary reviewer, in addition to members of the supervisory committee (Drs. Anderson, Terry, and Archie).

Chapter 4 used EMRs linked with health administrative data which was housed at ICES. In collaboration with Dr. Anderson, the statistical methods for this chapter were developed. Coding and cleaning of data, and interpretation of results were conducted with feedback from Rebecca Rodrigues, Drs. Anderson, Terry, and Archie.

Chapter 2

2 Background

2.1 Psychotic Disorders

This section will provide an overview of psychotic disorders and first-episode psychosis, including the definition, prevalence, and impact, as well as risk factors for developing psychosis.

2.1.1 Psychotic Disorders and First-Episode Psychosis

Psychotic disorders are a group of illnesses characterized by five domains of symptoms, including hallucinations, delusions, disorganized thought, disorganized or abnormal motor behaviour, and negative symptoms.[5] Psychotic disorders affect about 24 million people worldwide, and have an average lifetime prevalence of up to 1%.[6] In Ontario alone, there are nearly 5000 new cases of psychotic disorder every year.[7] These disorders are chronic and among the most debilitating illnesses worldwide,[8] with about 9% of patients experiencing lasting symptoms, and 43% experiencing symptoms that increase in severity, with no periods of complete remission.[2] There are many negative outcomes associated with experiencing psychosis, including a shorter lifespan,[3] and an increased risk of suicide, substance abuse, homelessness, and violence compared to the general population.[1] The first onset of psychotic symptoms, termed first-episode psychosis (FEP), often occurs in adolescence or young-adulthood, and can be variable in presentation.[2] The level of insight of patients experiencing FEP can also be quite variable, ranging from having full awareness of symptoms and illness, to having no insight at all.[2]

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), psychotic disorders are distinguished from one another by the duration of symptoms, symptom profile, the relationship between psychotic symptoms and mood disturbances, and by cause.[1] Psychotic disorders can be classified further as being affective or non-affective, where affective psychoses are marked by severe mood disturbances.[9] Disorders such as bipolar disorder, and major depression with psychotic features are considered to be affective, whereas schizophrenia, schizoaffective disorder, and other schizophreniform

disorders are considered to be non-affective.[9] The age of onset of different psychotic disorders may also differ accordingly. Symptom onset of common psychotic disorders – such as schizophrenia, bipolar disorder, and depression with psychotic symptoms – often occurs during adolescence and early adulthood, whereas the onset of delusional disorders often occurs in middle age.[1] The course of illness for psychotic disorders often evolve through stages of premorbid, prodromal, syndromal, progressive, and chronic; however, the duration, symptom presentation, and severity of the disorder can be unpredictable.[1]

2.1.2 Impact of FEP

Psychotic disorders have a great impact on both the person experiencing FEP, their families and carers, and the healthcare system.[2] Symptoms of psychosis, such as hallucinations, delusions, or depression, can cause disruptions to the lives of people with FEP, resulting in trauma, feelings of hopelessness, and an increased risk of suicide.[2] Suicide is one of the leading causes of death among people with schizophrenia, of which the risk is particularly high within the first six years after symptom onset.[2] The general population has a suicide risk of about 0.5-1%, whereas the risk for people experiencing psychotic disorders is estimated to be 15-25 fold higher.[6] Additionally, people with FEP are more likely to have substance use disorders, engage in violent behaviour,[10] and use tobacco at some point in their lives, putting their overall health at risk.[2] The risk of mortality from cardiovascular disease, respiratory disease, tuberculosis, cancer, and other infectious diseases is higher in people with psychotic disorders relative to people from the general population.[11]

FEP often presents in adolescence, a formative time when young people are making a transition to independence and establishing their own peer networks.[2] The occurrence of psychotic symptoms during this time can cause disruptions to this important development, and makes it difficult to maintain social connections and to achieve educational and career goals.[2] Although there is a great need for social support during this time, behaviours of people experiencing FEP (such as aggression or self-isolation), or the stigma surrounding mental illness may cause friends to withdraw.[2] Adolescents with FEP are also more likely

to engage in risk-taking behaviours, such as unprotected sex or substance use, further disrupting healthy relationships.[2]

In addition to the distress that experiencing the illness may cause, the treatment of psychosis can also have a traumatic impact on the patient, including the experience of involuntary hospitalizations, seclusions, and the use of restraints.[2] In a Canadian study conducted in 2004, patients with schizophrenia alone generated about 356,000 inmate days in federal and provincial jails and prisons,[6] which highlights the negative pathways many people with psychotic disorders experience. Psychotic disorders also have an impact on the families and carers of those experiencing the illness. The burden of care often falls on the families of those affected, causing emotional distress related to the patient's behaviour and negative symptoms.[2]

The financial impact of psychotic disorders is profound, including the burden placed on the Canadian healthcare system. In Canada, psychotic disorders account for 0.5% to 3.5% of national healthcare expenses every year.[6] Schizophrenia alone accounts for over 32,500 hospital stays and nearly 2.4 million days in the hospital annually, with a total cost amounting in $2.02 billion per year.[6] Furthermore, many people experiencing psychotic disorders are unable to work, resulting in high rates of unemployment and demand for government assistance.[6]

2.1.3 Risk Factors for Psychosis

A multitude of factors can increase the risk of developing psychotic disorders over the lifetime, including both genetic and environmental factors.[12] Genetic predisposition is known to have an effect on the risk of developing a psychotic disorder, especially when one or both parents have psychotic disorders.[13] Prior research has indicated that rates of psychotic disorders are 10 to 15 times higher among the siblings and parents of those with psychotic disorders, compared to the general population.[1]

This genetic predisposition may be necessary, but not sufficient for a psychotic disorder to develop; thus, the gene-environment interaction is most important to consider when

examining the cause of such disorders.[12] In the crucial developmental time before and shortly after birth, the body may be exposed to a variety of environmental risk factors that cause vulnerabilities to psychosis later in life.[12] It was found that in combination with genetic susceptibility to psychosis, obstetric complications or birth trauma contribute to the causation of psychosis.[12] Other factors, such as gestational infection, maternal stress, diabetes, and smoking, and childhood environment may also contribute to increased psychosis risk among offspring.[12] Childhood trauma is an important and well-known risk factor for developing a psychotic disorder, and can have an impact of symptoms in the early course of illness.[14]

Later in life, factors that can be considered etiological may also modify the course of illness after onset, such as drug abuse and dopamine desensitization.[12] Additionally, both migration and urbanicity have been identified as risk factors for psychotic disorders. A meta-analysis found that immigrants had a significantly increased risk of schizophrenia compared to native inhabitants, which may be due to excess stress and social adversity.[12] Prior research has indicated that urban and rural populations have different lifetime risks for psychotic disorders, with exposure to urban residence increasing the risk for later psychotic illness.[15] It has been speculated that this difference may be due to urban environmental factors that increases the vulnerability to psychosis.[15]

2.2 Primary Care

This section will provide an overview on primary care, including pathways to mental health care, the impact of early intervention, and the role primary care and the family physician plays in early psychosis.

2.2.1 Pathways to Mental Health Care

Prior research suggests that early intervention for psychotic disorders is a clinical imperative to reducing patient suffering and improving clinical and functional outcomes over the course of illness.[16] This has led to a great interest in the ways people experiencing psychosis access help, known as the pathway to care. The pathway to care for patients

experiencing FEP can be quite variable and complex, including the use of services at multiple levels of care.[17] Emergency department visits and inpatient admissions are quite common in these pathways.[18] The help-seeking behaviour of the patient and/or family members, accessibility of mental health services, and the response of health services at each level of care all have an impact on the pathway to care.[19] The process of help-seeking for mental health is outlined by the Goldberg and Huxley model, in which there are five levels with four "filters" between them deciding progression to the next level of care.[18] Factors that impact progression to the next level of care include patient characteristics, clinical features, physician characteristics, and systemic barriers.[18] The community is the first level in the model where psychotic symptoms may emerge. At the second level, a subset of these people with psychotic symptoms may seek help from a family physician (FP), where some may be identified as having a psychotic disorder, comprising the third level.[18] Patients in this level may then be referred to mental health services for the fourth level, and those that present to these services and are admitted to inpatient care comprise the final level.[18]

The duration of untreated psychosis (DUP) has a significant impact on the course of illness and long-term outcomes, and is affected by the pathway to care.[17] Longer DUP is associated with more severe positive and negative symptoms, reduced quality of life, and a lower probability of entering disease remission.[19] There are multiple factors that may act as barriers on the pathway to care in FEP, prolonging the DUP. Treatment delays may be due to affected individuals not seeking help early in their illness, or the difficulties faced by health-professionals in identifying early signs and symptoms of psychosis.[2] Factors that may influence help-seeking of those experiencing FEP include self-stigma and lack of knowledge surrounding symptom recognition and resources for psychotic disorders.[17] These barriers can lead to treatment delays, resulting in a longer DUP and poor physical and functional outcomes.[20] It has been reported that family members or significant others may play an important role in this initial help-seeking and maintenance of contact with services.[17] For persons experiencing FEP, family involvement can help decrease the probability of involuntary and negative care pathways, such as involuntary hospitalizations or involvement of police.[17] Public education on the signs and symptoms of psychosis, as

well as the resources available to those experiencing it is important for early recognition and treatment of the illness.[17]

2.2.2 Impact of Early Intervention

Early psychosis intervention (EPI) programs focus on the detection of psychotic symptoms and treatment in the early stages of illness for young people 14 to 35 years old.[20] These programs combine multiple interventions, such as pharmacologic and psychosocial, in a comprehensive team-based model of care.[21] There are over 50 EPI programs across Ontario, in which most participate in a government-funded Early Psychosis Intervention Ontario Network (EPION) to deliver standardized, high-quality care.[21] The main goals of EPI programs are to improve early access to services, promote recovery from the first psychotic episode, and to reduce the risk of future epsiodes.[22] Patients may be referred to these services by family physicians, psychiatrists, or access these programs on their own or with help from family. Short- and long-term outcomes of FEP can be improved by early intervention, where distress associated with psychotic symptoms can be reduced and risk of suicide is decreased.[2] Prior literature has indicated that outcomes in the early stage of illness can be predictive of illness severity in the later course of illness, emphasizing the importance of receiving treatment as early as possible.[2] Patient anxiety and distress from FEP can be mitigated by a shorter DUP, which reduces the chance of relapse.[2] Additionally, EPI services may be more cost-effective than standard psychiatric care,[23] largely due to its impacts on use of high-cost acute mental health services. For example, an Ontario study published in 2018 by Anderson et al. indicated that users of EPI services had more rapid access to psychiatric services, fewer emergency department visits, and lower rates of mortality for all causes.[20] Users of these early intervention services, however; had higher rates of hospitalizations and a lower rate of visits to primary care.[20] In another study, it was found that men with first onset psychotic disorder were more likely than women to be represented in EPI services.[24]

2.2.3 The Role of Primary Care

Although EPI programs have shown success and have provided a more optimistic outlook for young people experiencing FEP, primary care is often the first point of contact, with FPs playing an important role in the pathway to care and help-seeking.[4,25] Prior research has indicated that people experiencing FEP have a higher prevalence of primary care contacts for mental, physical, and preventative health compared to those of the general population.[26] In Ontario, about 30% of young people with FEP are first diagnosed by a FP, with an additional 30% receiving their diagnosis in secondary or tertiary care but having contact with a FP for mental health reasons in the 6-month period before the first diagnosis of psychosis.[18]

Evidence suggests that FPs may have difficulty identifying psychotic symptoms due to symptom subtlety or a lack of knowledge on psychosis, resulting in multiple contact points for FEP patients.[19] To recognize a psychotic disorder, FPs must obtain knowledge of family, medical, and cultural history of the patient, as these factors may provide clues to diagnosis.[4] Prior research on FPs' knowledge of early psychosis found that FPs are likely to identify more overt symptoms of psychosis such as hallucinations, delusions, and bizarre behaviour, but under-identify less obvious symptoms such as functional decline.[27] This is important because evidence also suggests that patients with these insidious symptoms are more likely to present to primary care.[27] Treatment for FEP patients can be delayed if FPs do not recognize more subtle symptoms of early psychosis, such as sleep disturbances, depression, and social withdrawal, which may be attributed to other conditions or normal adolescent behaviours.[2] Having contact with a FP, however, may have a strong impact on health service use patterns, reduce negative care pathways, and the DUP.[28]

Results from a population-based study in Quebec showed that people who were in contact with a FP prior to a first diagnosis of psychotic disorder had almost three times more contacts than those who were not.[29] Additionally, individuals with primary care contact had lower odds of contact with emergency services and lower odds of receiving a diagnosis of psychotic disorder in the emergency department.[29] Contacts with primary care were associated with longer referral delays to specialized care, which may suggest difficulties with symptom recognition or attempts made by the FP to manage psychotic symptoms

within primary care.[29] Taken together, these findings indicate that improvements in primary care access may help to decrease the use of emergency services for early psychotic disorders, although further training may be needed for FPs to recognize these symptoms and efficiently refer patients to specialized care.[29]

2.3 The Role of Sex and Gender

This section will provide a summary of the definitions of sex and gender, how this relates to psychosis, and the previous findings on sex and gender differences in early psychosis, including incidence, age of onset, clinical presentation, and service-use.

2.3.1 Sex and Gender

Sex and gender are terms that are often entangled in research, with difficulties in separating exactly what makes up a person's sex or gender. The biological aspects of a person, such as chromosomes, anatomy, genes, and hormones are constituted by sex, whereas gender is used to describe the nonphysiological components, such as a social labels/roles and cultural norms that are shaped by a person's environment and experience.[30] Gender may include both the attributions of others, as well as for one's self, which makes up gender identity.[30] Aspects of both sex and gender can contribute to a person's behaviour, with biological, social, and psychological factors contributing to sex and gender differences.[3]

Sex and gender are vastly important in mental health research for understanding and treating mental disorders, although there is criticism surrounding the dichotomous use of sex and gender.[31] There are many grey areas of sex and gender that binary definitions of these variables are unable to address. Differences exist in the epidemiology of mental disorders that can be attributed to sex.[31] For example, hormone levels can play a role in the clinical presentation of mental disorders and the effectiveness of medications, which differ by sex.[31] Furthermore, gender roles and social factors for men and women can help explain differences in prognosis, risk factors, protective factors, and treatment outcomes of various mental disorders.[31] There is significant overlap between qualities of sex and gender, which makes it difficult to disentangle them. Although both sex and gender play an important role

in how mental illness is experienced, these variables are often neglected in mental health research. This approach may result in biased findings, which can contribute to sub-optimal care and an inadequate understanding of how men and women experience mental illness differently.[31] More specifically, an understanding of sex and gender differences in psychotic disorders is important for early detection and intervention. Clinicians should understand how to recognize psychotic disorders, and how to tailor interventions specifically for men and women experiencing them.

2.3.2 Sex/Gender and Psychosis

Men and women experiencing FEP may differ in many ways, including in their age of onset, clinical presentation, help-seeking, and service-use behaviours. These differences may arise from a complex interaction of biological factors that make up sex, and psychosocial factors that make up gender.[32] Sex differences in early psychosis have been previously studied, but findings are often inconsistent across studies and are limited to patients specialized settings. Differences in treatment uptake and engagement may contribute to the evolution of sex differences in early psychosis, and sex differences that exist specifically in FEP remain a gap in the literature.

Prior studies have found that the lifetime risk of psychotic disorders is approximately the same for men and women, suggesting that sex does not impact disease risk, but instead modulates the timing of onset.[33] The most replicated finding regarding sex differences in early psychosis is the difference in age of onset.[34] The first psychotic episode often occurs earlier in life for men than women, with the average age of onset for men being 18 to 25 years, whereas women have an average age of onset of 25 to 35 years.[34] The incidence curves for age of onset also differ between men and women – evidence suggests that women have two peaks of onset, with the first peak in adolescence or early adulthood, then a second peak much later in life.[34]

These findings may be explained by the protective role that estrogens play in the development of a psychotic disorder, called the sex hormone hypothesis.[35] This theory

posits that from puberty to menopause, high estrogen levels protect women to some extent from the onset of psychotic symptoms; and when these hormone levels decline the protective factor is weakened.[35] The lower levels of estrogen in these time frames may lead to the presentation of psychotic symptoms, and a diagnosis of a psychotic disorder.[33] Evidence also suggests that rates of relapse in women with psychotic disorders are reduced at times of high estrogen levels, such as during pregnancy.[36] Elevated estrogen levels may also act as a protective factor against psychotic symptoms in men, but elevated testosterone levels have been linked to more severe psychiatric symptoms.[36] In contrast to the previous finding on testosterone, it has also been found that men with psychotic disorders have significantly lower levels of both estrogen and testosterone than healthy controls.[36]

2.3.3 Clinical Presentation

The clinical presentation of early psychosis can be quite variable, and sex or gender can help explain some of this variability. The clinical presentation in men is often characterized by a greater severity in negative and cognitive symptoms, and a higher frequency of comorbid substance use, whereas the clinical presentation in women is often characterized by the presence of affective symptoms.[37] Women are also more likely to have higher levels of functioning than men, particularly better social functioning and educational attainment.[38] This finding, however, may be partially explained by the difference in age of onset between men and women.[38] Because men tend to start experiencing psychotic symptoms earlier in life than women, their social networks are not yet established, and social functioning is therefore less favourable.[38] Although women may function better than men at baseline, some studies have also found that suicidal behaviours are more common in women than men.[38–40]

Due to the differences in symptoms experienced by men and women, women are more frequently diagnosed with schizoaffective disorder or other non-schizophrenia diagnoses,[37] whereas men are more frequently diagnosed with schizophrenia and schizotypal disorder.[38] Furthermore, women with emerging psychosis are likely to be initially misdiagnosed as

having a personality disorder, anxiety, post-traumatic stress disorder (PTSD), or depression.[37]

Although it is often thought that women with psychotic disorders experience a milder course of illness than men over the lifetime, recent findings suggest that the recovery rates are similar among men and women.[37] Furthermore, premorbid and baseline characteristics may appear to be better in women in the first three years of illness onset, but the clinical and functional outcomes in both sexes seem to balance after an average period of ten years.[37] Women are often underrepresented in in studies, and not all studies analyze results by sex.[37] This could reflect an underestimation of illness severity in women and highlight the need to better understand how men and women are differently affected by psychotic disorders.

2.3.4 Help-Seeking and Service-Use

Help-seeking behaviours differ among men and women, with a previous study from Fridgen and colleagues finding that among people experiencing FEP, women requested help almost twice as often as men.[25] This may be explained by a greater willingness of women to trust health professionals, or a greater openness toward mental health care.[25] As psychotic disorders often first present in adolescence, it is also important to consider factors that contribute to help-seeking and service-use during this time. In a study conducted on help-seeking for depression in early adolescents, it was found that older age and female gender contributes to the promotion of help-seeking behaviour.[41] Furthermore, it was found that recognition of stress, openness, recognition of help from adults, higher household income, parental divorce, and previous parental service use promoted help-seeking behaviours in adolescents.[41] It was hypothesized that gender norms surrounding problem solving between boys and girls inhibits boys from engaging in help-seeking behaviour. These findings may be applicable to adolescent girls and boys experiencing psychosis and may account for some of the sex differences seen in service-use. Although women may be more likely to seek help for mental health reasons than men, evidence suggests that the DUP may be longer in women compared to men.[37] This could be explained by misdiagnosis

of women with FEP, delaying the initiation of antipsychotic treatment.[37] In regards to sex differences in service-use, a Canadian study from 2004 found that men with schizophrenia had more hospitalizations than females in both acute and non-acute hospitals.[6] Further research is needed to fully understand sex differences in help-seeking and service-use for young people experiencing FEP.

2.4 Study Rationale and Objectives

Previous findings indicate that sex and gender differences in symptoms of psychosis exist, and that these differences are also present in the early stages or the first episode of psychosis.[32,34] There has been extensive research conducted on sex differences in symptoms of psychotic disorders, particularly schizophrenia, and how these differences present to specialized care settings.[14,42–44] The role that primary care plays in the identification and treatment of psychotic disorders is well-established,[19,26,29] but many aspects of psychosis in primary care remain unexplored. There is a paucity of research on how symptoms of early psychosis present in the primary care context, and how men and women differ in this clinical presentation.

2.4.1 Study Objectives

There is a need to evaluate sex differences in symptoms of early psychosis in the context of primary care. The overall objective of this thesis was to explore sex differences in the clinical presentation of early psychosis in the context of primary care. This was achieved through a systematic review and meta-analysis of the prior literature (Chapter 3) to identify what was already known about sex and gender differences in symptoms of early psychosis. Additionally, an analysis of the electronic medical records of FEP cases in primary care was conducted (Chapter 4) to identify and describe the sex differences in symptoms of early psychosis in a primary care context. To meet these objectives, our thesis aimed to answer the following questions:

1. Is there a significant difference between early psychosis symptoms for men and women? (Chapter 3)
2. What are the differences in clinical presentation (i.e., signs and symptoms) of early psychosis between men and women in a primary care context? (Chapter 4)
3. What are the sex differences in diagnoses made by the family physician for mental health related encounters one year prior to the first diagnosis of a psychotic disorder? (Chapter 4)
4. Do clinical and sociodemographic factors affect these sex differences in clinical presentation and diagnoses? (Chapter 4)

We hypothesized that men would present with more negative symptoms and substance use than women, whereas women would present with more general symptoms and display higher levels of functioning than men. We hope that findings from this study will facilitate a greater awareness of psychotic symptoms at the primary care level and help to clarify how men and women differ in these symptoms, as well as how sex differences in clinical presentation may differ from acute care settings. This information will assist FPs in their ability to detect psychotic disorders and to facilitate early intervention. In turn, clinical and functional outcomes of young people experiencing early psychosis in Ontario may be improved.

Chapter 3

3 Sex and Gender Differences in Symptoms of Early Psychosis: A Systematic Review and Meta-Analysis

3.1 Abstract

Background: First-episode psychosis (FEP) can be quite variable in clinical presentation, and both sex and gender may account for some of this variability. Prior literature on sex or gender differences in symptoms of psychosis have been inconclusive, and a comprehensive summary of evidence on the early course of illness is lacking. The objective of this study was to conduct a systematic review and meta-analysis of the literature to summarize prior evidence on the sex and gender differences in the symptoms of early psychosis. ***Methods:*** We conducted an electronic database search (MEDLINE, Scopus, PsycINFO and CINAHL) from 1990 to present to identify quantitative studies focused on sex or gender differences in the symptoms of early psychosis. We used random effects models to compute pooled standardized mean differences (SMD) and risk ratios (RR), with 95% confidence intervals (CI), for a range of symptoms. ***Results:*** Thirty-five studies met the inclusion criteria for the systematic review, and 30 studies were included in the meta-analysis. All studies examined sex differences. Men experienced more severe negative symptoms (SMD=-0.15, 95%CI=-0.21,-0.09), whereas women experienced more severe depressive symptoms (SMD=0.21, 95%CI=0.14,0.27) and had higher functioning (SMD=0.16, 95%CI=0.10,0.23). Women also had a lower prevalence of substance use issues (RR=0.65, 95%CI=0.61,0.69). ***Conclusions:*** Symptoms of early psychosis varied between men and women; however, we were limited in our ability to differentiate between biological sex and gender factors. These findings may help to inform early detection and intervention efforts to better account for sex and gender differences in early psychosis presentation.

Keywords Sex differences**;** Psychosis; Symptoms; First-episode psychosis

3.2 Background

Psychotic disorders are characterized by dysfunction in cognition or perception,[1] which may include the presence of positive symptoms (i.e. hallucinations, delusions), negative symptoms (i.e. anhedonia, social withdrawal), disorganized thoughts and behaviour, and impairments in functioning.[45] The symptoms of psychosis exist on a continuum with normal mental states, with each person's clinical presentation varying in severity along this continuum, defined by the level, number, and duration of symptoms.[5]

The first occurrence of psychotic symptoms, known as first-episode psychosis (FEP), usually presents in adolescence or early adulthood,[2] and the clinical presentation at onset may be quite variable.[34] Early intervention for psychotic disorders can optimize the course of illness and clinical prognosis of those affected, as a shorter duration of untreated psychosis is associated with a lower number of hospitalizations and a reduced risk of relapse.[45] In order for the duration of untreated psychosis to be minimized, clinicians must be able to identify psychotic symptoms in their varying presentations.

The sex and gender of a person experiencing FEP or early psychosis may account for some of the heterogeneity in clinical presentation, with respect to age of onset, symptom profile, level of functioning, and course of illness.[34] Sex is comprised of the biological aspects of a person, such as chromosomes, anatomy, genes, and hormones; whereas gender is used to describe the nonphysiological components of a person, such as social labels/roles and cultural norms that are shaped by a person's environment and experience.[30] Differences in age of onset of FEP have been well-documented in the literature, with the average age of onset of psychotic symptoms being higher in women than in men.[34] This imbalance has been attributed to the difference in timing of puberty between boys and girls, and estradiol being a protective hormone for psychotic disorders in both men and women.[46] This may also explain the second peak in psychosis incidence for women around menopause, when levels of these hormones decrease.[47] Similarly, some studies have found that estrogen may modulate the severity of psychotic symptoms, resulting in a lower disease severity in women.[48] Other studies have indicated that men experiencing psychotic symptoms have lower estradiol and testosterone levels compared to healthy controls, further indicating the

protective effect of estradiol in men.[36,47] Gender norms and behaviours may also play a role in symptom variation between males and females with psychotic disorders. For example, women tend to be more socially integrated, whereas men's social behaviours are more passive and dysfunctional.[49] In general, women tend to be more introspective toward their mental health, and are more willing to seek help than men.[25,50] These gender roles may contribute to differential help-seeking behaviours between men and women, and willingness to comply with treatment plans.[49] Adolescent girls are more likely to seek help on their own, while the parents of boys are more likely to seek help for them.[51] This behaviour carries over into adulthood, where women seek help for mental health reasons almost twice as often as men.[25] Men are also more likely to engage in substance use than women, and gender-related factors may have an impact on this difference.[49,52] For example, there is more societal acceptance surrounding men that use cannabis than women,[52] and peer pressure to use cannabis is elevated in men compared to women.[53,54] These factors may influence the risk of psychotic disorders and impact clinical presentation.[55] Sex and gender are often entangled in research, and it is difficult to differentiate the pathways between biological and social aspects that lead to differences in clinical presentation.

Sex and gender differences in symptoms of psychotic disorders have been studied extensively, although findings are often inconsistent across studies. It has been reported that men tend to experience more negative symptoms – including apathy, poverty of speech and thought, and social withdrawal – whereas affective symptoms, such as depression and mania, tend to occur more frequently in women.[32] Additionally, men often experience more social isolation, have poorer social functioning, and have more substance use than women with psychotic disorders.[32] Conversely, many other studies have concluded that there were no significant differences in symptoms by sex or gender.[34]

Prior literature on sex or gender differences in the symptoms of psychotic disorders are inconclusive, and have been limited by small sample sizes and methodological differences between studies.[32] A comprehensive summary of the evidence base on symptoms in the early course of illness is lacking. The aim of this study was to systematically review the literature on sex or gender differences in symptoms of early psychosis, and to quantify any observed differences. The findings from this systematic review and meta-analysis may be

used to profile the clinical presentation of FEP or early psychosis more accurately by sex and gender to support early identification and intervention for psychotic disorders.

3.3 Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guidelines (Appendix 3A).[56]

3.3.1 Search Strategy and Study Selection

We searched four electronic databases – including Medline (ProQuest), Scopus, PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL) – for studies related to sex or gender differences in symptoms of early psychosis or FEP. No limits were placed on language, and we restricted the search to studies published after 1990 to represent the current standard of care for treating psychosis.[57] The specific search terms used for each database can be found in Appendix 3B. Results from the search were imported into the Covidence systematic review management platform (www.covidence.org) for article screening. Grey literature searching was done using Google Scholar and Open Grey, and unpublished work was searched in a pre-print database (medRxiv). Additional studies were identified using forward and backward citation tracing of included articles.

We included studies if the sample consisted of first episode or early psychosis patients, defined by all definitions of FEP as reported by the original studies, which can vary across studies.[58] Both affective and non-affective psychotic disorders were included, and no restrictions were placed on the age of the sample. To be included in the review, studies must have compared symptoms of psychosis or other features of clinical presentation by sex or gender. We included any type of observational study that provided quantitative results, or interventional studies that provided baseline symptom differences by sex or gender. We excluded studies that included people with chronic psychotic disorders, non-psychotic mental disorders, and ultra-high risk (UHR), clinical high-risk patients (CHR), or prodromal patients. Other experimental or interventional studies, case-reports, case-series, and qualitative studies were also excluded from the review. See Appendix 3C for full inclusion and exclusion criteria.

Level one title and abstract screening was performed by one reviewer (BC) in Covidence, and level two full-text screening was performed by two independent reviewers (BC, JW), applying the inclusion and exclusion criteria. Reasons for exclusion were recorded in Covidence, and discrepancies between reviewers were handled by group discussion and consensus.

3.3.2 Data Extraction and Risk of Bias Assessment

Data extraction was completed by one reviewer, then verified by a second independent reviewer, using a form created and pilot-tested in Microsoft Excel using the Cochrane guidelines.[59] Three main categories for extraction were: study characteristics (e.g., study design, source of sample) sample characteristics (e.g., sample size, mean age of sample), and study findings (e.g., symptom scores by sex).

Risk of bias of each study was assessed by two independent reviewers using the "Tools to Assess Risk of Bias in Cohort Studies" by the CLARITY group at McMaster University,[60] which fit the needs of this review topic. To ensure comprehensive assessment of other non-cohort studies, two items from the "Risk of Bias for Cross-Sectional Surveys" created by the CLARITY group were also used. The domains assessed in the risk of bias tools included: representativeness of the sample, selection of cohorts, assessment of exposure/outcome, measurement and analysis of confounding factors, and missing data. For each study, each item was rated as low, intermediate, or high risk of bias.

3.3.3 Data Synthesis

We synthesized the data qualitatively by summarizing sex/gender differences in the most common symptoms of psychosis across the included studies.

Stata version 17.0 [61] was used to conduct all meta-analyses. The *metan* command was used with random effect models to account for study heterogeneity.[62] Meta-analyses were conducted for each symptom (with subgroup analyses by symptom measurement tool), which included each study that reported means and standard deviations on the symptom of interest. Studies that reported medians and interquartile ranges were not included in the

meta-analysis. We computed the standardized mean difference (SMD) in symptoms between men and women, with 95% confidence intervals (CI). Statistical heterogeneity was assessed using the I^2 statistic, where a value of less than 25% is considered to be low heterogeneity, 50% is considered to be moderate heterogeneity, and greater than 75% is considered to be high heterogeneity.[62] For symptoms where SMD was not applicable (i.e. binary variable), prevalence ratios (PR) for cross-sectional studies and risk ratios (RR) for cohort studies were pooled.[63]

3.4 Results

3.4.1 Study Selection and Characteristics

Our electronic database search yielded 4,955 studies published after 1990. Through a further search of pre-print databases, grey literature databases, and forward and backward citation tracing, 13 additional studies were obtained. After removing duplicates, 4,436 records were screened based on title and abstract, in which we excluded 4,120 studies. The remaining 316 studies underwent full-text screening by two reviewers. Of those, 35 studies were retained for qualitative synthesis, and 30 studies included data suitable for a meta-analysis. Of the studies chosen for inclusion in the systematic review and meta-analysis, all looked at the sex of participants as a main exposure, with no studies measuring gender. The PRISMA diagram outlining numbers and reasons for exclusion is presented in Figure 3.1.

Table 3.1 shows the study and sample characteristics of the 35 included studies. Seven studies were published in North America, 18 studies were published in Europe, one study was published in Africa, five studies were published in Asia, and the remaining four studies were published in Australia. Most included studies used either a cohort (n=25) or cross-sectional (n=7) design, and most (n=18) recruited the sample from early psychosis intervention services. Other studies recruited their samples from other outpatient mental health services (n=3), inpatient services (n=9), a combination of inpatient and outpatient sources (n=3), or used health administrative data (n=2). The sample size of included studies ranged from 39 to 3,350 patients, with males comprising a median of 64.2% (range = 33%-

80%) of the sample across studies. Most studies used standardized interviews to establish a diagnosis of psychotic disorder, with the majority using DSM-IV or ICD-10 diagnostic criteria. Listed diagnoses included schizophrenia, schizoaffective disorder, schizophreniform disorder, drug-induced psychosis, bipolar disorder, major depressive disorder with psychotic features, affective psychosis with mood-incongruent delusions, brief psychotic episode, non-affective psychosis, and psychotic disorder not otherwise specified. A summary of the tools used to measure symptoms in each study can be found in Appendix 3D.

Figure 3.1: PRISMA diagram of study identification and selection for systematic review and meta-analysis

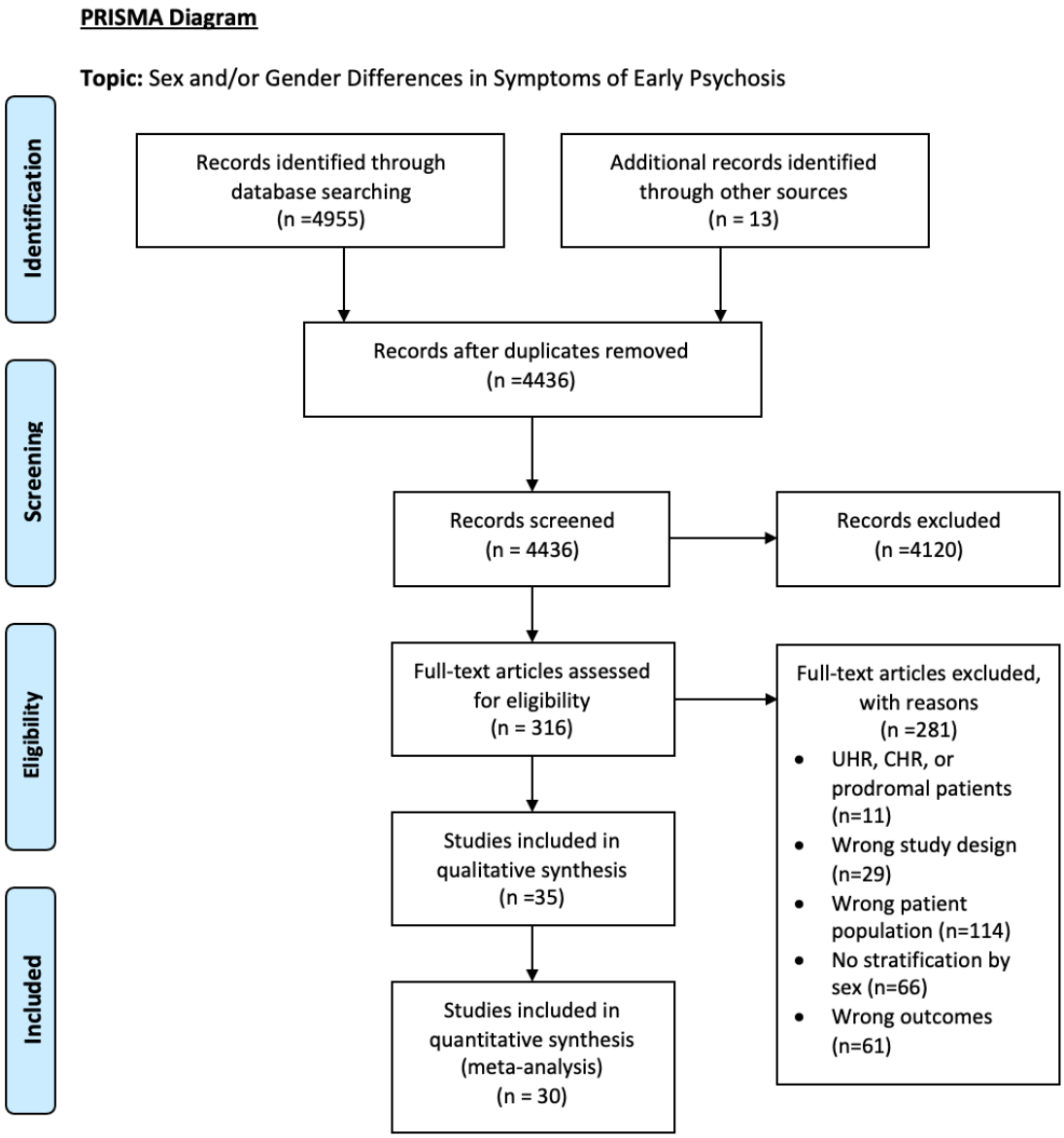


Table 3.1: Summary of study/sample characteristics of included studies (n=35)

Study ID, Author	Year	Country	Study Design	Sample Source	Sample Size	Age Range	Diagnoses Included	Definition of FEP/ Early Psychosis
1. Arnold et al. [64]	2002	United States	cohort	inpatient	180	18-45	SCZ, SCZA, NAP, BD, MDD	Presence of at least one psychotic symptom
2. Arranz et al.[43]	2020	Spain	cohort	inpatient	204	18-35	N/A	Admitted to inpatient unit for first time for FEP with psychotic symptoms of <1 year duration
3. Austad et al.[40]	2015	Norway	cohort	outpatient-EPI	246	15-65	SCZ, SFD, SCZA, BPD, DD, AP, PDN, DIP	<12 weeks of antipsychotic treatment,
4. Ayesa-Arriola et al.[65]	2014	Spain	cohort	outpatient-EPI	161	15-60	BPD, SFD, SCZ, SCZA, PDN	No prior antipsychotic treatment
5. Barajas et al.[66]	2010	Spain	cohort	outpatient-all	53	7-65	PDN	Two or more psychotic symptoms for <1 year, <6 months since first contact
6. Bertani et al.[67]	2012	Italy	cross-sectional	outpatient-all	397	15-54	NAP, AP	Presence of 1+ positive symptoms or 2+ negative symptoms
7. Buck et al.[68]	2020	Canada	cohort	outpatient-EPI	435	18-35	SCZ, SCZA, NAP, DD, BPD, PDN, BD, MDD	No past antipsychotic treatment for >1 month
8. Caton et al.[42]	2014	United States	cohort	inpatient	217	17-45	PDN	Presence of 1+ psychotic symptoms
9. Chang et al.[39]	2011	China	cohort	outpatient-EPI	700	18-55	SCZ, AP, SCZA, PDN	>3 years from first episode
10. Chen et al.[69]	2018	China	case-control	outpatient-all	110	18-35	SCZ	No past antipsychotic treatment
11.Cocchi et al.[70]	2014	Italy	case-control	outpatient-EPI	152	17-30	SCZ	DUP <24 months
12. Cotton et al.[44]	2009	Australia	cohort	outpatient-EPI	661	15-29	SCZA, NAP	First treated psychotic episode
13. Dama et al.[71]	2019	Canada	cohort	outpatient-EPI	569	14-35	SCZA, NAP	No past antipsychotic treatment for >1 month
14. Danaher et al.[72]	2018	Australia	cross-sectional	outpatient-EPI	134	15-25	SCZ, SFD, SCZA, BPD, DD, AP, PDN	>6 months remaining in EPI treatment
15. Garcia et al.[73]	2016	Spain	case-control	outpatient-EPI	79	18-35	SCZ, SFD, BD, PDN	<3 years since onset of illness
16. Heitz et al.[74]	2016	Switzerland	cohort	outpatient-EPI	89	18+	PDN	Attenuated or brief limited intermittent psychotic symptoms
17. Hui et al.[75]	2016	China	cohort	population-based survey	360	26-55	SCZ, DD, SFD, BPD, PDN, SCZA	<1 year antipsychotic treatment
18. Køster et al.[49]	2008	Denmark	cohort	outpatient-EPI	269	16-35	PDN	First psychotic episode
19. Lang et al. [76]	2018	China	cohort	outpatient-EPI	39	16-45	SCZ	Experiencing acute psychotic episode

Notes: SCZ = Schizophrenia, SCZA = Schizoaffective disorder, NAP = non-affective psychoses, BD = bipolar disorder, MDD = major depressive disorder, SFD= Schizophreniform disorder, BPD = brief psychotic disorder, DD = delusional disorder, AP = affective psychosis, PDN = psychotic disorder not otherwise specified, DIP = drug-induced psychosis, MD = mood disorders, AD = anxiety disorders, PD = personality disorders, FEPM= first episode psychotic mania. Symptoms were measured at index for all included studies.

Table 3.1 con't: Summary of study/sample characteristics of included studies (n=35)

Study ID, Author	Year	Country	Study Design	Sample Source	Sample Size	Age Range	Diagnoses Included	Definition of FEP/ Early Psychosis
20. Malla et al.[77]	2002	Canada	cohort	outpatient-EPI	88	N/A	SCZ, SFD, BD, PDN	>1 week psychotic symptoms
21. Mbewe et al.[78]	2006	Zambia	cohort	inpatient	160	12-86	SCZ, SFD, BD, PDN	Diagnosis of psychotic disorder by DSM-IV, positive on Psychosis Screening Questionnaire
22. Navarro et a. [79]	1996	UK	cohort	inpatient	166	16-60	SCZ, SFD, SCZA, AP, NAP	Presence of at least one positive symptom
23. Penney et al.[80]	2020	Canada	cross-sectional	outpatient-EPI	171	18-35	SCZ, SCZA, DD, SFD, DIP, PDN	<6 months from onset
24. Preston et al.[81]	2002	Australia	cross-sectional	outpatient-EPI	44	15-35	SCZ, SFD, PDN	Diagnosis of FEP by Operational Checklist for Psychotic Illness and Affective Illness
25. Pruessner et al.[82]	2019	Canada	cohort	outpatient-EPI	210	14-35	AP, NAP	<1 month antipsychotic treatment
26. Rapado-Castro et al. [83]	2015	Spain	cohort	in/outpatient	61	7-17	SCZ, BD, PDN	<6 months from onset
27. Segarra et al.[84]	2012	Spain	cohort	in/outpatient	231	15-65	SCZ, SFD	Presence of positive symptoms, no prior antipsychotic treatment
28. Suhail & Chaudry[85]	2006	Pakistan	cross-sectional	inpatient	140	16-40	SCZ	First admission, >4 weeks duration
29. Talonen et al.[86]	2017	Finland	cohort	inpatient	106	13-17	DIP, SCZ, MD, AD, PD	First diagnosis of psychotic disorder
30. Vila-Badia et al.[87]	2020	Spain	cross-sectional	inpatient	70	13-55	PDN	Presenting with psychotic symptoms (positive, negative, disorganized) for at least one week and <5 years
31. Irving et al.[88]	2021	UK	cross-sectional	registry/admin data	3350	16-65	BD, DIP, SCZ, SCZA, PDN	<1 year from onset
32. Cotton et al[8.6]	2013	Australia	cohort	outpatient-EPI	118	15-29	FEPM	First psychotic episode
33. Häfner et al.[90]	1992	Germany	cohort	inpatient	267	12-59	SCZ	First admission for psychotic episode
34. Gonzaáez-Rodriguez et al.[91]	2014	Switzerland	cohort	outpatient-EPI	87	18+	FEP	FEP diagnosis by the Basel Screening Instrument for Psychosis, symptoms at least several times a week
35. Thorup et al.[38]	2007	Denmark	cohort	In/outpatient	578	18-45	SCZ, DD, SCZA, PDN	<12 weeks antipsychotic treatment

Notes: SCZ = Schizophrenia, SCZA = Schizoaffective disorder, NAP = non-affective psychoses, BD = bipolar disorder, MDD = major depressive disorder, SFD= Schizophreniform disorder, BPD = brief psychotic disorder, DD = delusional disorder, AP = affective psychosis, PDN = psychotic disorder not otherwise specified, DIP = drug-induced psychosis, MD = mood disorders, AD = anxiety disorders, PD = personality disorders, FEPM= first episode psychotic mania. Symptoms were measured at index for all included studies.

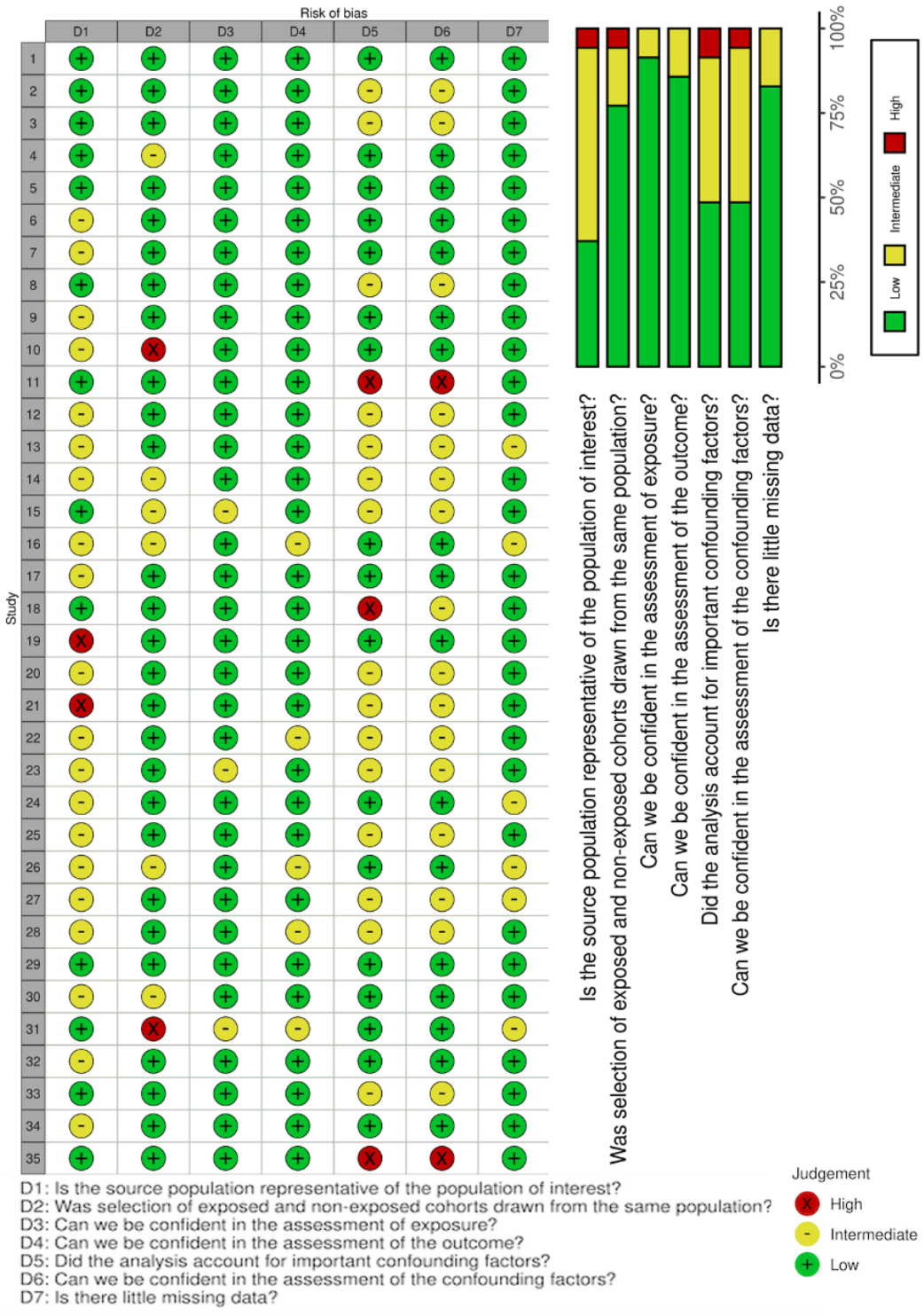
3.4.2 Risk of Bias

Figure 3.2 presents the findings from the risk of bias assessment. Representativeness of the source population was a concern in the majority of included studies, as only 37% of studies had a low risk of bias on this domain. Studies with a low risk of bias recruited samples though early psychosis intervention clinics or other mental health services. Small sample sizes – often consisting of many more males than females – accounted for a large portion of this intermediate and high risk across studies.

Measurement and adjustment for confounding factors in the analysis was another common risk of bias, with only half of studies having a low risk of bias in these domains (measurement = 49%; adjustment = 49%). There is potential for other factors, such as ethnicity or age of participants, to bias the relationship between sex and clinical presentation, although these factors were not mentioned or accounted for in many analyses.

Most studies had a low risk of bias in the domains of selection of exposed and non-exposed cohorts (77%), assessment of exposures (91%), and assessment of outcomes (86%), with the latter largely due to the use of standardized interviews and measures to obtain diagnoses and symptoms. There was also a low risk of bias due to missing data, with 83% of studies having a low risk of bias.

Figure 3.2: Summary of findings from the risk of bias assessment



Figures generated from https://mcguinlu.shinyapps.io/robvis/

3.4.3 Summary of Findings

The results from individual studies can be found in Appendix 3E-3I and are summarized in Table 3.2. Mean scores and standard deviations on each symptom scale were recorded from each study for both males and females. A wide range of psychotic symptoms were reported across the included studies, and the most common symptoms were compiled. Positive symptoms – such as hallucinations, delusions, and paranoia – and negative symptoms, such as apathy, poverty of speech/thought, and emotional/social withdrawal, were two of the main categories of symptoms recorded. Other common categories of symptoms assessed in the included studies were depression, general psychopathology symptoms, functioning, and substance use (alcohol and drug use). The results from the meta-analysis can be found in Figure 3.3.

Among the included studies that looked at positive symptoms of psychosis (n=31), 16 found more severe positive symptoms among men, 8 studies found more severe positive symptoms among women, and the remaining 7 studies found no differences between men and women (Appendix 3D). Twenty-one studies included data on positive symptom severity that were suitable for a meta-analysis (Figure 3.3, Appendix 3J). The overall SMD for positive symptoms was -0.03 (95%CI: -0.09, 0.03; I^2=46.8%), which suggests no difference in positive symptoms between men and women, and the findings were largely consistent across measurement tools.

Thirty studies looked at negative symptoms of psychosis, and 25 studies found more severe negative symptoms among men, while only one study reported more severe negative symptoms among women, and four reported no difference between men and women (Appendix 3D). Twenty-one studies included data on negative symptoms suitable for a meta-analysis (Figure 3.3, Appendix 3K), in which the overall SMD was found to be -0.15 (95%CI: -0.21, -0.09, I^2=50.9%), indicating that women experience significantly lower negative symptom severity than men. Consistent with the findings from the meta-analysis on positive symptoms, the findings were consistent across measurement tools.

Depressive symptoms were assessed in 20 of the included studies and of those, 14 found more severe depressive symptoms in women, three studies found more severe depressive

symptoms in men, and three studies found no difference between men and women (Appendix 3E). Twelve studies included data on depressive symptoms suitable for meta-analysis, (Figure 3.3, Appendix 3L) in which the overall SMD was 0.21 (95%CI: 0.14, 0.27, I^2=76.1%), indicating that women experience significantly more severe depressive symptoms than men.

Symptoms of general psychopathology were assessed in 14 of the included studies (Appendix 3F), in which six studies found more severe symptoms among men, four studies found more severe symptoms among women, and four studies found no difference between men and women. Twelve studies were included in the general psychopathology meta-analysis (Figure 3.3, Appendix 3M), where the overall effect was found to be -0.06 (95%CI: -0.16, 0.04, I^2=50.0%), suggesting no significant difference between men and women.

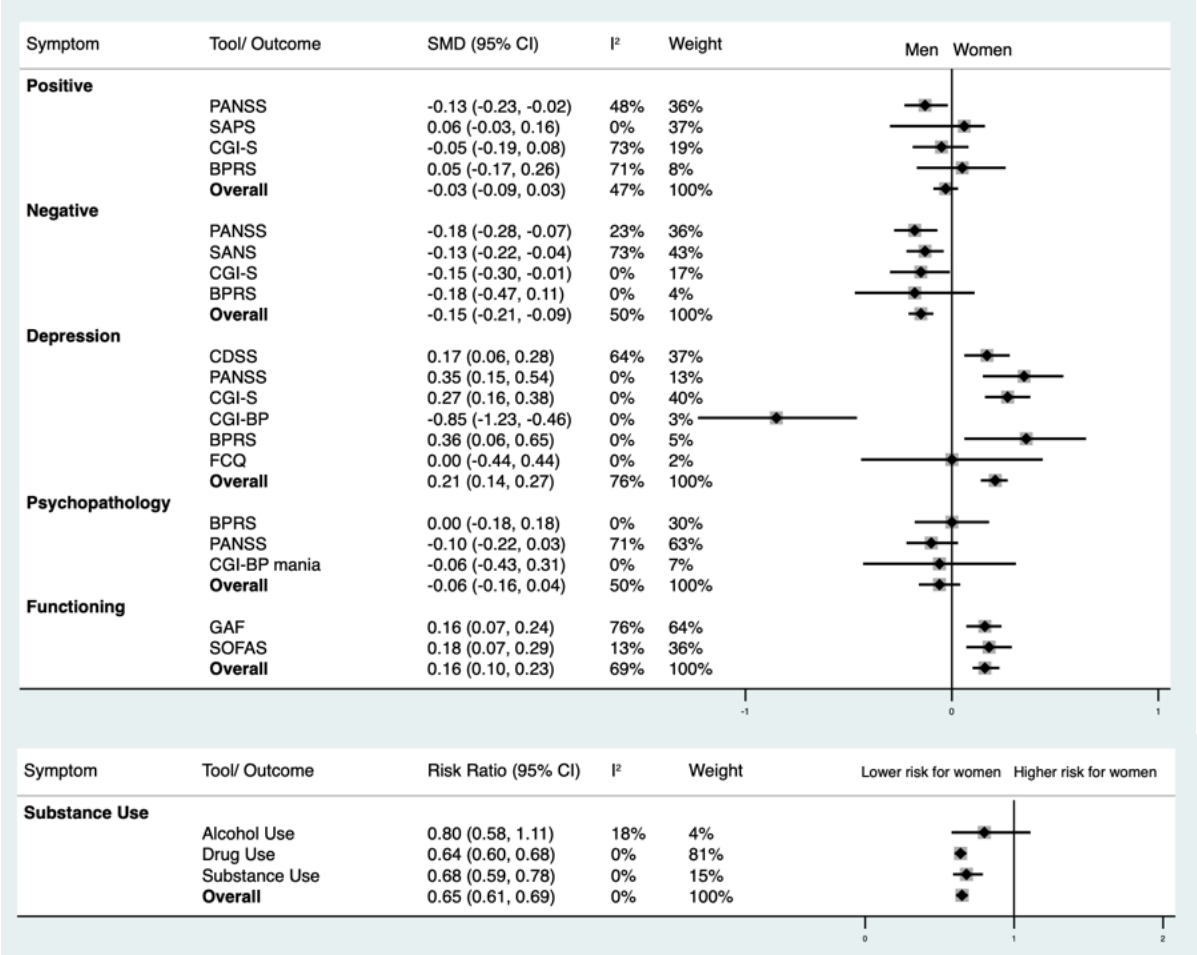
Sixteen included studies assessed overall level of functioning (Appendix 3G), and of these, 13 studies reported that women had higher levels of functioning, two studies reported that men had higher levels of functioning, and one study reported that men and women had similar levels of functioning. Fifteen studies provided data suitable for a meta-analysis (Figure 3.3, Appendix 3N), in which the pooled effect was 0.16 (95%CI: 0.10, 0.23, I^2=68.5%), suggesting that women had significantly higher levels of functioning than men.

The findings from studies looking at substance use can be found in Appendix 3H. Five studies assessed overall substance use among their sample, with all studies reporting a higher prevalence of substance use among men than women. Six studies assessed alcohol use among their sample, with four reporting a higher prevalence of alcohol use among men compared to women. Ten studies assessed drug use among their sample, and all reported a higher prevalence of drug use among men compared to women. Thirteen studies were used in the meta-analysis (Figure 3.3, Appendix 3O), in which the pooled risk ratio was 0.65 (95%CI: 0.61, 0.69, I^2=0.0%), suggesting that women had a significantly lower risk of substance use compared to men.

Table 3.2: Main findings by symptom category across studies

Symptom Category	Number of Studies	Overall Trend Direction
Positive	31	16/31 more severe symptoms in men
Negative	30	25/30 more severe symptoms in men
Depression	20	14/20 more severe symptoms in women
Psychopathology	14	6/14 more severe symptoms in men
Functioning	16	13/16 higher functioning in women
Substance Use (combined alcohol and drug use)	5	5/5 higher prevalence in men
Alcohol Use	6	4/6 higher prevalence in men
Drug Use	10	10/10 higher prevalence in men

Figure 3.3: Results from meta-analysis by symptom measure, with subgroup analysis by measurement tool (n=30)



Notes: SMD = Standardized Mean Difference, PANSS = Positive and Negative Syndrome Scale, SAPS = Scale for the Assessment of Positive Symptoms, CGI-S/BP = The Clinical Global Impression-Severity Scale/ Bipolar, BPRS = Brief Psychiatric Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, CDSS = The Calgary Depression Scale, FCQ = Frankfurt Complaint Questionnaire, GAF = Global Assessment of Functioning Scale, SOFAS = Social and Occupational Functioning Assessment Scale

3.5 Discussion

3.5.1 Summary of Evidence

The findings from our systematic review and meta-analysis suggest that men with FEP or early psychosis experience greater severity of negative symptoms and a higher likelihood of substance use, whereas women experience greater severity of depressive symptoms and a higher level of functioning. Symptom severity is often characterized by the level of interference with day-to-day functioning. Less severe symptoms interfere little in day-to-day functioning, while the most severe symptoms drastically interfere with functioning, with the possible need of supervision and assistance.[92] We did not find differences between men and women in positive symptoms or symptoms of general psychopathology. These findings on sex differences in the symptoms of early psychosis are consistent with findings from previous reviews on sex differences in chronic schizophrenia.[93,94]

Prior literature suggests that men have a higher incidence of psychotic disorders than women,[34] which may account for the gender distributions observed in the study samples. Ochoa and colleagues discussed the differences in diagnoses of psychotic disorders between men and women, and alluded to the idea that although more cases of psychosis are recorded among men, this difference may be due to difficulties detecting the illness among women.[34] The average age of onset for women with psychotic disorders tends to be later in life than men, which can be explained by the second peak in onset that women experience post-menopause, raising the group mean for women.[32,34,95] It is still largely unknown why men may present with psychotic symptoms earlier in life than women, but some hypothesize that higher cannabis consumption in men,[32] or protective hormones in women [96] may account for this difference.

Previous research on sex differences in the symptoms of psychosis have been well documented, however; it is less clear whether sex differences are present at the initial presentation for psychotic disorders or emerge later in the course of illness due to differences in service engagement and treatment adherence. It is generally acknowledged that men present with more severe negative symptoms than women, whereas women

display more severe affective symptoms, such as depression and lack of energy.[32] This systematic review and meta-analysis clarifies these differences and provides evidence for sex differences in the early course of illness. It was found that men experienced more severe negative symptoms, such as apathy or social/emotional withdrawal, than women, whereas we did not find evidence of sex differences in positive symptoms, such as hallucinations and delusions. Additionally, we found that women experienced more severe depressive or affective symptoms than men. These findings align with a prior literature review on gender differences in schizophrenia symptoms, which found more severe negative symptoms in men, more severe affective symptoms in women, but inconclusive findings on positive symptoms.[34] Lower symptom severity in women supports our finding that women have higher levels of functioning than men, however; further research is needed to confirm this relationship.

The studies included in this review focused on differences in clinical presentation of psychosis in men and women through the lens of biological sex; however, it is important to highlight the role that gender could play in this relationship. Although examining these differences in terms of sex may provide information regarding the biological influences on psychosis presentation, examining these differences in terms of social implications of sex, referred to as gender may provide information regarding how factors related to socialization influence the presentation of psychosis. We did not identify any studies focused on how gender may impact psychosis presentation, but these influences could stem from differences in patterns of behaviour, thinking, and feeling between the genders.[49] For example, men are more likely to smoke cannabis, and women may exhibit more social behaviours and willingness to accept help.[49] Some of the findings from the current review could also be explained through a gender lens, for example where men have higher rates of substance use and women have higher levels of functioning. Future research on the relative contributions of sex and gender to differences in clinical presentation in FEP or early psychosis is warranted.

It is generally accepted that men and women present with psychosis in different ways; however, there is still a considerable knowledge gap about how the illness presents in the early stages with regards to sex/gender differences. Based on findings from this study and

from prior literature, it is presumed that women with psychotic disorders present with more subtle symptoms than men, due to less severe negative symptoms and higher functioning. This may cause the illness to be harder to detect, especially in the early course. Clinicians may be able to tailor interventions specifically toward young men or women experiencing early psychosis by better recognizing how symptoms differ between the sexes. Early detection and intervention is of utmost importance in psychotic disorders,[45] and understanding sex and gender differences in clinical presentation can help advance the aim of early detection.[45]

3.5.2 Limitations

The evidence from this review should be interpreted with consideration of several limitations of the included studies, and of the review itself. Many of the studies included in the review had small sample sizes, with more men than women. Although this is representative of the distribution of FEP in clinical populations,[24] this may limit the ability to generalize the study results to all people experiencing FEP or early psychosis, especially to women who may be receiving care outside the context of specialized early intervention services.[24] Definitions of FEP or early psychosis varied among the included studies, which may have impacted the clinical presentation noted in each study. Many of the studies limited their sample to those of a certain age, duration from symptom onset, or to those that spoke a certain language. These restrictions may also limit the external validity of the study findings, as the results may not be applicable to all people with early psychosis. Furthermore, given that women tend to have a later age at onset,[34] any age restrictions would function to underrepresent women with FEP. Another limitation of most of the included studies is the omission of cognitive symptoms. Evidence suggests that men and women with early psychosis may differ in cognitive functioning,[34] which may be due to the positive role that estrogen plays in cognition.[32] However, these symptoms were not commonly reported throughout the literature. Lastly, sex and gender differences within the included studies were often conflated, with the role of gender in the incidence and presentation of psychosis being ignored. A major gap in the literature remains on the grey areas of gender, and how these impact the clinical presentation of early psychosis. Future research should explore exposures that differ between genders, such as childhood trauma

or abuse, head injury, spring birth, in-utero or birth complications, or pregnancy,[93] and areas of gender fluidity, including LGBTQ+ people, intersex individuals, or individuals with hormone dysfunction. Further research on the topic should include data from these individuals to create a more cohesive understanding of the relative contributions of sex and gender on symptoms of psychosis.

There are also several limitations of the overall review that should be considered. Inclusion and exclusion criteria differed significantly across the included studies. Criteria such as age of the patient, amount of time from symptom onset, inclusion of drug-induced psychosis, and criteria used to define FEP or early psychosis varied between studies, which limits our ability to draw conclusions about subgroups of early psychosis patients and increases the heterogeneity in our data. The exclusion of UHR, CHR, or prodromal patients may decrease generalizability of the findings, however; sex differences in symptoms for these populations are out of the scope of this review. Additionally, although validated scales were used in all included studies to obtain measures of symptomology, these scales differed between studies and may have introduced heterogeneity in our pooled estimates, although the findings were largely consistent across measurement tools in our subgroup analyses. Finally, we were unable to differentiate between sex and gender in the present review. It is still unknown whether differences in psychotic symptoms are due to biologic sex differences or if gender may also play a role.

3.5.3 Conclusions

Our findings suggest that men with FEP or early psychosis experience more negative symptoms and substance use than women, whereas women experience more depressive symptoms and have higher functioning than men. Gender differences were not found for positive symptoms or general psychopathology. The evidence from this study may help to inform clinicians and researchers on better identifying FEP and early psychosis to facilitate early intervention. Further population-based studies are needed to provide more substantial evidence on sex/gender differences in clinical presentation of early psychosis, and additionally, how these symptoms present outside the context of specialized early

intervention services. Further research on the role of biological sex and gender factors in the clinical presentation of psychotic disorders is warranted.

Chapter 4

4 Sex Differences in the Clinical Presentation of Early Psychosis in a Primary Care Setting

4.1 Abstract

Background: Primary care plays an important role in the help-seeking pathway for young people experiencing early psychosis, but sex differences in clinical presentation in these settings is unexplored. We used electronic medical records to explore sex differences in clinical presentation to primary care in the one-year period prior to a first diagnosis of psychotic disorder. ***Methods:*** We identified first-onset cases of non-affective psychotic disorder over a 10-year period (2005-2015) using health administrative data (*n*=465). This cohort was linked with electronic medical records (EMR) from primary care, where detailed information on encounters in the year prior to first diagnosis was abstracted, including a checklist of recorded psychiatric symptoms and other relevant behaviours, and whether the first diagnosis was made by the family physician (FP). We used modified Poisson regression models to examine the effect of sex on signs, symptoms, and diagnoses, adjusted for various clinical and sociodemographic factors. ***Results:*** In the period one year prior to first diagnosis of psychotic disorder, positive symptoms (PR=0.76, 95%CI:0.58,0.98) and substance use (PR=0.54, 95%CI:0.40,0.72) were less prevalent in the medical records of women. No other sex differences in symptoms were found. Visits by women were more likely to be assigned a diagnosis of depression or anxiety (PR=1.18, 95%CI:1.00,1.38), personality disorder (PR=5.49, 95%CI:1.22,24.62), psychological distress (PR=11.29, 95%CI:1.23,103.91), and other mental or behavioural disorders (PR=3.49, 95%CI:1.14,10.66), and less likely to be assigned a diagnosis of substance use (PR=0.33, 95%CI:0.13,0.87) in the year prior to first diagnosis. ***Conclusions:*** We identified some evidence of sex differences in the clinical presentation of early psychosis and recorded diagnoses in the primary care EMR. Further research is needed to better understand sex differences in clinical presentation in the primary care context.

Keywords: sex differences, first-episode psychosis, symptoms, primary care, family physicians**,** electronic medical records

4.2 Introduction

Psychotic disorders are a class of severe mental illnesses that typically have an onset in adolescence or young adulthood and can cause a significant burden on those experiencing them, their carers, and the healthcare system.[8] The clinical presentation of these disorders can be quite variable in terms of the age of onset, symptomatology, and course of illness,[8,32] and the sex or gender of the person experiencing psychosis may explain some of this variability.[34] For example, the age of onset for psychotic disorders occurs later in life for women than men, possibly owing to protective effects of hormones or difficulty identifying the illness in women, resulting in a later age at diagnosis.[34] The incidence of psychotic disorder also tends to be slightly higher in men than women,[32] which may be explained by narrow diagnostic criteria or age restrictions, or women being less likely to be recognized as having a psychotic disorder than men.[32] Although women may not be diagnosed as frequently as men, evidence suggests that women are more likely than men to voluntarily seek help for mental health reasons.[25,99] Finally, prior research suggests that women with psychotic disorders may receive sub-optimal care due to an insufficient understanding of how women are differently affected by these illnesses.[37]

These sex and gender differences in psychotic disorder likely arise from a complex interaction of both biological and psychosocial factors,[32] which may also have an impact on clinical presentation. Individual studies on sex differences in symptoms have varying results, but evidence from reviews indicate that men experience more severe negative symptoms (i.e., social withdrawal, anhedonia, blunted affect) and have higher levels of substance use than women, whereas women experience more severe affective symptoms (i.e. depression, anxiety, mania) but have higher levels of functioning.[34,100] Findings on sex differences in the symptoms of psychosis are abundant; however, these differences have yet to be studied outside of the context of specialized psychiatric services.

The identification of psychotic symptoms early in the course of illness is imperative for improving clinical and functional outcomes, and can reduce suffering for the patients and families involved.[18] Timely access to treatment can be facilitated by family physicians (FP), who are often the first point of contact for young people experiencing early

psychosis.[101] The pathways to care for early psychosis can be complex, involving multiple contacts and services, including emergency departments.[18] FPs and other primary care practitioners play a key role in this pathway to care, with about one third of young people with early psychosis in Ontario (Canada) receiving their first diagnosis of a psychotic disorder in primary care.[18] An additional third of early psychosis patients who received their diagnosis in secondary or tertiary care had mental health contacts with a FP in the 6-month period prior to first diagnosis.[18] People experiencing early psychosis have been found to make twice as many contacts with primary care practitioners in the period 6 years leading up to a first diagnosis, compared to the general population.[26] This includes visits for all reasons, including mental, physical, and preventative health.[26] Furthermore, those that initiate their own help-seeking are more likely to seek help in a primary care setting than in psychiatric or emergency services.[18] Differences exist between men and women with regards to help-seeking in primary care for early psychosis.[25] Prior research indicates that women seek help almost twice as often,[25] and are more likely than men to contact primary care practitioners for all reasons, including mental, physical, and preventative health.[26]

Given the vital role that primary care physicians play in the pathway to care for people with early psychosis, understanding clinical presentation in a primary care context is important. Young people presenting to primary care are likely at an earlier stage of illness than those presenting to secondary or tertiary care services, thus having a less acute presentation and more insidious symptoms.[18] The knowledge base on sex differences in symptoms of early psychosis is limited to specialized settings, such as Early Psychosis Intervention (EPI) services or other psychiatric settings, with a gap in the literature on how young men and women experiencing early psychosis may present to primary care. To more effectively detect and intervene for people with early psychosis who seek help in primary care, we need a thorough understanding of the sex differences in symptoms that present in these settings.

The overall objective of this study was to use electronic medical records, linked to population-based health administrative data in Ontario, to explore sex differences in the clinical presentation of early psychosis at presentation to primary care in the one-year

period leading up to the first diagnosis of psychotic disorder. Specifically, we aimed to 1) identify and describe sex differences in clinical presentation (i.e., signs and symptoms) of early psychosis; 2) identify and describe sex differences in diagnoses made by the FP; and 3) adjust for the effect of clinical and sociodemographic factors on these sex differences. In this paper, we use the term "early psychosis" to describe patients experiencing FEP, as well as those in the prodromal phase of illness.

4.3 Methods

This study follows the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines for observational studies (Appendix 4A).[102]

4.3.1 Study Design and Case Definition

We obtained access to the administrative data holdings at ICES (formerly known as the Institute for Clinical Evaluative Sciences), which is a not-for-profit research institute that works with health-related data for the province of Ontario.[103] Health administrative data is generated by health care providers every time a service is delivered to a person in Ontario, which may be used for billing, registration, transactions, record-keeping, and also to study and evaluate health care delivery, use, and costs.[104] Analysts at ICES used unique identifiers to link patients between datasets.

We used the following health administrative databases to identify people with first onset psychotic disorders:

- The Registered Persons Database (RPDB) contains socio-demographic information on all people covered by the Ontario Health Insurance Program (OHIP),[105] including age, sex, and neighbourhood income quintile. OHIP covers all medically necessary services for nearly the entire population of Ontario, such as appointments with FPs, visits to walk-in clinics and the emergency department, and medical tests and surgeries.[106]
- The OHIP database contains information from physician billings, including the type of service provided and the diagnosis assigned to each visit.[107] It is estimated that 95% of Canadian physicians submit billing claims.

- The National Ambulatory Care Reporting System (NACRS) database includes ambulatory care data for both hospital-based and community-based care, including day surgeries, outpatient clinics, and emergency departments.[108]
- The Ontario Mental Health Reporting System (OMHRS) database includes information on people admitted to designated adult psychiatric inpatient beds in Ontario.[109]
- The Discharge Abstract Database (DAD) contains data on all discharges from inpatient facilities, including deaths, sign-outs, and transfers.[110] Any inpatient psychiatric admissions not captured by the OMHRS database is included in DAD.

Using these databases, we identified first-onset cases of non-affective psychotic disorder (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis not otherwise specified [NOS]) among people aged 14 to 35 years over a ten-year period (2005 to 2015), based on the presence of at least one of the following:

1. A primary discharge diagnosis of a non-affective psychotic disorder from a general hospital bed [International Classification of Diseases (ICD), 9th Revision code 295.X, 297.X, 298.X; ICD-10 code F20 or F25]; or
2. A discharge diagnosis of non-affective psychotic disorder from a psychiatric hospital bed [Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV, Axis I) code 295.X, 297.X, 298.X]; or
3. Two or more outpatient OHIP billing claims or emergency department visits within a 12-month period with a diagnostic code for non-affective psychotic disorder (ICD-9 code 295.X, 297.X, 298.X; ICD-10 code F20 or F25).

Prevalent cases were removed if there was evidence of contact with mental health services for non-affective psychosis prior to the case accrual window (lookback of 25 to 35 years based on year of diagnosis). People with a prior diagnosis of affective psychosis were not excluded, and instead included as an incident case of non-affective psychosis from the date of diagnosis change. This algorithm has been previously used by Anderson et al. to estimate the incidence of first-onset psychotic disorders in Ontario.[111] A modified version of the algorithm has been validated against medical records and found to have a sensitivity of 91.6%, a specificity of 61.3%, a positive predictive value (PPV) of 67.4%, and a negative predictive value (NPV) of 89.3% for chronic psychotic disorders.[112]

4.3.2 Symptom and Behaviour Variables

Cases of first-onset non-affective psychotic disorder identified in the health administrative data were then linked with the primary care EMR database at ICES to identify cases who had records in the EMR in the one-year period prior to the first diagnosis of psychotic disorder. The Electronic Medical Records Primary Care (EMRPC) database includes detailed free-text information from visits to primary care, as well as other sources such as consultation notes from specialists.[113] The EMRPC database includes approximately 360 FPs practicing under a primary care reform model across Ontario, with similar gender and urban/rural distributions compared to the broader population of Ontario FPs. Almost all FPs in the EMRPC database are in group practice, and all FPs practice in a rostering model. Over 300,000 patients and 400,000 physician-patient encounters are included in the database over a one-year period. This represents approximately 2% of FPs in Ontario and approximately 2% of the total Ontario population. This database was used to abstract more detailed clinical information on encounters with primary care prior to first diagnosis of psychotic disorder than would typically be available in the health administrative data, including information on patient characteristics, psychotic disorder diagnosis, social support, and signs/symptoms of psychosis.

We abstracted data on the symptoms and behaviours that early psychosis patients presented with during primary care encounters in the one-year period leading up to the first diagnosis. Prior studies[114,115] and input from clinicians on the team (LP, AGM, AV, SHJ) were used to develop the list of symptoms and behaviours to abstract. The data were abstracted from the EMR using an abstraction platform at ICES, and a standardized abstraction manual was created to guide this process for the abstractor. After linkage with the administrative data cohort, 719 charts were identified in the EMRPC database. A FP (NS) abstracted data from all charts using the abstraction platform and manual. A 5% selection of patient records were abstracted twice to ensure quality control and assess intra-rater reliability, and agreement ranged from 75% to 100%. To assess inter-rater reliability, the signs and symptoms abstracted from the charts were validated by a second abstractor. Of the 719 charts, 381 patients had at least one symptom abstracted in the period 6-months prior to index. We randomly selected 15% of this sample for validation, where a second abstractor

independently abstracted data from these charts using the ICES platform and abstraction manual, and agreement ranged from 92% to 100%.

Psychotic symptoms were abstracted from the EMR using items from the Early Detection Primary Care Checklist (PCCL), consisting of 20 items. The PCCL is a validated tool used to help identify first-episode psychosis in young people in primary care. Other signs, symptoms, and vulnerabilities associated with psychosis that were not captured by the PCCL were also abstracted, as well as any diagnosis or provisional diagnosis made by the FP at each encounter. Signs and symptoms were flagged as yes or no based on whether the primary care provider noted them in the medical record during the encounter. Symptoms and behaviours were grouped to increase comparability with prior studies that explored similar broad symptom groups,[43,66,76,89] and to combine individual symptoms with low frequencies.

1. Positive symptoms of psychosis, including delusions, hallucinations, and disorganized thoughts or behaviour.
2. Negative symptoms of psychosis, including anhedonia, blunted affect, diminished speech, social withdrawal, and avolition.
3. Mood symptoms, including depression and mania symptoms.
4. Anxiety symptoms, including anxiety, restlessness, and tension or nervousness.
5. Decreased functioning, including issues with personal hygiene, increased stress, or deterioration in functioning.
6. Cognitive symptoms, including poor memory and poor concentration.
7. ADHD symptoms, including hyperactive behaviour and impulsivity.
8. Substance use, including cigarette smoking, alcohol use, cannabis use, and use of other street drugs.
9. Self-harm/suicidal behaviours.
10. Other symptoms and behaviours, including poor appetite, sleep difficulties, aggression, lack of insight into mental health, psychosomatic complaints, and psychosocial stressors.

We also abstracted information on the diagnosis assigned to the encounter by the FP and whether the diagnosis was provisional.

4.3.3 Other Variables

The main exposure of interest was the sex of each patient, which was obtained from the health administrative data. Sex was used as a binary variable *(Male, Female).*

We obtained information on other patient characteristics that may be differentially associated with clinical presentation of early psychosis among men and women. These included age at first diagnosis, neighbourhood-level income quintile, and rurality of residence. Age at first diagnosis was used as an ordinal variable (*15-20 years, 21-25 years, 26-30 years, 31-35 years)*, and was included because among people with psychotic disorders, the age of onset or age of diagnosis often differs among men and women.[34] Furthermore, the age of the person experiencing early psychosis may have an impact on the clinical presentation of the illness.[116] Neighbourhood-level income quintile was an ordinal variable, ranging from lowest to highest income quintile, and was included because prior research indicates that those with lower incomes may experience more psychotic symptoms,[117,118] and incomes differ between men and women with psychotic disorders.[119] Rurality of residence was used as a binary variable (*Rural, Non-Rural*), which was included because evidence also suggests that living in urban areas may increase psychotic symptoms and risk of developing a psychotic disorder,[15] and this risk may be stronger for men than women.[120] We obtained other patient information for the purpose of describing the sample. These variables include index diagnosis (*Schizophrenia Spectrum Disorder, Psychosis NOS*), family history of bipolar or psychosis, and if the family is concerned/expressed worry about the patient.

Service-related variables included the number of help-seeking visits prior to the index date, whether or not the patient was rostered to the FP, time on EMR, and number of John Hopkins ADGs (Aggregated Diagnosis Groups), Number of help-seeking visits was used as a count variable, rostering to the FP was a binary variable (*True, False*), and time on EMR is the number of days the patient has been on the EMR, which was used as a continuous variable. These were included in the analysis because evidence suggests that primary care service use differs between men and women with early psychosis,[25,26] which may encompass number of help-seeking visits, whether a patient is rostered to a FP, and

the amount of time spent on the EMR. Furthermore, it is well-established that timely access to treatment and contact with a FP can improve clinical presentation and long-term outcomes.[18] John Hopkins ADGs are diagnostic clusters derived from the health administrative data, ranging from zero to 32.[121] ADGs are used to identify and score comorbidities, and are based on five clinical criteria of the condition, including the duration, severity, diagnostic certainty, etiology, and specialty care involvement.[122] Number of ADGs was used as a categorical variable (*Low (<5), Medium (6-9), High (10 or more)*), and was included because comorbidities are common among people with psychotic disorders,[123] and prior research suggests there are sex differences in patterns of multimorbidity.[124]

4.3.4 Data Analysis

All analyses were conducted using SAS Enterprise Guide 7.1.[125] People missing data on age and sex were excluded (<1%). We calculated descriptive statistics for sociodemographic, clinical, and service use characteristics. Descriptive characteristics of the sample were summarized using frequencies and percentages for categorical data and means with standard deviations (SD) for continuous data. Our descriptive analyses were stratified according to sex. We also computed variance inflation factors (VIF) and tolerance to investigate multicollinearity for the following: age category, time on EMR, total ADGs, and number of help-seeking visits. If values of VIF were below 10, and values of tolerance above 0.1, it can be assumed that multicollinearity is not a threat in the analysis.[126]

First, we limited the sample to those who had a record in the EMR and data on clinical presentation in the one-year period leading up to a first diagnosis of psychotic disorder. Second, we estimated the proportion of men and women who experienced each sign and symptom of early psychosis in the one-year period leading up to a first diagnosis. Next, we compared these proportions using modified Poisson regression models with robust variance estimators for each symptom using the *proc genmod* command in SAS Enterprise Guide 7.1. Modified Poisson regression models are suitable for the analysis of binomial data, and robust variance estimators prevent the error from being overestimated.[127]

We then further limited the sample to those who had a diagnosis made by the FP in the EMR in the period one year leading up to a first diagnosis. We estimated the proportion of men and women with each diagnosis over this period, and whether the diagnosis was provisional. These proportions were then compared using modified Poisson regression models with robust variance estimators using the *proc genmod* command.

Next, we fit adjusted modified Poisson regression models to adjust for the effect of clinical and sociodemographic factors (i.e., age at index, neighbourhood income quintile, rurality, number of help-seeking visits, rostered to FP, time on EMR, number of ADGs) on the sex differences in clinical presentation or diagnoses made by the FP. This was done to determine whether these factors had an effect on the relationship between sex and clinical presentation of early psychosis.

The results of the unadjusted and fully adjusted analyses were similar; therefore, we present fully adjusted prevalence ratios (PRs) with associated 95% confidence intervals (CI). PRs were reported instead of odds ratios (ORs) because the outcomes of interest are not rare, and ORs would be overestimated. Associations were considered statistically significant when the 95% confidence intervals did not include one.

4.4 Results

The initial sample consisted of 572 people (255 women, 317 men) identified with a first onset of non-affective psychotic disorder in the health administrative data who also had an electronic medical record in the EMRPC database. People who did not have a visit with a FP for the one-year period prior to the first diagnosis of a psychotic disorder and were therefore missing symptom data were removed from the sample (n=107). People who did not have a diagnosis assigned by the FP recorded in the EMR were not removed from the sample but were not included in the analyses on sex and diagnosis (n=163). The final sample consisted of 465 people, of whom 215 were women (46.2%) and 250 were men (53.8%).

The characteristics of the analytic sample are summarized in Table 4.1. Women had a mean age at diagnosis of 24.5 years, and men had a mean age at diagnosis of 23.4 years. Women

had an average of 1036 days (SD=1042.1) on the EMR and had an average of 9 (SD=9.1) help-seeking visits in the year leading up to first diagnosis, whereas men had an average of 979 days (SD=1049.7) on the EMR had had an average of 5 (SD=5.0) help-seeking visits in the year leading up to first diagnosis. Seventy percent of women and 72% of men were rostered to a FP. About 14% of both women and men's families expressed worry or concern for their well-being. No threat of multicollinearity was indicated through the analysis of tolerance or VIF.

Table 4.1: Sample characteristics of early psychosis patients (n=465)

Variable	Women (n=215)		Men (n=250)	
	Mean	**SD**	**Mean**	**SD**
Age at index	24.46	5.97	23.36	5.42
Time on EMR (days)	1036.48	1042.09	979.45	1049.66
Number of help-seeking visits	8.88	9.13	5.35	4.98
	N	**%**	**N**	**%**
Age category				
15-20 years	70	32.6	94	37.6
21-25 years	51	23.7	66	26.4
26-30 years	49	22.8	55	22.0
31-35 years	45	20.9	35	14.0
Neighbourhood income quintile				
1 (lowest)	50	23.3	59	23.6
2	50	23.3	49	19.6
3	46	21.4	47	18.8
4	36	16.7	43	17.2
5 (highest)	33	15.3	52	20.8
Rurality				
Rural	32	14.9	37	14.8
Non-Rural	183	85.1	213	85.2
Total ADG category				
Low (<5)	75	34.9	147	58.8
Medium (6-9)	79	36.7	72	28.8
High (10 or more)	61	28.4	31	12.4
Rostered to family physician	151	70.2	181	72.4
The family is concerned/has expressed worry about the patient	29	13.5	36	14.4
Index diagnosis				
Schizophrenia Spectrum Disorder	88	40.9	111	44.4
Psychosis NOS	127	59.1	139	55.6
Family History of Bipolar or Psychosis	<6	<2.8	8	3.2

Note: ADG = Aggregated Diagnosis Group, Psychosis NOS= Psychosis Not Otherwise Specified.

The results from the analysis of sex differences in the signs and symptoms of psychosis are presented in Table 4.2. In early psychosis presentations to primary care, the most commonly recorded symptoms were positive symptoms (33.5% of women, 38.0% of men), mood symptoms (54.4% of women, 47.6% of men), anxiety symptoms (61.9% of women, 56.4% of men), decreased functioning (36.7% of women, 34 4% of men), substance use (25.1% of women, 37.6% of men), and sleep difficulties (37.2% of women, 31.2% of men). In the fully adjusted analyses, we found that positive symptoms were less prevalent in women compared to men (PR=0.76, 95%CI=0.58,0.98), specifically delusions (PR=0.57, 95%CI=0.40,0.82). Women had a lower prevalence of overall substance use (PR=0.54. 95%CI=0.40,0.72) relative to men, specifically alcohol use (PR=0.45, 95%CI:0.24,0.85) and cannabis use (PR=0.38, 95%CI:0.24,0.60). There were no significant differences between women and men in the prevalence of negative symptoms, mood symptoms, anxiety symptoms, functioning, cognitive symptoms, ADHD symptoms, self-harm or suicidal behaviours, or other symptoms and behaviours.

Table 4.2: Unadjusted and adjusted analysis of sex on clinical presentation of early psychosis

Symptom	Women (n=215)		Men (n=250)		Unadjusted		Adjusted	
	N	%	N	%	PR	95%CI	PR	95%CI
Positive Symptoms	72	33.5	95	38.0	0.88	0.69, 1.13	0.76	0.58, 0.98*
Delusions	42	19.5	73	29.2	0.67	0.48, 0.93*	0.57	0.40, 0.82*
Hallucination	35	16.3	36	14.4	1.13	0.74, 1.73	1.02	0.65, 1.61
Disorganized Thoughts/ Behaviours	30	14.0	38	15.2	0.92	0.59, 1.43	0.79	0.50, 1.26
Negative Symptoms	50	23.3	56	22.4	1.04	0.74, 1.45	0.90	0.63, 1.27
Mood Symptoms	117	54.4	119	47.6	1.14	0.96, 1.37	0.98	0.82, 1.18
Depressive Mood	111	51.6	110	44.0	1.17	0.97, 1.42	1.01	0.83, 1.23
Mania Symptoms	52	24.2	43	17.2	1.41	0.98, 2.02	1.10	0.76, 1.60
Anxiety Symptoms	133	61.9	141	56.4	1.10	0.94, 1.28	0.94	0.81, 1.10
Decreased Functioning	79	36.7	86	34.4	1.07	0.84, 1.36	0.88	0.68, 1.13
Cognitive Symptoms	38	17.7	42	16.8	1.05	0.71, 1.57	0.92	0.60, 1.42
ADHD Symptoms	30	14.0	22	8.8	1.59	0.94, 2.66	1.11	0.65, 1.88
Substance Use	54	25.1	94	37.6	0.67	0.50, 0.88*	0.54	0.40, 0.72*
Smoking	36	16.7	38	15.2	1.10	0.73, 1.67	0.86	0.55, 1.35
Alcohol	15	7.0	34	13.6	0.51	0.29, 0.92*	0.45	0.24, 0.85*
Cannabis	24	11.2	66	26.4	0.42	0.28, 0.65*	0.38	0.24, 0.60*
Other Street Drugs	14	6.5	21	8.4	0.78	0.40, 1.49	0.53	0.26, 1.08
Self-Harm/ Suicidal Behaviours	67	31.2	58	23.2	1.34	0.99, 1.81	1.11	0.80, 1.52
Other Symptoms/ Behaviours								
Poor Appetite	38	17.7	28	11.2	1.58	1.00, 2.48*	1.39	0.86, 2.24
Sleep Difficulties	80	37.2	78	31.2	1.19	0.93, 1.54	1.02	0.78, 1.34
Aggression	59	27.4	69	27.6	0.99	0.74, 1.34	0.77	0.56, 1.05
Lack of Insight	<6	<2.8	7	2.8	0.17	0.02, 1.34	N/A	
Psychosomatic Complaints	<6	<2.8	<6	<2.4	1.74	0.29, 10.34	0.91	0.74, 1.12
Psychosocial Stressors	102	47.4	112	44.8	1.06	0.87, 1.29	N/A	

Note: All estimates are women compared to men. N/A analyses were unable to be computed due to low sample sizes.

*p < .05

The results from the analysis on sex differences in the diagnoses made by the FP can be found in Table 4.3. This sample consisted of 302 people, 144 women (47.7%) and 158 men (52.3%). The diagnoses that were most commonly recorded during visits to primary care included depression or anxiety (71% of women, 60.8% of men), psychotic disorder (32.6% of women, 27.2% of men), or psychosis symptoms (22.2% of women, 29.1% of men). In the fully adjusted analysis, we found that a diagnosis of substance/alcohol use/addiction was less prevalent in women compared to men (PR=0.33, 95%CI=0.13,0.87). Additionally, a diagnosis of psychological distress was more prevalent in women than men (PR=11.29, 95%CI=1.23,103.91). We were unable to run fully adjusted models for personality disorder and other mental health diagnoses due to small numbers, however these were both significantly more prevalent among women (PR=5.49, 95%CI=1.22, 24.62 and PR=3.49, 95%CI=1.14, 10.66, respectively). No differences were found between men and women for a diagnosis of psychotic disorder, psychosis symptoms, self-harm/suicidality, other nonspecific prodromal symptoms, neurological or neurodevelopmental condition. There was also no difference between men and women in whether the diagnosis made by the FP was provisional.

Table 4.3: Unadjusted and adjusted analysis of sex on diagnoses made by the FP prior to psychotic disorder diagnosis

Diagnosis	Women (n=144)		Men (n=158)		Unadjusted		Adjusted	
	N	%	N	%	PR	95% CI	PR	95% CI
Depression/ anxiety	103	71.5	96	60.8	1.18	1.00, 1.38*	1.10	0.93, 1.30
Substance/ alcohol use/addiction	<6	<4.2	11	7.0	0.50	0.18, 1.40	0.33	0.13, 0.87*
Personality disorder	10	6.9	<6	<3.8	5.49	1.22, 24.62*	N/A	
Psychological distress	12	8.3	<6	<3.8	13.17	1.73, 100.00*	11.29	1.23, 103.91*
Psychotic disorder	47	32.6	43	27.2	1.20	0.85, 1.70	1.11	0.77, 1.60
Psychosis symptoms	32	22.2	46	29.1	0.76	0.52, 1.13	0.83	0.56, 1.24
Self-harm/ suicidality	7	4.9	<6	<3.8	2.56	0.67, 9.71	N/A	
Other nonspecific prodromal symptoms	<6	<4.2	<6	<3.8	1.46	0.33, 6.43	N/A	
Other Mental or Behavioural Disorders	12	8.3	<6	<3.8	3.49	1.14, 10.66*	N/A	
Neurological or Neurodevelopmental Condition	21	14.6	24	15.2	1.02	0.58, 1.78	0.95	0.54, 1.67
FP was sure of psychotic disorder diagnosis	38	26.4	33	20.9	1.05	0.85, 1.31	1.06	0.86, 1.30

Note: Frequency missing = 163. All estimates are women compared to men. N/A analyses were unable to be computed due to small sample sizes.

*p < .05

4.5 Discussion

Our findings suggest that women with early psychosis are less likely to present to primary care with positive symptoms than men, particularly delusions. Some prior studies from specialized psychiatric services are consistent with these findings;[43,76,89] however, many studies have found no differences between men and women on positive symptoms.[66,80,128] Men tend to have a less insidious clinical presentation at first onset than women,[37] and women are more likely to seek help in primary care than men.[26] This could indicate that women without positive symptoms are overrepresented in primary care, and women with positive symptoms may be going straight to secondary or tertiary care. This could account for the sex differences found in presentation to primary care, but not later in the course of illness in secondary or tertiary care. It was also found that men present to primary care with more substance use than women, particularly alcohol and cannabis use. These findings align with evidence from prior studies in specialized care.[32,34,66,88] A higher prevalence of alcohol and substance use among men is also evident in the general population,[129] so it is unsurprising that these tendencies carry over to people with early psychosis. Additionally, evidence from previous studies suggests that substance use, specifically the use of cannabis, can act as a risk factor for developing psychotic symptoms and disorders.[130] This may help explain why substance use is common in the clinical presentation of young people in primary care.

There were no sex differences found for other signs and symptoms of early psychosis, including negative symptoms, mood symptoms, anxiety, and functioning. This contradicts findings in reviews from Ochoa at al. and Riechler-Rössler et al., where it was found that men experience more negative symptoms than women, and women experience more mood symptoms and anxiety, and have higher levels of functioning than men.[32,34] The trends we observed may be due to physicians' difficulty in recognizing symptoms and recording them in the EMR due to variability in clinical presentation over time.[131] Evidence suggests that FP's are more comfortable identifying overt symptoms of psychosis such as hallucinations, delusions, and bizarre behaviour, but struggle to identify less obvious psychotic symptoms such as functional decline.[27] Furthermore, patients with these insidious symptoms are more likely to present to primary care.[27] Negative symptoms may be less likely to be identified

by the FP, which may explain why differences in these symptoms were not found. The ability of FPs to recognize psychotic symptoms may also differ by sex – it has been suggested that physicians have greater difficulty detecting the presence of a psychotic disorder in women relative to men,[34,37] which would be heightened in the context of early psychosis presentations in a primary care context. It has been estimated that FPs only come into contact with one or two patients per year with early psychosis, which would explain a low comfort level in identifying symptoms of psychosis.[26] It is also possible that FPs recognize certain early psychosis symptoms, but attribute them to something other than psychosis. For instance, although depression and anxiety are often observed throughout the course psychotic disorders,[132] negative symptoms of psychosis, such as social withdrawal, may be mistaken as a depressive symptom.

We found that a diagnosis of depression or anxiety, personality disorder, psychological distress, or other mental or behavioural disorders (i.e., behaviour disorders, PTSD, eating disorders, sleep disorders) were more common among women, whereas a diagnosis of substance use, alcohol use, or addiction was more common among men. This is consistent with prior literature on gender differences in mental disorder diagnoses, which suggests that women are more likely to be diagnosed with internalizing disorders, such as mood and anxiety disorders, and men are more likely to be diagnosed with externalizing disorders such as substance use disorders.[129] There are many possible explanations for this observed sex difference, including biologic factors, psychosocial factors, and a combination of these.[129] Given the wide range of signs and symptoms of early psychosis, the diagnostic process is often complex.[26] It is possible that patients were in the prodromal phase of a psychotic disorder at the time that a FP gave these diagnoses, and full criteria for a psychotic disorder may not have been met. This would explain the high frequencies of other diagnoses such as depression or anxiety, and a high likelihood that the physician was unsure of the diagnosis. Additionally, FPs may be hesitant to assign a psychotic disorder diagnosis due to the consequences this may hold for the patient.[133]

Our findings suggest that women make more help seeking visits to primary care than men in the one-year period preceding a first diagnosis of psychotic disorder. This trend is consistent with prior research, where women with psychotic disorders were found to make

almost twice as many help-seeking contacts for mental health reasons as men.[25] Additionally, young women were more likely than young men to initiate mental health help-seeking contacts on their own,[25] whereas young men often relied on friends or family to make the first help-seeking contact.[51] This could indicate that women have more opportunities to report their symptoms, but also that women may not receive referrals from family physicians as quickly as men. People with early psychosis who first present to primary care are likely different from those first presenting to secondary or tertiary care services,[18] making it difficult to directly compare our findings to studies conducted in other settings. Furthermore, the patients that make up our sample may be in the prodromal phase of illness and have not yet had psychosis onset. This could mean that our sample is not comparable to samples from secondary or tertiary care. These patients are likely in an earlier stage of illness than those presenting to specialized services, which may mean a less acute clinical presentation and more insidious symptom profile.

Our study is the largest Canadian study to date to explore sex differences in symptoms of psychosis, and the first to explore psychotic disorder symptomology with a focus on presentation in a primary care context. Further research on this topic could incorporate information from electronic medical records, patient self-reports, and standardized symptom measurement tools such as the Positive and Negative Syndrome Scale.[134] This would allow better quantification of sex differences in symptoms, including both prevalence and symptom severity. Future studies should also examine early psychosis symptoms at multiple time points to explore the stability in sex differences over time.

4.5.1 Limitations

This study has some important limitations to consider. The use of pre-existing databases and retrospectively constructed cohorts limits our analyses to variables that are available in the data holdings. The variables available from ICES do not include symptom severity, which allows us to comment only on sex differences in the presence of symptoms. Additionally, there may be differences across physicians in charting practices with respect to the level of detail on symptoms that are recorded in the EMR. We were unable to account for physician characteristics that may contribute to these differences. Charting practices

among FPs may also differ across male and female patients, with prior research on the general population indicating that women may give a more complete history, but also may receive less care than men.[37,135] Due to the lack of a standardized screening tool used among FPs, we are unable to identify whether symptoms of psychosis were not present, or if the FP failed to record them in the EMR. The data holdings also do not include important confounding factors such as culture or ethnicity,[136] which may play a role in differential clinical presentation by sex. We are unable to identify affective psychotic disorders within the health administrative data, limiting our cohort to non-affective psychoses only. A four-digit diagnostic code is used to identify affective psychotic disorders; however, three-digit diagnostic codes are used in the OHIP database, which limits our ability to identify these disorders in outpatient settings. Therefore, we are unable to generalize our findings to all cases of early psychosis. Further, diagnostic codes may not be a reliable source for identifying cases of psychosis, as they may not provide an accurate description of the reason for contact with mental health services. All contacts with primary care in Ontario were not represented in the data holdings, as only a small proportion of Ontario FPs and patients are represented in the EMRPC database. Our analysis on sex differences in diagnoses assigned by the FP was further limited by missing data. Additionally, we were unable to see the diagnostic codes FPs submitted for OHIP billing, which may differ from the diagnoses recorded by the FP in the EMR. Lastly, we were unable to account for the role that gender identity may play in psychotic symptom differences.[32]

4.5.2 Conclusions

Our study identifies some sex differences in the clinical profile of early psychosis presenting to primary care for mental health services. Our findings indicate that one year preceding the first diagnosis of a psychotic disorder, men present with more positive symptoms and substance use than women. No sex differences were noted for other symptoms of early psychosis. We found that one year before the psychotic disorder diagnosis, more women were diagnosed with depression or anxiety, personality disorders, psychological distress, and other mental or behavioural disorders by the FP, whereas more men were diagnosed with substance use, alcohol use, or addiction. Given the crucial role that the FPs and primary care play in the pathway to care for early psychosis, there is a

need to understand the differences in clinical presentation between men and women. Findings from this study may be used to highlight the need for continued education for primary care practitioners. This would facilitate better detection of first-episode psychosis at the primary care level and allow for early intervention of psychotic disorders. In turn, decreasing the duration of untreated psychosis could allow for improved clinical and functional outcomes for young people with first-episode psychosis. Further research is needed to better understand sex differences in symptoms of early psychosis outside the context of specialized services.

Chapter 5

5 Synthesis and Conclusion

This chapter aims to synthesize and contextualize the findings from Chapters 3 and 4 of this thesis to the larger body of literature. Together, these studies build a greater understanding of sex differences in the clinical presentation of psychosis in primary care. The research contributions and limitations of our studies will be noted. Finally, we will discuss clinical implications, and direction for future studies in this area.

5.1 Summary of Studies

Although sex differences in symptoms of psychosis have been well documented in specialized services, findings are inconsistent across studies, and a gap remains on the clinical presentation of young men and women with early psychosis in other settings. The overall aim of thesis was to explore sex differences in clinical presentation of early psychosis in the context of primary care using two independent analyses. First, we conducted a systematic review and meta-analysis to synthesize existing literature on sex/gender differences in symptoms of early psychosis (Chapter 3). This provided context for our subsequent study, in which we used health administrative data linked with electronic medical records (EMR) in Ontario, Canada to explore sex differences in clinical presentation of early psychosis in a primary care setting (Chapter 4).

Our systematic review and meta-analysis included studies that examined sex or gender differences in symptoms of early psychosis. All 35 included studies examined sex of participants, with no studies measuring gender, and all studies drew their samples from specialized settings. We found that men with early psychosis experienced more severe negative symptoms (SMD=-0.15, 95%CI=-0.21, -0.09), whereas women experienced more severe depressive symptoms (SMD=0.21, 95%CI=0.14,0.27) and had higher functioning (SMD=0.16, 95%CI=0.10,0.23). We also found that women with early psychosis had a lower prevalence of substance use issues than men (PR=0.65, 95%CI=0.61,0.69).

Our EMR analysis from primary care found that one year preceding the first diagnosis of psychotic disorder, positive symptoms (PR=0.76, 95%CI:0.58,0.98) and substance use

(PR=0.54, 95%CI:0.40,0.72) were less prevalent in the medical records of women. We did not find any other sex differences in symptoms at presentation to primary care. We also found that visits by women were more likely to be assigned a diagnosis of depression or anxiety (PR=1.18, 95%CI:1.00,1.38), personality disorder (PR=5.49, 95%CI:1.22,24.62), psychological distress (PR=11.29, 95%CI:1.23,103.91) and other mental or behavioural disorders (PR=3.49, 95%CI:1.14,10.66), and less likely to be assigned a diagnosis of substance use, alcohol use, or addiction (PR=0.33, 95%CI:0.13,0.87).

5.2 Synthesis

In this section, we will compare findings from our two studies and discuss these findings in the context of existing literature.

In our EMR analysis, we found that positive symptoms were less prevalent in the medical records of women (PR=0.76, 95%CI:0.58,0.98). This is in contrast with our findings from the systematic review and meta-analysis, in which we found no differences in positive symptoms between men and women with early psychosis. Prior research indicates that women are more likely to seek help in primary care than men,[26] but also that men have a more acute clinical presentation than women at first onset.[37] Taken together, this may account for the difference in findings between studies, as women without positive symptoms may be overrepresented in primary care. Our two studies had similar findings with regards to sex differences in substance use among people with early psychosis. We found that substance use was less prevalent in the medical records of women than men (PR=0.54, 95%CI:0.40,0.72) (Chapter 4), and similarly, that the risk of substance use was lower in women than in men (RR=0.65, 95%CI=0.61,0.69) (Chapter 3). Although we did not find any other sex differences in signs and symptoms of early psychosis in our EMR analysis, our systematic review and meta-analysis found that men experienced more severe negative symptoms (SMD=-0.15, 95%CI=-0.21, -0.09), whereas women experienced more severe depressive symptoms (SMD=0.21, 95%CI=0.14,0.27) and had higher functioning (SMD=0.16, 95%CI=0.10,0.23).

The small sample size and lack of standardization in charting practices across physicians may help explain why findings from our EMR analysis differed from the systematic review

and meta-analysis. Furthermore, although our systematic review and meta-analysis captured sex differences in the severity of psychotic symptoms, the EMR analysis was limited to comment only on the presence of symptoms as recorded in the medical records, making it difficult to directly compare results from the separate studies. This may help explain some of the differences found between our study and prior literature, as many other studies examined symptom severity using validated instruments.[66,80,128] Our EMR analysis included only cases of non-affective psychosis, whereas our systematic review and meta-analysis included cases of both affective and non-affective psychosis. This may also help explain contrasting findings, as people with affective and non-affective psychotic disorders differ in a number of ways, including their gender and clinical presentation.[137] Moreover, the different clinical settings between the studies can account for differences in findings. Evidence suggests that people with early psychosis who first present to primary care are different than those presenting to secondary or tertiary care, and that people access primary care earlier in the course of illness.[18,25] People presenting to primary care may have more subtle and insidious symptoms, which may be difficult for FPs to identify.[114] This could indicate differences in clinical presentation to primary care compared to other services, and account for differences in findings between the two studies. Results from this study cannot be easily compared to prior research; however, our findings are highly novel and important to the larger body of literature.

5.3 Research Contributions

The chapters of this thesis add to the body of literature on how young men and women with early psychosis present differently to mental health services, specifically in the primary care context. To our knowledge, we conducted the first systematic review and meta-analysis to quantify sex differences in symptoms of psychosis specifically in the early course of illness (Chapter 3). This study clarified findings from the larger body of literature and contributed to understanding how sex differences in the early course may differ from sex differences later in the course of illness. Our study using EMR data is the first study to explore sex differences in clinical presentation of early psychosis with a focus on primary care, and the largest Canadian study to date to explore sex differences in symptoms of psychosis (Chapter 4). Prior literature has focused on the presentation of early psychosis

in specialized settings, with our study filling the gap of presentation to a primary care setting.

5.4 Limitations

Our systematic review and meta-analysis has some important limitations. Of the studies included, small sample sizes and narrow inclusion criteria (such as age or duration from symptom onset) were concerns for generalizability of findings. Furthermore, sex differences in cognitive symptoms of psychosis were overlooked throughout the literature. The overall review was also limited by heterogeneity of data, and the inability to distinguish between sex and gender. The role of gender in the clinical presentation of early psychosis is still underrepresented in the literature, and we were unable to determine whether the differences we found in psychotic symptoms were due to biologic sex or gender factors.

The primary limitation of our EMR analysis stems from the small sample size captured by the EMRPC database. Only a small proportion of Ontario family physicians (FPs) and people with early psychosis were captured in this study, impacting the representativeness of our findings. The use of administrative data limits our ability to determine whether symptoms of psychosis were not present, or if the FP did not record them in the EMR. There may be differences between FPs in terms of their charting practices, which also may differ between men and women patients.[37,135] The use of a standardized screening tool for identifying early psychosis in primary care would help to mitigate this limitation in future studies. Due to the use of pre-existing databases and the variables that were available to us, our study was limited to a focus on the presence of symptoms, rather than symptom severity. This study was able to capture sex of the patients included, however, there was no measurement of gender. This concept has often been ignored in mental health research, and is also a limitation of the present study.[31]

5.5 Clinical Implications

Our study highlights the importance of recognizing sex differences in the clinical presentation of early psychosis, namely in the context of primary care. Given that family

physicians (FPs) and primary care are often the first point of contact for early psychosis help-seeking,[25,138] and early intervention can help improve clinical and functional outcomes,[2] recognizing psychotic symptoms at this stage is a clinical imperative. Our findings suggest that men and women differ in their clinical presentation of early psychosis, which has important implications for clinical practice. Although we found that positive symptoms and substance use were less common in the medical records of women, we did not find any other sex differences in clinical presentation, which could indicate that FPs are not identifying or recording all early psychosis symptoms.

The findings from this thesis demonstrates the need for further education of the signs and symptoms of early psychosis, and how they differ among men and women. Such opportunities should be available for primary care providers in particular, allowing for more timely recognition and intervention of psychotic disorders. Prior research has indicated that FPs only come into contact with one to two early psychosis patients per year and they lack knowledge on identifying more subtle symptoms of psychosis, such as functional decline.[27] We found that FPs were more likely to assign a diagnosis of depression or anxiety, personality disorders, psychological distress and other mental or behavioural disorders to women, whereas they were more likely to assign a diagnosis of substance use, alcohol use, or addiction to men. This could further indicate a low comfort level with early psychosis among FPs in Ontario. Prior research, as well as findings from the present study, emphasize the need for continuing medical education of primary care providers in recognizing and responding to early psychosis symptoms.

5.6 Future Studies

Future research is needed to better assess sex and gender differences in the clinical presentation of early psychosis in the context of primary care. Integration of information from medical records, patient self-reports, and a standardized symptom measurement tool used across FPs would allow for the symptom profile of patients to be examined in much greater detail, examining both symptom prevalence and severity. The use of both administrative and patient-level data would provide more certainty about accuracy of data, and increase comparability with prior studies in specialized settings.[139] Furthermore, it would be useful to explore the effect of clinical and sociodemographic factors on sex

differences in clinical presentation. Although we adjusted for these factors in the present study, it would be an interesting point of future studies to explore these factors further.

Studies with larger sample sizes, a wider age and criteria of inclusion, and records at multiple time points are needed to better quantify sex differences in clinical presentation, which may evolve over the course of illness. Larger studies that include patients of all ages with both affective and non-affective psychotic disorders are needed to help generalize findings to all patients experiencing early psychosis in Ontario, and to understand sex differences between different populations of early psychosis patients. Longer term studies would enable us to see the stability of clinical presentation over the course of illness, and moreover, how sex plays a role in changes in clinical presentation over time.

Lastly, future studies should consider the role of both sex and gender in differences in clinical presentation of early psychosis. There are many grey areas of these variables that prior research, including the present study, have not accounted for. Future studies should consider populations such as LGBTQ+ people, intersex people, or individuals with hormone dysfunction to provide clarity on biological, social, and psychological factors that impact clinical presentation of early psychosis. Furthermore, it would be useful to consider exposures that differ between men and women that could contribute to differential clinical presentation. Some of these factors could include childhood trauma or abuse, head injury, spring birth, in-utero or birth complications, or pregnancy.[12,98]

5.7 Conclusions

The primary objective of this thesis was to identify and describe sex differences in the clinical presentation of early psychosis in the context of primary care. Our systematic review and meta-analysis found that among people with early psychosis, men with early psychosis experienced more severe negative symptoms, whereas women experienced more severe depressive symptoms and had higher functioning. We also found that women with early psychosis had a lower prevalence of substance use issues than men. However, these findings were limited to samples recruited from specialized psychiatric services. Our subsequent analysis of medical records in primary care found that in the period one year preceding the first diagnosis of psychotic disorder, positive symptoms and substance use

were less prevalent in the medical records of women. No sex differences were noted for other symptoms of early psychosis. We also found that one year before the psychotic disorder diagnosis, more women were diagnosed with depression or anxiety, personality disorders, psychological distress and other mental or behavioural disorders by a family physician and were less likely to be assigned a diagnosis of substance use, alcohol use, or addiction. Overall, this thesis contributes evidence on the sex differences in symptoms of early psychosis, and further contextualizes these differences in a primary care setting. The findings from this thesis highlight the importance of understanding how men and women differently present with early psychosis outside of specialized services and serves to allow for better detection of early psychosis at the primary care level.

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Appendices

Appendix 3A: PRISMA Checklist

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.

Section and Topic	Item #	Checklist item
RESULTS		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Appendix 3B: Sex/gender differences in symptoms of psychosis – term harvesting table

Concept	Medline (ProQuest)	CINAHL	Scopus	PsycInfo (Ovid)	Keywords
Psychosis	psychosis OR psychotic OR schizophreni* OR "Affective Disorders, Psychotic" OR "Psychotic Disorders	(MH "Psychotic Disorders+") OR "psychosis OR psychotic OR schizophreni*"	(TITLE-ABS-KEY (psychosis OR psychotic OR schizophreni*)	exp psychosis OR psychosis OR psychotic OR schizophreni*	Psychosis, psychotic, schizophreni*
First-episode	(early adj3 (psycho* OR schizophreni* OR intervention)) OR (first adj3 episode) OR (acute adj3 psycho*) OR (recent onset adj3 psychosis)	none	early W/3 (psycho* OR schizophreni* OR intervention)) OR first W/3 episode OR acute W/3 psycho*) OR (recent AND onset W/3 psychosis	(early adj3 (psycho* OR schizophreni* OR intervention)) OR (first adj3 episode) OR (acute adj3 psycho*) OR (recent onset adj3 psychosis)	early adj3 (psycho* OR schizophreni* OR intervention)) OR (first adj3 episode) OR (acute adj3 psycho*) OR (recent onset adj3 psychosis)
Symptoms	symptom* OR "Behavioral Symptoms" OR "Symptom Assessment" OR "Affective Symptoms"	(MH "Signs and Symptoms+") OR "symptom" OR (MH "Symptoms+")	symptom*	symptom* OR exp Symptoms	Symptom*
Sex/Gender differences	sex OR gender OR "sex difference" OR "gender difference" OR men OR women OR male OR female OR "Gender Identity" OR "Sex Factors" OR "Sex Differentiation"	(MH "Sex Factors") OR "sex difference*" OR "gender difference*" OR "sex" OR "gender"	sex OR gender OR "sex difference" OR "gender difference"	sex OR gender OR exp Human Sex Differences OR "sex difference" OR "gender difference"	Sex, gender, difference
No limits	7,603	1,505	597	821	Total: 10,526
Limit by 1990-present, humans	2,068	1,499	581	807	Total: 4,955
			TOTAL AFTER REMOVING DUPLICATES:		4,436

Appendix 3C: Inclusion and exclusion criteria

PECOS Component	Inclusion Criteria	Exclusion Criteria
Population	First episode or early psychosis patients – must either have a diagnosis of psychosis/psychotic disorder based on any criteria (DSM, ICD) Both affective and non-affective psychotic disorders will be included. There will be no restrictions on the age of the sample.	Studies that include chronic patients, patients with other mental illnesses that do not fall under psychotic disorders, UHR, CHR, or prodromal patients
Exposure & Comparison	First episode psychosis with the comparison of symptoms between sexes/genders	Studies that do not compare symptoms of psychosis between the sexes/genders
Outcome	Any study that evaluates symptoms of early psychosis.	Studies that do not include symptoms of psychosis
Study Design	Any observational study with quantitative results.	Experimental or interventional studies, case-reports, case-series, qualitative studies.
Time Frame	Must be published within 1990-2021 No limits on follow up time will be placed.	Publications prior to 1990.
Other Exclusions	No limits on language or sample size will be placed.	Non-peer reviewed articles will be excluded. Abstracts will be excluded unless a subsequent publication can be obtained.

Appendix 3D: Symptom measurement tools across included studies (n=35)

Study ID, Author	Positive	Negative	Depression	Psychopathology	Functioning	Alcohol Use	Drug Use
1. Arnold et al. [64]	SAPS*	SANS*	HDRS*	N/A	GAF*	N/A	N/A
2. Arranz et al.[43]	PANSS	PANSS	CDSS*	N/A	N/A	N/A	N/A
3. Austad et al.[40]	PANSS	PANSS	PANSS	N/A	GAF	Prevalence	Prevalence
4. Ayesa-Arriola et al.[65]	SAPS	SANS	CDSS	BPRS	GAF	N/A	N/A
5. Barajas et al.[66]	PANSS	PANSS	N/A	N/A	GAF	Prevalence	Prevalence
6. Bertani et al.[67]	N/A	N/A	PANSS*	N/A	N/A	N/A	N/A
7. Buck et al.[68]	SAPS	SANS	CDSS	N/A	SOFAS	N/A	N/A
8. Caton et al.[42]	PANSS	PANSS	PANSS	PANSS	N/A	N/A	N/A
9. Chang et al.[39]	CGI-S	CGI-S	CGI-S	N/A	N/A	Prevalence (combined with drug use)	
10. Chen et al.[69]	PANSS	PANSS	N/A	PANSS	N/A	N/A	N/A
11.Cocchi et al.[70]	N/A	N/A	N/A	BPRS	GAF	Prevalence (combined with drug use)	
12. Cotton et al.[44]	N/A	N/A	CGI-S	N/A	GAF	Prevalence (combined with drug use)	
13. Dama et al.[71]	SAPS	SANS	CDSS	N/A	SOFAS	N/A	N/A
14. Danaher et al.[72]	Sum of 4 items*	SANS	N/A	BPRS	SOFAS	N/A	N/A
15. Garcia et al.[73]	PANSS*	PANSS*	CDSS*	PANSS*	GAF	Prevalence	Prevalence
16. Heitz et al.[74]	BPRS	SANS	N/A	N/A	N/A	N/A	N/A
17. Hui et al.[75]	PANSS, SAPS	PANSS, SANS	N/A	PANSS	SOFAS	N/A	N/A
18. Køster et al.[49]	PANSS*	PANSS*	N/A	N/A	GAF*	Prevalence	Prevalence
19. Lang et al. [76]	PANSS	PANSS	N/A	PANSS	N/A	N/A	N/A
20. Malla et al.[77]	SAPS	SANS	CDSS	N/A	N/A	N/A	N/A
21. Mbewe et al.[78]	Criteria checklist*	Criteria checklist*	Criteria checklist*	N/A	N/A	N/A	N/A
22. Navarro et a. [79]	N/A	Criteria checklist*	N/A	N/A	N/A	Prevalence (combined with drug use)	
23. Penney et al.[80]	SAPS	SANS	CDSS	N/A	N/A	N/A	N/A
24. Preston et al.[81]	PANSS	PANSS	N/A	PANSS	N/A	N/A	N/A
25. Pruessner et al.[82]	BPRS	BPRS	BPRS	N/A	GAF	N/A	Prevalence
26. Rapado-Castro et al. [83]	PANSS	PANSS	N/A	PANSS	GAF	N/A	N/A
27. Segarra et al.[84]	PANSS	PANSS	N/A	PANSS	GAF	N/A	N/A
28. Suhail & Chaudry[85]	PANSS*	PANSS*	N/A	N/A	N/A	N/A	N/A
29. Talonen et al.[86]	Criteria checklist*	N/A	Criteria checklist*	N/A	N/A	Prevalence	Prevalence
30. Vila-Badia et al.[87]	PANSS	PANSS	N/A	N/A	N/A	N/A	N/A
31. Irving et al.[88]	Criteria checklist*	Criteria checklist*	Criteria checklist*	Criteria Checklist*	Criteria checklist*	N/A	Prevalence
32. Cotton et al[8.6]	CGI-S	N/A	CGI-BP	CGI-BP mania	GAF	Prevalence	Prevalence
33. Häfner et al.[90]	PSE, CATEGO	SANS, DAS	DAS	N/A	N/A	N/A	PSE
34. Gonzaáez-Rodriguez et al.[91]	BPRS	SANS	FCQ	BPRS	N/A	N/A	Prevalence
35. Thorup et al.[38]	SAPS	SANS	N/A	N/A	GAF	N/A	N/A

Notes: SAPS = Scale for Assessment of Positive Symptoms, SANS = Scale for Assessment of Negative Symptoms, HDRS = Hamilton Depression Rating Scale, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions Scale, SOFAS = Social Occupational Functioning Assessment Scale, SOPS = Scale of Psychotic-Risk Symptoms, BPRS = Brief Psychiatric Rating Scale. ***** Means not available

Appendix 3E: Positive and negative symptoms among included studies (n=32)

Study ID, Author	Positive Symptoms				Negative Symptoms			
	Women		Men		Women		Men	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1. Arnold et al. [64]	AA: 12 EA: 11	AA:4 EA:4	AA: 13 EA: 11	AA: 3 EA: 3	AA: 13 EA: 13	AA: 5 EA: 5	AA: 13 EA: 13	AA: 5 EA: 5
2. Arranz et al.[43]	24.5	6.2	26.81	6.22	16.29	8.63	15.23	6.64
3. Austad et al.[40]	14.1	3.2	14.9	4.4	18.6	7.6	19	7.3
4. Ayesa-Arriola et al.[65]	14.48	4.34	13.84	4.23	6.43	5.8	6.83	6.41
5. Barajas et al.[66]	25.69	8.51	25.75	7.92	27.06	12.2	27.42	7.62
7. Buck et al.[68]	16.54	16.82	14.43	14.24	21.68	13.82	23.09	13.82
8. Caton et al.[42]	17.6	8	19.1	6.9	13.8	6.3	14.3	6.2
9. Chang et al.[39]	4.2	0.9	4.2	0.9	2.5	1.3	2.7	1.3
10. Chen et al.[69]	15.82	4.6	16.26	4.97	15.89	5.23	16.8	6.22
13. Dama et al.[71]	34.63	16.62	34.04	14.35	22.39	13.07	25.64	13.73
14. Danaher et al.[72]	8.77	4.7	8.74	4.39	24.82	13.43	26.35	12.13
15. Garcia et al.[73]	(Median) 9	(Range) 7-17	10	7-24	(Median) 14	(Range) 7-28	14	7-39
16. Heitz et al.[74]	14.4	3.58	12.8	4.2	20.6	16.2	27.2	16.7
17. Hui et al.[75]	5	9.3	4.5	7.2	9.7	4.3	10.9	4.6
18. Køster et al.[49]	18		19		19		21	
19. Lang et al. [76]	22.8	5.3	28.7	7.4	18.5	5.5	23.3	11.2
20. Malla et al.[77]	2.12	2.7	2.7	3.3	5.3	4.5	6.7	4.2
21. Mbewe et al.[78]	(n) Delusions: 27 Hallucinations: 33	(%) 60 73	(n) 84 87	(%) 73 76	(n) 15	(%) 33	(n) 37	(%) 32
22. Navarro et a. [79]					0.8	1.2	1.2	1.5
23. Penney et al.[80]	4.38	4.07	4.5	3.87	7.46	3.86	8.31	3.65
24. Preston et al.[81]	13.07	6.05	18.33	7.9	11.28	4.17	14.73	5.28
25. Pruessner et al.[82]	24.7	6.06	26.11	6.66	6.23	3.32	6.84	3.34
26. Rapado-Castro et al. [83]	20.4	10.5	19.4	8.5	43.3	13.6	46.7	10.2
27. Segarra et al.[84]	26.18	7.23	25.71	7.2	22.32	9.34	25.48	9.53
28. Suhail & Chaudry[85]	(n) 8	(%) 12	(n) 10	(%) 13	(n) 18	(%) 28	(n) 29	(%) 39
29. Talonen et al.[86]	(n) 70	(%) 100	(n) 36	(%) 100				
30. Vila-Badia et al.[87]	10.33	4.95	11.51	4.78	16.48	8.98	19.02	6.58
31. Irving et al.[88]	(n) Delusions: 957 Halluc (aud/vis): 503 Halluc (olfact/gust/tact): 162 Aggression: 802 Agitation: 879 Hostility: 477 Paranoia: 1122	(%) 76 40 12.9 63.8 69.9 37.9 89.2	(n) 1596 869 204 1494 1545 801 1917	(%) 76.3 41.5 9.8 71.4 73.9 38.3 91.6	(n) 150	(%) 11.9	(n) 411	(%) 19.6
32. Cotton et al[8.6]	5.5	0.7	5.8	0.8				
33. Häfner et al.[90]	(% only) Non-specific psychosis	91.6		97.7	(% only) Social withdrawal Anhedonia Social inattentiveness	56.5 62.6 32.6		77.9 76.6 47.6
34. Gonzaáez-Rodriguez et al.[91]	3.1	0.9	2.8	0.9	1.1	0.8	1.4	0.9
35. Thorup et al.[38]	2.92		2.56		2.02		2.29	

Note: All values are presented as means or SD unless otherwise specified. AA = African American, EA = European American

Appendix 3F: Depressive symptoms among included studies (n=20)

Study ID, Author	Depressive Symptoms			
	Women		Men	
	Mean	SD	Mean	SD
1. Arnold et al. [64]	AA: 23 EA: 22	AA: 10 EA: 9	AA: 21 EA: 20	AA: 10 EA: 9
2. Arranz et al.[43]	(Median) 3	(Range) 0-7.75	(Median) 2	(Range) 0-6
3. Austad et al.[40]	13.4	3.7	12	3.6
4. Ayesa-Arriola et al.[65]	2.24	3.2	3.08	4.01
6. Bertani et al.[67]	3.41	1.78	2.92	1.77
7. Buck et al.[68]	3.92	4.5	2.5	3.98
8. Caton et al.[42]	12.1	3.9	10.8	4.9
9. Chang et al.[39]	2.6	1.3	2.2	1.4
12. Cotton et al.[44]	2.3	1.8	1.9	1.54
13. Dama et al.[71]	5.77	4.75	4.68	4.72
15. Garcia et al.[73]	(Median) 1	(Range) 0-14	(Median) 1	(Range) 0-14
21. Mbewe et al.[78]	1.9	3	1.5	2.5
22. Navarro et a. [79]	(n) 9	(%) 20	(n) 12	(%) 10
23. Penney et al.[80]	2.92	3.39	3.06	3.85
25. Pruessner et al.[82]	13.11	4.83	11.46	4.51
29. Talonen et al.[86]	(n) 64	(%) 91.4	(n) 22	(%) 61.1
31. Irving et al.[88]	(n) Worthless: 129 Anhedonia: 207 Low mood: 1162 Guilt: 426 Poor concentration: 817 Reduced appetite: 593 Low energy: 503	(%) 10.3 16.5 92.4 33.9 63.9 47.1 40	(n) 171 333 1874 576 1265 794 622	(%) 8.2 15.9 89.4 27.5 60.3 37.9 29.7
32. Cotton et al[8.6]	1.4	1.3	1.5	1.3
33. Häfner et al.[90]	(% only) Lack of interest in job Underactivity during past month	 34.3 59.3		 69.4 83.7
34. Gonzaáez-Rodriguez et al.[91]	0.4	0.2	0.4	0.3

Note: All values are presented as means or SD unless otherwise specified
AA = African American, EA = European American

Appendix 3G: General psychopathology symptoms among included studies (n=14)

Study ID, Author	General Psychopathology Symptoms			
	Women		Men	
	Mean	SD	Mean	SD
1. Arnold et al. [64]	AA: 24 EA: 23	AA: 8 EA: 8	AA: 22 EA: 24	AA: 6 EA: 8
4. Ayesa-Arriola et al.[65]	64.82	13.1	64.62	12.52
8. Caton et al.[42]	33.5	10.7	33.3	10.4
10. Chen et al.[69]	30.52	7.49	31.76	8.4
11.Cocchi et al.[70]	14.8	6.3	14.8	6.4
14. Danaher et al.[72]	46.27	11.02	45.69	12.55
15. Garcia et al.[73]	(Median) 23	(Range) 16-41	(Median) 26	(Range) 16-55
17. Hui et al.[75]	23.3	7.1	22.6	7.4
19. Lang et al. [76]	36.3	5.8	50.5	13
24. Preston et al.[81]	27.92	6.9	31.9	10.38
26. Rapado-Castro et al.[83]	22.9	6.8	25.3	5.9
27. Segarra et al.[84]	45.42	12.2	47.56	12.86
32. Cotton et al.[89]	4.6	1.5	4.7	1.8
34. González-Rodriguez et al.[91]	2.6	1.0	2.7	1.1

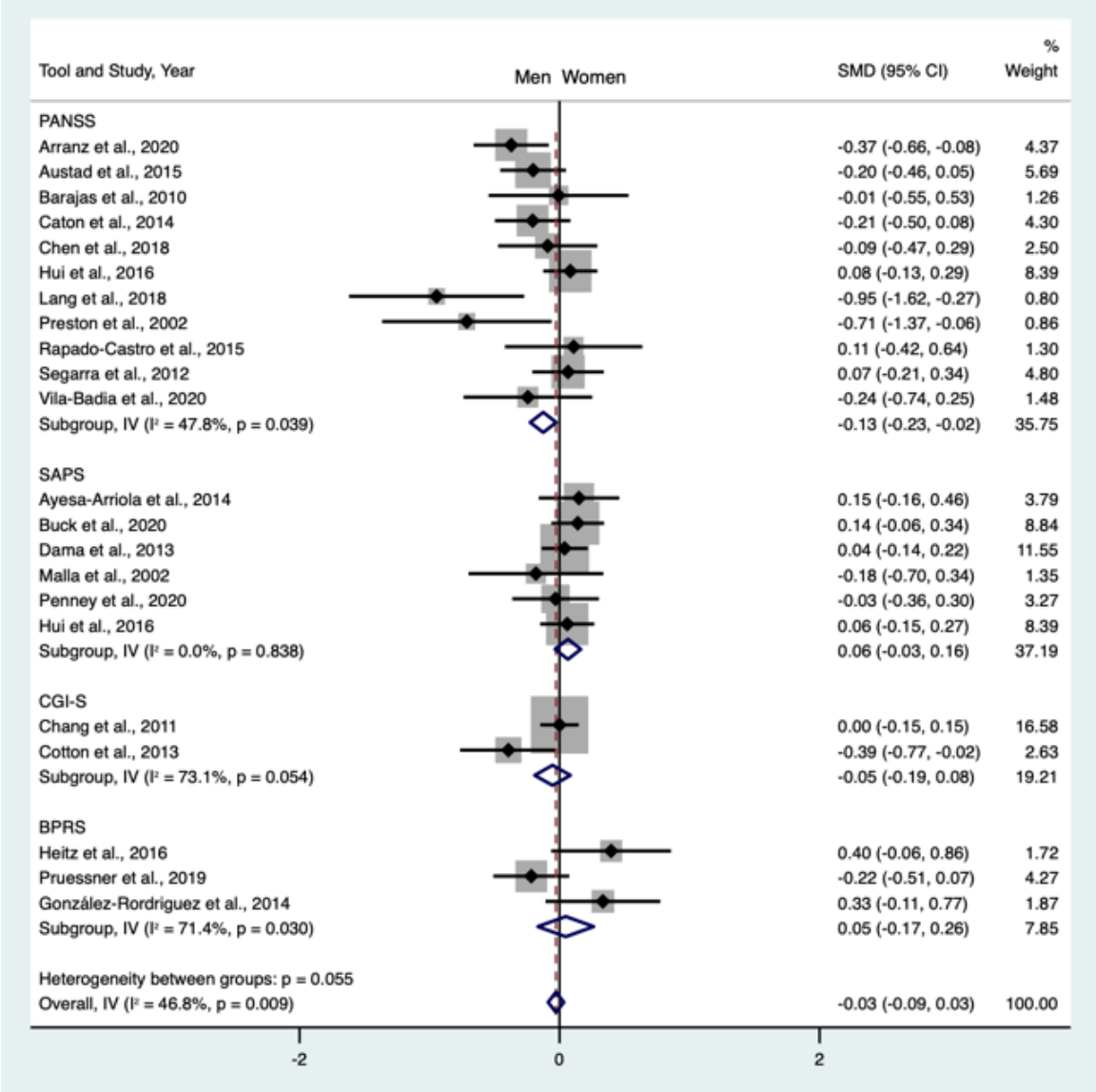
Appendix 3H: Functioning among included studies (n=16)

Study ID, Author	Functioning			
	Women		Men	
	Mean	SD	Mean	SD
3. Austad et al.[40]	32.3	6.5	30.8	7.7
4. Ayesa-Arriola et al.[65]	59.05	30.24	50.36	30.29
5. Barajas et al.[66]	35.36	15	34	9.66
7. Buck et al.[68]	63.27	18.5	61.98	17.04
11. Cocchi et al.[70]	45.6	14.3	45.3	10.4
12. Cotton et al.[44]	33.6	9.2	31.4	10
13. Dama et al.[71]	44.04	13.79	39.98	12.79
14. Danaher at al.[72]	52.32	8.72	51.43	11.44
15. Garcia et al.[73]	66	12.1	64	12.5
17. Hui et al.[75]	60.2	12.7	58.2	14.4
18. Køster et al.[49]	37		38	
25. Pruessner et al.[82]	31.44	9.16	29.43	8.71
26. Rapado-Castro et al.[83]	32.3	16.8	36	14.6
27. Segarra et al.[84]	40.11	17.49	37.35	14.78
32. Cotton et al.[89]	33.5	9.1	29.7	10.1
35. Thorup et al.[38]	42.78	14.22	39.66	12.34

Appendix 3I: Substance use symptoms among included studies (n=14)

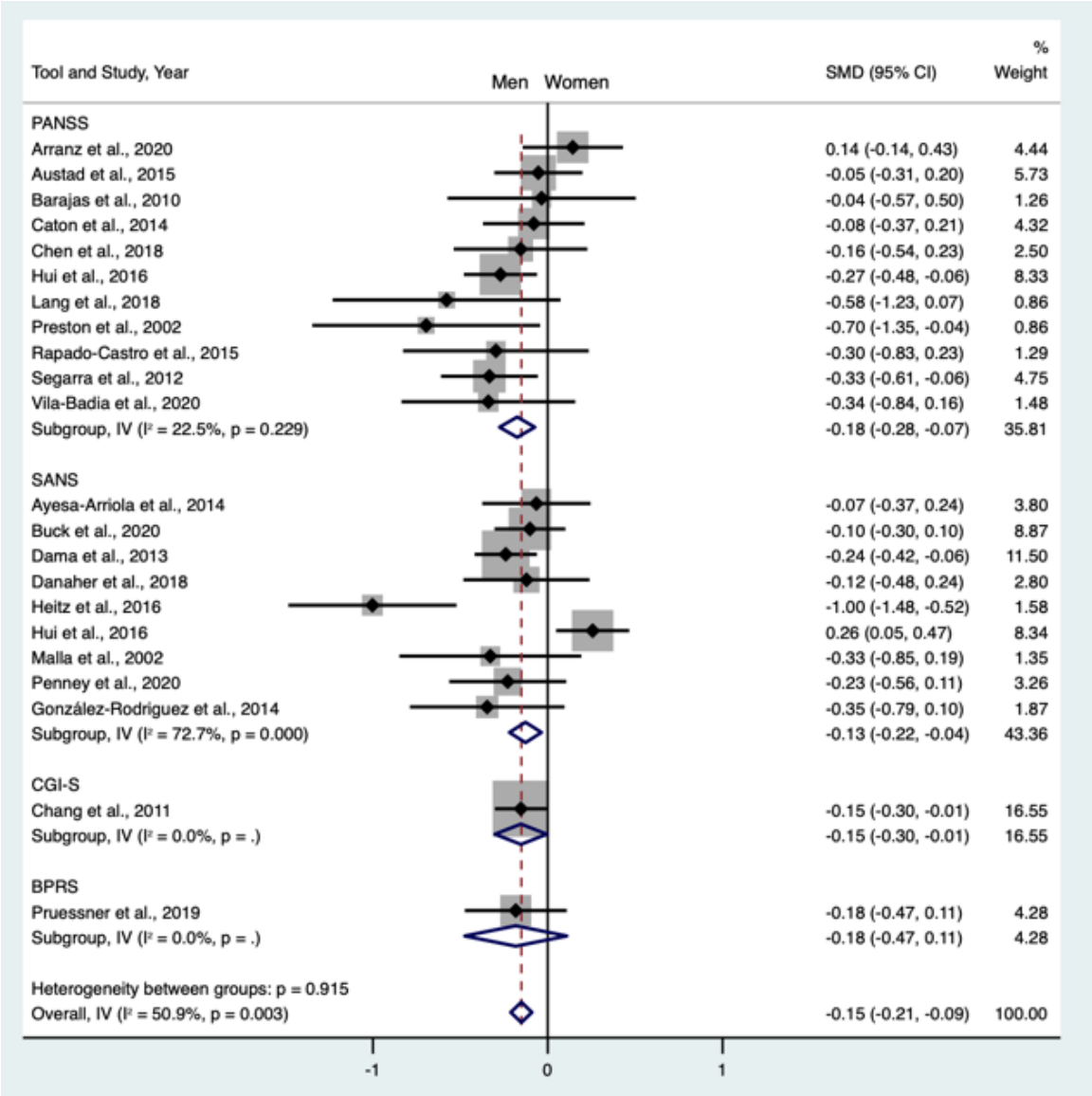
Study ID, Author	Substance Use				Alcohol Use				Drug Use			
	Women		Men		Women		Men		Women		Men	
	n	%	n	%	n	%	n	%	n	%	n	%
3. Austad et al.[40]					15	14.3	17	12.1	29	27.9	61	43.6
5. Barajas et al.[66]					1	3.7	3	11.5	6	22	16	59
9. Chang et al.[39]	19	5.6	33	9.2								
11. Cocchi et al.[70]	2	6	14	12								
12. Cotton et al.[44]	109	48.2	297	68.3								
15. Garcia et al.[73]					2	6.5	7	14.6	7	22.6	21	43.8
18. Køster et al.[49]					7	8	13	7	8	9	23	13
22. Navarro et al.[79]	6	13	20	25								
25. Pruessner et al.[82]									21	31.8	90	63.4
30. Talonen et al.[86]					20	28.6	19	52.8	14	20	9	25
31. Irving et al.[88]									611	48.6	1570	74.9
32. Cotton et al.[89]	4	8.5	10	14.1	6	12.8	8	11.3	17	36.2	39	54.9
33. Häfner et al.[90]										4.2		14.8
34. González-Rodriguez et al. [89]									8	25.8	26	46.4

Appendix 3J: Meta-analysis of positive symptoms, with subgroup analysis by measurement tool (n=21)



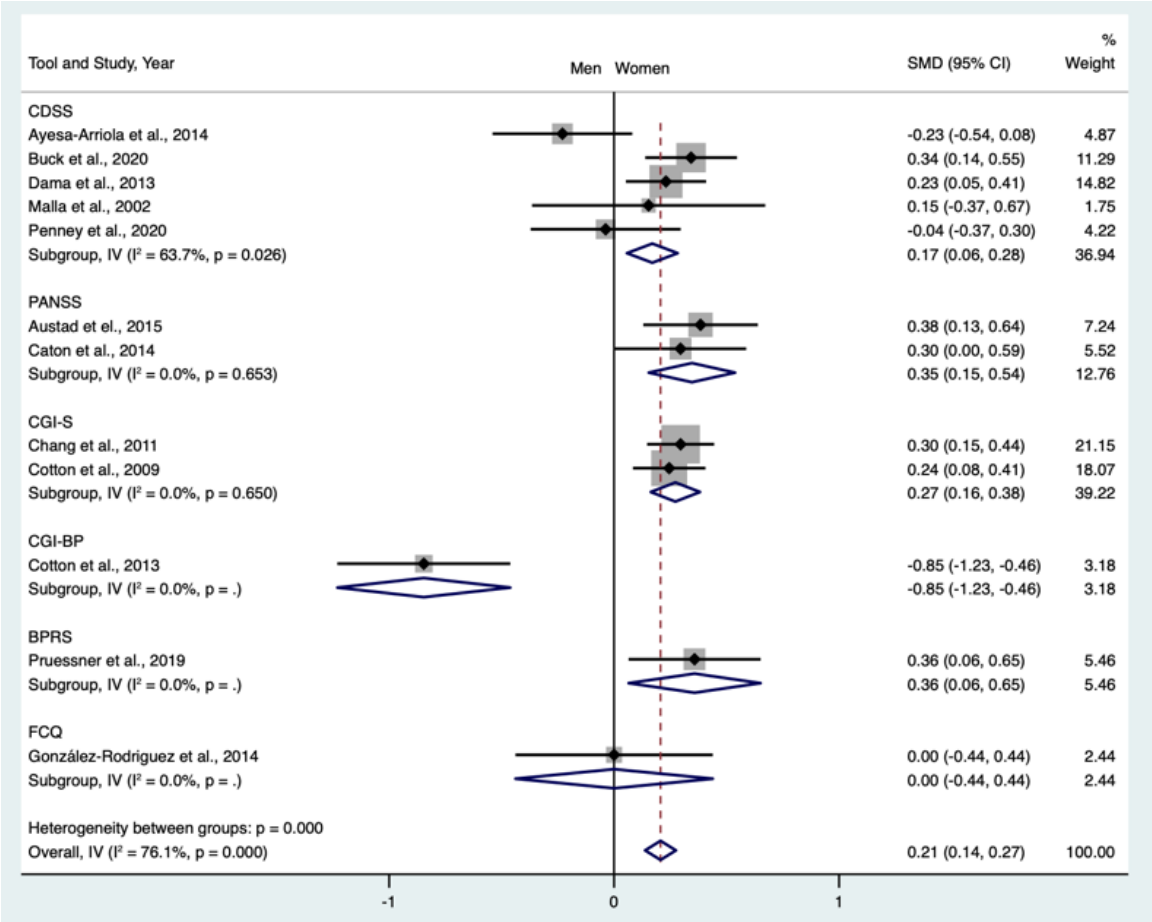
Notes: PANSS = Positive and Negative Syndrome Scale, SAPS = Scale for the Assessment of Positive Symptoms, CGI-S = The Clinical Global Impression-Severity Scale, BPRS = Brief Psychiatric Rating Scale

Appendix 3K: Meta-analysis of negative symptoms, with subgroup analysis by measurement tool (n=21)



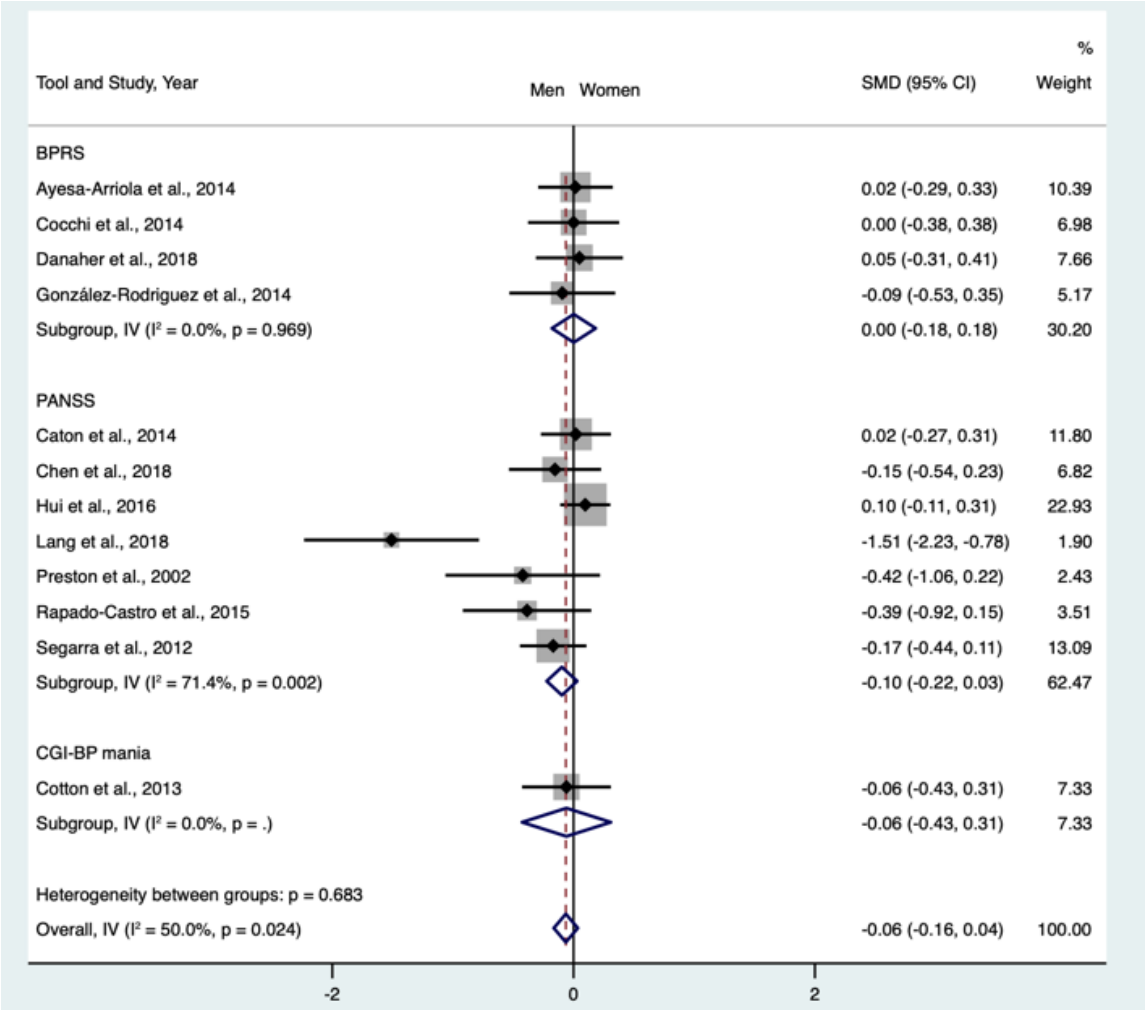
Notes: PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, CGI-S = The Clinical Global Impression-Severity Scale, BPRS = Brief Psychiatric Rating Scale

Appendix 3L: Meta-analysis of depressive symptoms, with subgroup analysis by measurement tool (n=12)



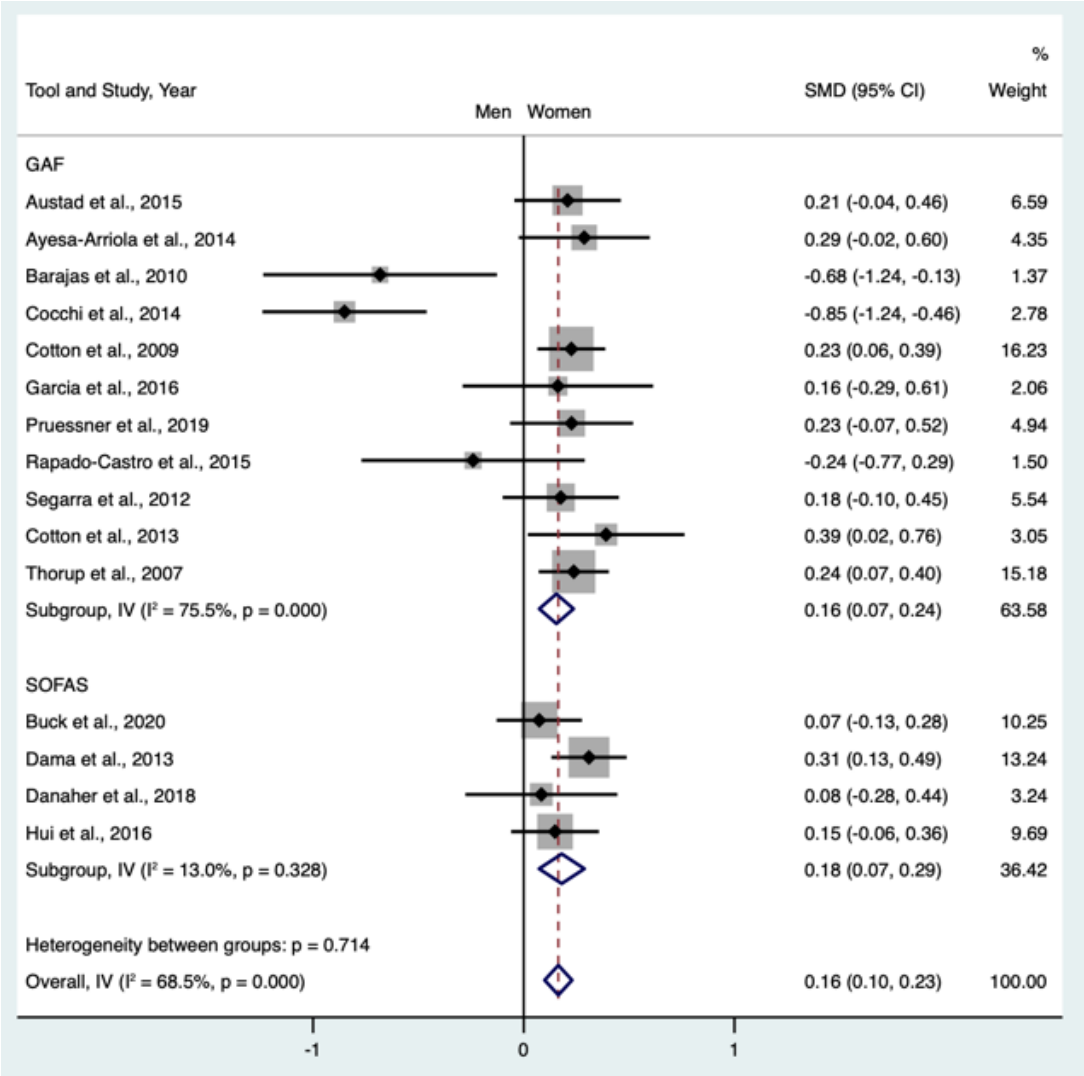
Notes: CDSS = The Calgary Depression Scale, PANSS = Positive and Negative Syndrome Scale, CGI-S/BP = The Clinical Global Impression-Severity Scale/ Bipolar, BPRS = Brief Psychiatric Rating Scale, FCQ = Frankfurt Complaint Questionnaire

Appendix 3M Meta-analysis of general psychopathology with subgroup analysis by measurement tool (n=12)



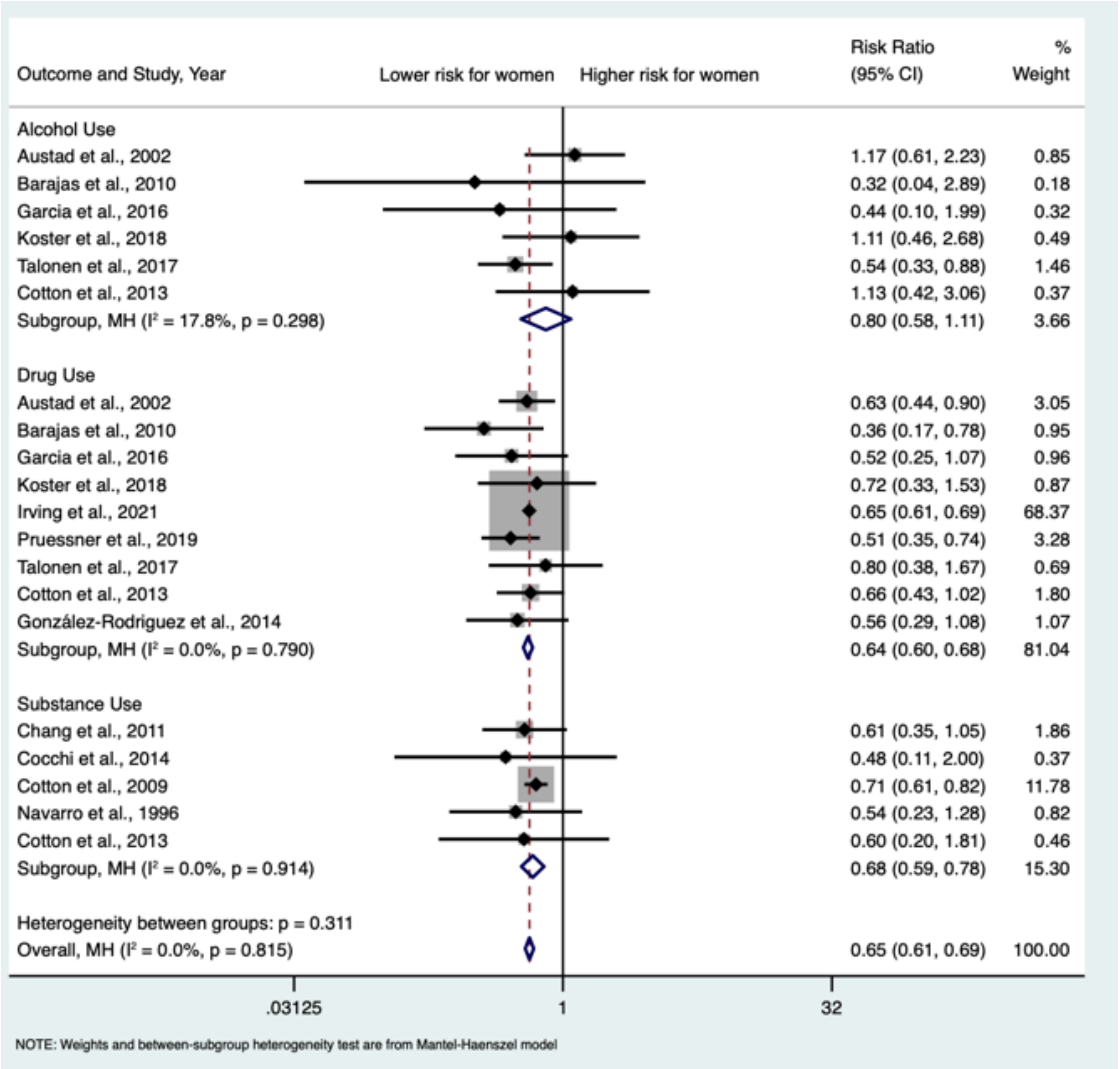
Notes: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale, CGI-BP = The Clinical Global Impression- Bipolar

Appendix 3N: Meta-analysis of functioning, with subgroup analysis by measurement tool (n=15)



Notes: GAF = Global Assessment of Functioning Scale, SOFAS = Social and Occupational Functioning Assessment Scale

Appendix 3O: Meta-analysis of substance use, with subgroup analysis by outcome (n=13)



Appendix 4P: The RECORD statement for observational studies using routinely collected health data

	Item No.	STROBE items	RECORD items
Title and abstract			
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.
Introduction			
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	
Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.
Linkage		..	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.
Results			
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	
Accessibility of protocol, raw data, and programming code		..	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.

Appendix Q: ICES Dataset Creation Plan

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation			
Project Title:	Sex Differences in Symptoms of Early Psychosis at Presentation to Primary Care		
Project TRIM number:	2022 0906 328 005		
Research Program:	MHA		
Site:	ICES Western		
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA*		
	1. Identify and describe differences in clinical presentation (i.e., age at onset/presentation, symptoms, behavioural factors, functioning) between men and women with psychosis at presentation to primary care. 2. Explore clinical and sociodemographic factors associated with these sex differences in clinical presentation. Brief Summary (Purpose) This study will use data from EMRPC to examine sex differences in symptoms of psychosis at presentation to primary care in the period one-year and 6-months leading up to the first diagnosis in a population-based retrospective cohort of FEP over a ten-year period (2005-2015) in Ontario.		
ICES Project PIA Initial Approval Date:	*The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)*		
	September 24, 2020		
Principal Investigator (PI):	Brooke Carter		
Check the applicable box if the PI is an ICES Student/Trainee	☒ ICES Student ☐ ICES Fellow ☐ ICES Post-Doctoral Trainee ☐ Visiting Scholar		
Responsible ICES Scientist:	*Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist*		
	Dr. Kelly K. Anderson		
Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):	*All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) and the date they joined the project must be recorded*		
	Brooke Carter		2020-09-01
Other ICES Project Team Members and date joined (list all):	*All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) and the date they joined the project must be recorded*		
	TBD		yyyy-mon-dd
Confirmation that DCP is consistent with Project Objectives:	*The following individuals must confirm that the ICES Data provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA prior to initial Project Dataset creation: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research and Analysis Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.*		
	Principal Investigator	☒	2021-09-08
	Responsible ICES Scientist or Second ICES Scientist/Lead	☒	2021-Oct-18
	ICES Research and Analysis Staff Creating the DCP	☐	yyyy-mon-dd
	ICES Analytic Staff	☐	yyyy-mon-dd
	The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as		

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation		
Designated ICES Research and Analysis Staff accountable for Project Documentation:	*required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion*	
DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*
	Date	***Name***
	2021-09-08	Brooke Carter

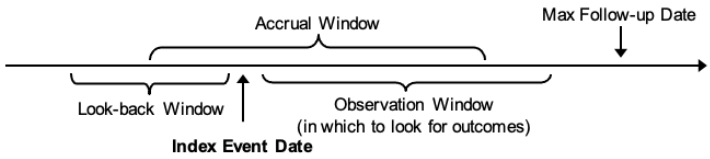
ICES Data This Section must be Completed Prior to Project Dataset(s) Creation	
The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA *Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment*	*Mandatory for all datasets that are available by individual year*
General Use Datasets – Health Services	***Years (where applicable)***
CIHI DAD	1988-2017
OHIP	1991-2017
NACRS	2000-2017
OMHRS	2005-2017
General Use Datasets – Care Providers	
See list	
General Use Datasets – Population	
RPDB	1990-2017
See list	
General Use Datasets – Coding/Geography	
See list	
See list	
General Use Datasets – Facilities	
See list	
General Use Datasets – Other	
ONMARG	1990-2017
Controlled Use Datasets	
See list	
Other Datasets	
EMRPC	2005-2015

Project Amendments and Reconciliation			
ICES Project PIA Amendment History (add additional rows as needed):	*Privacy approval date*	*Person who submitted amendment*	*Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
DCP Amendment History (add additional rows as needed):	*Date DCP amended*	*Person who made the DCP amendment*	*Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
Date Programs/DCP reconciled	*The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed*		
	yyyy-mon-dd		

Project Cohort	
Study Design	☒ Cohort study ☐ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	The index event is an incident case of nonaffective psychosis (ie., schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis NOS) in the health administrative data. (Note: this admin cohort has already been built for p0906 328 001) EMRPC inclusion criteria: 1. A primary discharge diagnosis of a nonaffective psychotic disorder from a general hospital bed [International Classification of Diseases (ICD), 9th Revision code 295.X, 297.X, 298.X; ICD-10 code F20 or F25] 2. A diagnosis of nonaffective psychotic disorder from a psychiatric hospital bed [Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV, Axis I) code 295.X, 297.X, 298.X] 3. Two or more outpatient OHIP billing claims or emergency department visits within a 12-month period with a diagnostic code for non-affective psychotic disorder (ICD-9 code 295.X, 297.X, 298.X; ICD-10 code F20 or F25). NOTE: Diagnostic codes for index event listed in Appendix A
Estimated Size of Cohort (if known)	N = 719 from Administrative cohort linked to EMRPC

Project Cohort		
Exclusions (in order) Note: this has already been done for p0906 328 001, details are included here for reference.	*Step*	Description
	1	Data cleaning of admin cohort a) Missing or invalid IKN b) Missing or invalid age (>105) c) missing or invalid sex d) Death on or before the index date
	2	Age <14 or >35
	3	Non-Ontario resident (first 2 characters of PRCDDA is NE '35' – use %GETDEMO)
	4	Presence of a diagnostic code for a psychotic disorder prior to the index date to remove prevalent cases • OMHRS: AXIS1_DSM4CODE_DISCH1-3 code for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [October 2005] up to March 31, 2015, inclusive) • DAD: DXCODE or DX10CODE (dxtype=alldx) for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [April 1988]-March 31, 2015, inclusive) • OHIP: DXCODE for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [July 1991]-March 31, 2015, inclusive) • NACRS: DXCODE or DX10CODE (dxtype=alldx) for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [July 2000]-March 31, 2015, inclusive) NOTE 1: Diagnostic codes listed in Appendix A

Exclusions (in order) for linkage of admin cohort with EMRPC (pre-abstraction)	1	EMRPC exclusion after linking admin cohort with EMRPC: a) Physician non DSA and non-active during load period (use d_DSA_status = 0 and d_active = 0 for the load) b) Patient belongs to a non DSA/non active physician (PS_DW.dbo.tb_basic_info.d_primary_entry = 0)
Exclusions (in order) for linkage of EMRPC back with admin cohort (post-abstraction) Note: this has already been done for p0906 328 002, details are included here for reference	1	Data cleaning of EMRPC data (Abstraction dataset) a) Separate comma-delimited acronyms in SYMPTOMS variable into individual variables (one 1/0 indicator variable for each acronym) b) Transform Abstraction dataset so one row per IKN c) Link abstraction cohort with abstraction dataset by IKN d) Link abstraction cohort-dataset with original admin cohort (p0906328002)
	2	No visists to primary care clinic in EMR prior to index date

Project Time Frame Definitions	
	
Accrual Start/End Dates	Index diagnosis of non-affective psychosis in admin cohort (April 1, 2005 to March 31, 2015)
Max Follow-up Date	31Mar2016
When does observation window terminate?	Index date + 1 year (365 days)
Lookback Window(s)	All visits in the EMR for the 6-month and 1-year period prior to the index date

Variable Definitions (add additional rows as needed)	
Main Exposure or Risk Factor	Patient sex abstracted from the administrative database
Seconday Exposure	Clinical and sociodemographic factors associated with these sex differences in clinical presentation
Primary Outcome Definition	Signs and symptoms of early psychosis in EMR data noted in primary care visits in the period 1-year and 6-months prior to first diagnosis of psychotic disorder (list of 45 specific signs/symptoms abstracted from EMR data in appendix)
Baseline Characteristics	At index date a) Age b) Sex c) Rurality d) Income quintile e) Index diagnosis f) Patient language Prior to index date a) Number of Johns Hopkins ADGs b) Rostered to family physician c) Time on EMR
Other Variables	Number of help-seeking visits prior to index date a) Number of primary care visits in EMR in the period 1 year and 6-months prior to index date

Analysis Plan and Dummy Tables

(Below is a guide – please MODIFY/EXPAND as appropriate)

Step 1: Cohort Build

Note: this has already been done for p0906 328 001, details are included here for reference

I. Cleaning of Abstraction dataset
   a. Separate comma-delimited acronyms in SYMPTOMS variable into individual variables (one 1/0 indicator variable for each acronym)

II. Link EMRPC data (Abstraction dataset and abstraction cohort tables) with admin cohort p0906 328 001
   a. Link abstraction dataset, abstraction cohort, and admin-derived cohort from p0906.328.001 by IKN

III. Apply exclusion criteria.
   a. Remove cases with no primary care visits prior to the index date and track number excluded in Appendix B, Tbl1 InclusionExclusion (see Appendix C, Table C1 for details)

*****STOP FOR REVIEW*****

Step 2: Obtain Exposure, Baseline Characteristics, Outcomes, and Other Concepts

I. Obtain exposure (see Appendix C, Table C2 for details).
II. Obtain outcomes (see Appendix C, Table C3 for details).
III. Obtain other concepts (see Appendix C, Table C4 for details).

*****END OF WORK BY ICES ANALYST*****

Step 3: Primary & Secondary Outcomes (TO BE COMPLETED BY STUDENT)

I. Create an outcome table reporting prevalence of each sign/symptom by sex
   a. Compare differences across groups using standardized differences, where a difference of >0.10 is considered statistically significant (Appendix B Tbl2 PrimaryOutcomes)

II. Create an outcome table reporting prevalence of each sign/symptom by sex, clinical and sociodemographic factors
   a. Compare differences across groups using standardized differences, where a difference of >0.10 is considered statistically significant (Appendix B Tbl3 SecondaryOutcomes)

Analysis Plan and Dummy Tables

(Below is a guide – please MODIFY/EXPAND as appropriate)

Step 4: Unadjusted and Adjusted Analyses

I. Fit unadjusted modified Poisson regression models with robust variance estimators, reporting PRs, 95% CIs, and p-values for effect of sex on each primary outcome (signs/symptom of early psychosis) (Appendix B Tbl4 Unadjusted PR)
   a. Model: Modified Poisson regression model with robust standard errors
   b. Outcome: Signs/symptoms of early psychosis
   c. Independent variable: Patient sex

II. Fit adjusted modified Poisson regression models with robust variance estimators, reporting PRs, 95% CIs, and p-values for effect of sex and clinical/sociodemographic factors on each primary outcome (signs/symptoms of early psychosis) (Appendix B Tbl5 Adjusted PR)
   a. Model: Modified Poisson regression model with robust standard errors
   b. Outcome: Signs/symptoms of early psychosis
   c. Independent variables: Patient sex, clinical/sociodemographic factors (i.e., age, rurality, income quintile, index diagnosis, patient language, number of help-seeking visits, number of John Hopkins ADGs, rostered to family physician, time on EMR)

*****STOP FOR REVIEW*****

Quality Assurance Activities

RAE Directory of SAS Programs			
RAE Directory of Final Dataset(s)	*The final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn't make the final cut. This would permit an analyst to easily re-run the models in the future.*		
RAE README file available:	☐Yes ☐No		
Date results of quality assurance tools for final dataset shared with project team (where applicable):			
		%assign	yyyy-mon-dd
		%evolution	yyyy-mon-dd
		%dinexplore	yyyy-mon-dd
		%track / %exclude	yyyy-mon-dd
		%codebook	yyyy-mon-dd
Additional comments:			

Appendices (add appendices as needed)

Appendix A: Codes	Refer to the "DCP Appendix A Template" Excel document

Inclusion/ Exclusion Criteria	Data Sources	Variables/ Code Types	Window	Notes (including algorithm details)
Inclusion Criteria				
Incident case of nonaffective psychotic disorder & EMRPC alignment	OMHRS DAD OHIP NACRS EMRPC.cohort EMRALD.EMR_MASTER	DSM4 ICD9 ICD10 OHIPDX	2005-2015	See Appendix A: OUT_PSY 1. **DAD:** • Primary discharge diagnosis (dxtype=M, dx10code) of schizophrenia, schizoaffective disorder, schizophreniform, or psychosis NOS with a valid IKN • Restrict to the first date per patient • Use the discharge date in DAD (DDATE) as the **index date** OR 2. **OMHRS:** • Most responsible discharge diagnosis (AXIS1_DSM4CODE_DISCH1) of schizophrenia, schizoaffective disorder, schizophreniform, or psychosis NOS in OMHRS with a valid IKN • Restrict to the first date per patient • Use the discharge date date in OMHRS (DDATE) as the **index date** • Using OMHRS_ADMISSION database OR **3. Ambulatory:** • All OHIP billings during the accrual period with a diagnostic code (DXCODE) for schizophrenia, schizoaffective disorder, schizophreniform, or psychosis NOS with a valid IKN, COMBINED WITH: • All emergency department (ED) visits in NACRS (on REGDATE) with a diagnostic code (DX10CODE) for schizophrenia,

Inclusion/ Exclusion Criteria	Data Sources	Variables/ Code Types	Window	Notes (including algorithm details)

				schizoaffective disorder, or psychosis NOS
				• **Exclude** if there is no evidence of two OHIP physician billing claims or two emergency department (ED) visits with a diagnostic code for schizophrenia, schizoaffective disorder, or psychosis NOS occurring in ANY 12 month period (365 days)
				• Restrict to the first date per patient.
				  • Use SERVDATE in OHIP or REGDATE in NACRS from the first ever claim as the **index date**.
				  • If the OHIP servdate and NACRS regdate fall on the same date, preferentially select the OHIP observation
				Restrict to the first episode:
				1. In cases where a IKN appears in more than one cohort, use the date of the first event as the index date.
				2. If the first date is the same for more than one cohort, preferentially select Ambulatory > OMHRS > DAD
				
				EMRPC alignment:
				
				First make EMRALD.EMR_MASTER unique by ikn and d_ices_patient_id where d_ices_patient_id^=. And ikn^=''.
				
				Then pull IKNs from above cleaned EMRALD.EMR_MASTER and join to EMRPC.cohort by d_ices_patient_id.

Inclusion/ Exclusion Criteria	Data Sources	Variables/ Code Types	Window	Notes (including algorithm details)
				Join EMRPC.cohort from above with IKN's to p0906.328.001 by IKN.
Exclusion Criteria				
No primary care visits before index date	EMRPC (Abstraction dataset)	d_type d_appointment_date	Before index date	Include cases where d_type=PN and d_appointment_date < index date

Exposure	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Sex	RPDB	SEX	Ref date=Index date	N (%) female	

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Age at psychosis diagnosis	RPDB	BDATE	Ref date=Index date	Mean (SD), Median (IQR), N (%) each category: 15-20, 21-25, 26-30, 31-35	
Income quintile at psychosis diagnosis	RPDB	INCQUINT	Ref date=Index date	N (%) each category, missing	
Index diagnosis	OHIP NACRS OMHRS DAD	DSM4 ICD9 ICD10 OHIPDX	Ref date=Index date	N(%) in each category 1. Schizophrenia spectrum disorder 2. Psychosis NOS	

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Final Diagnosis	EMRPC.abstraction	DX_FINAL	Ref date=index date, 1 year prior to index	Free text input by FP	
Number of Johns Hopkins ADGs	DAD OHIP NACRS	ADG1-34 from %GETACG	Ref date=Index date, 2 years prior to index	Mean (SD), Median (IQR), N (%) each category: Low (< 5) Medium (6-9) High (10 or more)	
Number of primary care help-seeking visits	EMRPC.abstraction	d_type, d_appointment_date	Ref date=Index date, 1 year prior to index	Mean (SD), Median (IQR), Range	d_type=PN and d_appointment_date < index date
Rostered to FP	EMRPC.cohort	d_is_roster	Ref date=Index date	Flag Yes/No N(%) and missing	d_is_roster=TRUE then yes, d_is_roster=FALSE then no.
Time on EMR	EMRPC.cohort	d_start_onEMR	Ref date=Index date	Mean (SD), Median (IQR), Range	Time on EMR=Indexdate-d_start_onEMR
Exposures (signs/symptoms of early psychosis abstracted from EMRs)					
The family is concerned/has expressed worry about the patient.	EMRPC.abstraction	FMCON	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Excess use of alcohol.	EMRPC.abstraction	ALCHL	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Use of other street drugs (i.e., other than cannabis; e.g., inhalants, hallucinogens, cocaine and crack, stimulants, opiates).	EMRPC.abstraction	DRGS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Arguing with friends and family.	EMRPC.abstraction	ARG	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Spending more time alone.	EMRPC.abstraction	ALNE	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Sleep difficulties.	EMRPC.abstraction	SLEEP	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Poor appetite.	EMRPC.abstraction	APPTT	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Depressive mood.	EMRPC.abstraction	DPRSN	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Poor concentration.	EMRPC.abstraction	CNCTN	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Restlessness	EMRPC.abstraction	RSTLS	Ref date=Inde	Flag Yes/No	

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
			x date, 6-m, 1 yr prior to index	N(%)	
Tension or nervousness	EMRPC.abstraction	TNSN	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Less pleasure from things (ie, anhedonia)	EMRPC.abstraction	PLSR	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Feeling people are watching you or giving you a hard time for no reason	EMRPC.abstraction	WTCH	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Feeling, hearing or seeing things that others cannot	EMRPC.abstraction	HALLU	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Feeling that everyday things have a special meaning just for you (delusions/ideas of reference)	EMRPC.abstraction	SPC MNG	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Feeling that something odd is going on that you cannot explain (odd beliefs or magical thinking)	EMRPC.abstraction	ODD FLNG	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Odd manner of thinking or speech (disorganized/disconnected thoughts/speech)	EMRPC.abstraction	ODD SPCH	Ref date=Index date, 6-m, 1 yr	Flag Yes/No N(%)	

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
			prior to index		
Inappropriate affect	EMRPC.abstraction	INAPP EMTN	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Odd behaviour or appearance	EMRPC.abstraction	ODD BHVR	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
First-degree family history of psychosis	EMRPC.abstraction	FAM HIST	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Increased stress or deterioration in functioning	EMRPC.abstraction	FUNCT	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	
Experienced a psychosocial stressor	EMRPC.abstraction	SYMPTOMS PS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable labelled "PS" Note: the specific psychosocial stressor was also written out in the SYMPTOMS textbox variable – this can be disregarded. If

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
					"PS" is present, or there was a psychosocial stressor written out, flag that visit as yes for "PS"
Disorganized or abnormal motor behaviour	EMRPC.abstraction	SYMPTOMS DAMB	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "DAMB"
Blunted affect	EMRPC.abstraction	SYMPTOMS BA	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "BA"
Lack of interest/decreased motivation	EMRPC.abstraction	SYMPTOMS Avolition	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "avolition"
Diminished speech	EMRPC.abstraction	SYMPTOMS Alogia	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
					to be labelled "alogia"
Anxiety symptoms	EMRPC.abstraction	SYMPTOMS AS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "AS"
Psychomotor slowing	EMRPC.abstraction	SYMPTOMS PSL	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "PSL"
Hyperactive behaviour	EMRPC.abstraction	SYMPTOMS HB	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "HB"
Poor memory	EMRPC.abstraction	SYMPTOMS PM	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "PM"
Psychosomatic complaints	EMRPC.abstraction	SYMPTOMS PC	Ref date=Index date, 6-	Flag Yes/No N(%)	This is an item from "SYMPTOMS

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
			m, 1 yr prior to index		” variable to be separated out and the new variable to be labelled “PC”
Impulsivity	EMRPC.abstraction	SYMPTOMS Impulsivity	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from “SYMPTOMS” variable to be separated out and the new variable to be labelled “impulsivity”
Mania-like symptoms	EMRPC.abstraction	SYMPTOMS MLS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from “SYMPTOMS” variable to be separated out and the new variable to be labelled “MLS”
Obsessive-compulsive disorder-like symptoms	EMRPC.abstraction	SYMPTOMS OCDS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from “SYMPTOMS” variable to be separated out and the new variable to be labelled “OCDS”
Poor insight into mental health	EMRPC.abstraction	SYMPTOMS PIIMH	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from “SYMPTOMS” variable to be separated out and the new variable to be labelled “PIIMH”

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Suicidal behaviour/self-harm	EMRPC.abstraction	SYMPTOMS SBSH	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "SBSH"
Issues with personal hygiene	EMRPC.abstraction	SYMPTOMS IWPH	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%) and missing	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "IWPH"
Current problems with cigarette smoking	EMRPC.abstraction	SYMPTOMS CPCS	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%) and missing	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "CPCS"
Family history of bipolar disorder in a first-degree relative	EMRPC.abstraction	SYMPTOMS FHBP	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "FHBP"
Low IQ/intellectual or developmental disability	EMRPC.abstraction	SYMPTOMS LIQIDD	Ref date=Index date, 6-m, 1 yr	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
			prior to index		out and the new variable to be labelled "LIQIDD"
Autism spectrum disorder	EMRPC.abstraction	SYMPTOMS ASD	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "ASD"
A prior diagnosis of any psychiatric disorder	EMRPC.abstraction	SYMPTOMS PDPD	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "PDPD"
Borderline traits	EMRPC.abstraction	SYMPTOMS BT	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "BT"
Schizotypal	EMRPC.abstraction	SYMPTOMS SC	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "SC"

Clinical Presentation	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Aggressive behaviour	EMRPC.abstraction	SYMPTOMS AB	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "AB"
Poor premorbid adjustment	EMRPC.abstraction	SYMPTOMS PPA	Ref date=Index date, 6-m, 1 yr prior to index	Flag Yes/No N(%)	This is an item from "SYMPTOMS" variable to be separated out and the new variable to be labelled "PPA"
Other Concepts	Data Sources	Variables/ Code Types	Window	Reporting Detail	Notes (including algorithm details)
Rurality (rural vs. urban) at psychosis diagnosis	RPDB	RURAL	Ref date=Index date	N (%) rural, urban, missing	
Patient language	EMRPC.abstraction	FIRST LANG SPKN LANG	Ref date=index date	English, non-English	

Curriculum Vitae

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Carter, B., Wootten, J., Archie, S., Terry., A. L., & Anderson., K. K. 2022. "Sex and gender differences in symptoms of early psychosis: A systematic review and meta-analysis". *Archives of Women's Mental Health*, accepted, pending revision.