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The Prevalence of Multimorbidity among People with Non-Affective Psychotic Disorders 10-Years After First Diagnosis

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Abstract

Prior research suggests that people with psychotic disorders have an excess risk of individual chronic conditions, however less is known about their risk of co-occurring multiple chronic health conditions; that is, multimorbidity. The overall objective of this thesis was to examine the association between psychotic disorders and multimorbidity using two complementary studies. First, our systematic review and meta-analysis of fourteen studies found that people with psychotic disorders had an increased risk of 2+ chronic conditions relative to those without psychosis (RR=1.69, 95%CI=1.37,2.08). Second, our retrospective matched cohort study found that people with psychotic disorders treated by an early psychosis intervention program (*n*=439) may have a 26% higher prevalence of multimorbidity relative to people without psychosis (*n*=1,759), although our findings include the possibility of a null effect (PR=1.26, 95%CI=0.96,1.66). We suggest future research using larger sample sizes and longer follow-up periods to better understand the association between psychotic disorders and multimorbidity.

Keywords

comorbidity, multimorbidity, multiple chronic conditions, physical health, psychotic disorders

Summary for Lay Audience

Chronic health conditions such as diabetes, cardiovascular disease and cancer require long-term ongoing management by patients, clinicians, and healthcare systems. Mental illnesses such as depression and schizophrenia are also examples of chronic conditions. Psychosis or the presence of sensory perceptions or false beliefs is present in schizophrenia and other psychotic disorders. Prior research indicates that people with psychotic disorders experience a higher percentage of one other chronic health condition (e.g. diabetes or cancer) as compared to people without psychosis. However, we do not know whether people with psychotic disorders also experience multimorbidity or the co-occurrence of two or more (2+) chronic health conditions, e.g. psychosis in addition to diabetes and cancer. Multimorbidity is challenging for clinicians who provide treatment to patients and for healthcare systems which allocate the appropriate number of resources for patient care. Therefore, it is important to understand multimorbidity so that we can better meet the needs of patients with psychotic disorders. The overall goal of this thesis was to compare the occurrence of multimorbidity between people with psychosis and those without psychotic disorders through two research studies. Our first study pooled findings from fourteen prior research studies and found that people with psychotic disorders may have a higher risk of developing 2+ other chronic health conditions as compared to people without psychosis. Our second study focussed on people with psychotic disorders who were treated by an early psychosis intervention program in London, Ontario. We tracked healthcare records for people with and without psychotic disorders for ten years to estimate the percentage of people who experienced 2+ other chronic health conditions in each of these groups, and we then compared those two estimates. We found that there was a higher percentage of multimorbidity among people with psychotic disorders as compared to people without psychosis. It is recommended that future researchers follow the health records of patients with psychotic disorders for a longer period of time to better estimate multimorbidity.

Co-Authorship Statement

This thesis includes two integrated articles, which have been or will be submitted for publication to a peer-reviewed journal. Chapter 3 is in the exact state in which it was prepared for submission, whereas Chapter 4 will be condensed prior to submission. The co-authorship details for both articles are presented below.

Chapter 3: Rodrigues M, Wiener JC, Stranges S, Ryan BL & Anderson KK. The Risk of Physical Multimorbidity in People with Psychotic Disorders: A Systematic Review and Meta-Analysis. Submitted for publication to an academic journal.

Myanca Rodrigues was involved in the conception and design of the study, in the extraction of data and assessment of risk of bias, in the analysis and interpretation of data, and in writing the first and subsequent drafts of the paper. Joshua C. Wiener was involved in the extraction and interpretation of data and the assessment of risk of bias, and in the critical revision of the article for intellectual content. Drs. Saverio Stranges and Bridget L. Ryan were involved in the interpretation of data and in critical revision of the article for intellectual content. 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 for intellectual content.

Chapter 4: Rodrigues M, Stranges S, Ryan BL & Anderson KK. The Prevalence of Multimorbidity among People with Non-Affective Psychotic Disorders 10-Years After First Diagnosis. Prepared for submission to an academic journal.

Myanca Rodrigues 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. Drs. Saverio Stranges and Bridget L. Ryan were involved in the interpretation of data and in critical revision of the article for intellectual content. Dr. Kelly K. Anderson was involved in the conception and design of the study, in the statistical analysis plan, the interpretation of data, in writing drafts of the paper, and in the critical revision of the article for intellectual content.

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Abbreviations

ACG – Adjusted Clinical Groups

BMI – Body Mass Index

CCDSS – Canadian Chronic Disease Surveillance System

CCHS – Canadian Community Health Survey

CHF – Congestive heart failure

CI – Confidence Interval

CIHI – Canadian Institute for Health Information

CKD – Chronic Kidney Disease

CLD – Chronic Liver Disease

COPD – Chronic Obstructive Pulmonary Disease

CVD – Cardiovascular disease

DAD – Discharge Abstract Database

DSM – Diagnostic and Statistical Manual of Mental Disorders

EHR – Electronic health record

EMR – Electronic medical record

FGA – First-generation antipsychotics

HbA1C – Hemoglobin A1C

HIC – High-income countries

HIV – Human Immunodeficiency Virus

HR – Hazard Ratio

IBD – Inflammatory Bowel Disease

ICD – International Classification of Diseases

IRR – Incidence Rate Ratio

LMIC – Low- and middle-income countries

MDD – Major Depressive Disorder

MeSH – Medical Subject Headings

MI – Myocardial Infarction

MRR – Mortality Rate Ratio

NACRS – National Ambulatory Care Reporting System

NHANES – National Health and Nutrition Examination Survey

NMA – Network meta-analysis

NOS – Psychosis not-otherwise specified

NR – Not reported

ODB – Ontario Drug Benefit

OHIP – Ontario Health Insurance Plan

OMHRS – Ontario Mental Health Reporting System

OR – Odds Ratio

PEPP – Prevention and Early Intervention Program for Psychoses

PHAC – Public Health Agency of Canada

PR – Prevalence Ratio

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

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

RPDB – Registered Persons Database

RR – Relative Risk or Risk Ratio

SD – Standard deviation

SDS – Same Day Surgery Database

SES – Socioeconomic status

SGA – Second-generation antipsychotics

SIR – Standardized Incidence Ratio

SMD – Standardized Mean Difference

SMR – Standardized Mortality Rates

WMD – Weighted Mean Difference

Y/N – Yes/No variables

Chapter 1

1 Overview of Thesis

People with psychotic disorders have a reduced life expectancy compared to members of the general population, which is primarily due to differences in physical health and preventable physical health conditions.[1–3] Compared to people without psychotic disorders, those with psychosis have a higher prevalence of conditions such as diabetes mellitus and various cardiovascular and respiratory ailments.[4] Ongoing treatment with second-generation antipsychotic medications, which results in weight gain and other metabolic side effects[4–7] and increases risk for cardiometabolic conditions,[8–10] may explain to some extent this excess prevalence observed by people with psychosis. Additionally, lifestyle factors such as smoking[11–13] and poor nutritional habits[14,15] may explain why this clinical population has an excess prevalence of respiratory and cardiovascular conditions.[4]

Although there is evidence on the association between psychosis and individual chronic conditions, there is limited research on the co-existence of multiple co-occurring chronic conditions – known as multimorbidity – among people with psychotic disorders.[3] Both psychosis and multimorbidity share common risk factors, such as smoking, sedentary behaviour, older age, and material deprivation, which may be interrelated and form a unique cluster of conditions.[11–13,16–22]

We sought to investigate whether people with psychotic disorders may have an excess risk or prevalence of multimorbidity through two complementary studies. Our systematic review and meta-analysis synthesized the existing body of evidence and found that people with psychotic disorders had an increased risk of 2+ chronic conditions (risk ratio (RR)=1.69, 95%CI=1.37,2.08), relative to those without psychosis (Chapter 3). We then assessed the excess prevalence of multimorbidity experienced by people treated by an early psychosis intervention program in London, Ontario, compared to those without psychosis through a retrospective matched cohort study (Chapter 4). We found that people with psychotic disorders may have a 26% higher prevalence of multimorbidity ten

years following first diagnosis, although our findings include the possibility of a null effect (prevalence ratio (PR)=1.26, 95%=CI 0.96,1.66).

1.1 Role of the Student

The research question was identified by Myanca Deanne Rodrigues and her supervisor Dr. Kelly K. Anderson, and refined through consultation with Drs. Saverio Stranges and Bridget L. Ryan, members of her supervisory committee. All chapters of this thesis were written by Ms. Rodrigues as partial fulfillment of requirements for the Master of Science degree in Epidemiology and Biostatistics, and she incorporated feedback from Drs. Anderson, Stranges and Ryan.

Ms. Rodrigues 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 Mr. Joshua C. Wiener who was a secondary reviewer, in addition to members of the supervisory committee (Drs. Anderson, Stranges, and Ryan).

The retrospective matched cohort study used data from the Prevention and Early Intervention Program for Psychoses program, which was linked to ICES datasets. Access was granted to Ms. Rodrigues through the Data & Analytics Services department of ICES. The thesis student was added to an existing Health Sciences Research Ethics Board application at Western University (protocol #112446), which was used for the aforementioned data linkage study. The statistical methods for the primary analysis (Chapter 4) were developed by Ms. Rodrigues and Dr. Anderson. Coding and cleaning of data, and interpretation of results was conducted by Ms. Rodrigues, in consultation with Drs. Anderson, Stranges and Ryan.

Chapter 2

2 Psychosis, Chronic Health Conditions, and Multimorbidity

People with psychosis often have other co-occurring chronic health conditions. This chapter describes the natural history of psychosis, the chronic conditions faced by this clinical population, and the phenomenon of multiple chronic conditions or *multimorbidity*.

2.1 Psychosis and Psychotic Disorders

This section will provide an overview of psychosis and psychotic disorders and their prevalence, risk factors, and impact on patients, clinical teams, and healthcare systems.

2.1.1 Psychosis and Psychotic Symptoms

The American Psychiatric Association and World Health Organization characterize *psychosis* by the presence of hallucinations (without insight), delusions, or both hallucinations without insight and delusions.[23,24] Hallucinations are sensory perceptions that occur without corresponding external or somatic stimuli, whereas *delusions* are fixed false beliefs.[25] People with psychosis therefore experience a break with reality, and a *psychotic episode* occurs when a person has trouble distinguishing reality from these false perceptions. The *first episode of psychosis* is a person's first experience of the symptoms of psychosis that would meet the threshold for a psychotic disorder,[26] and may be defined by the duration of prior antipsychotic medication use, duration of psychosis, or the first treatment contact for psychosis.[27]

Psychotic episodes are characterized by the presence of positive or negative symptoms. *Positive symptoms* can be thought of as symptoms added to a person's usual behaviour and may include: hallucinations, delusions, disorganized speech or thoughts, or *catatonia* (disorganized motor behaviours).[23,25,26,28] *Negative symptoms* can be thought of as symptoms missing from a person's usual behaviour and include: *alogia* (restricted speech), *affective flattening* (blunted emotional or facial expressions), *anhedonia*

(inability to feel pleasure), *avolition* (reduced motivation) and *asociality* (reduced desire to partake in social activities).[23,25,26,28–30]

2.1.1.1 Psychotic Disorders

Psychosis occurs in several mental illnesses such as schizophrenia spectrum disorders, mood disorders, and substance abuse disorders. Schizophrenia spectrum disorders are primary psychotic disorders for which psychosis is the hallmark and include: schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, brief psychotic disorder, and psychosis not-otherwise-specified (NOS).[23,25,26,28,31] People with major depressive disorder (MDD), bipolar disorder, or other affective disorders may also experience psychosis.[23,25,26,28] Psychosis may also develop due to intoxication or withdrawal from substances, neurocognitive or neurodegenerative disorders (e.g. Alzheimer's or Parkinson's Disease), or as a result of traumatic brain injury.[25] Psychotic disorders can be broadly categorized as affective or non-affective. *Affective psychotic disorders* are primarily defined by mood symptoms and include MDD with psychosis or bipolar disorder with psychosis.[32] *Non-affective psychotic disorders* do not have prominent mood symptoms and include delusional disorder and schizophrenia spectrum disorders.[32]

2.1.2 Risk Factors for Psychosis

Factors that are associated with an increased risk of psychosis include: family history, sex, socioeconomic status (SES), ethnicity, migrant status, and age.[33] Psychosis is thought to be the result of a complex interplay between genetic susceptibility and familial environmental influences,[34,35] and offspring of parents with schizophrenia have an increased risk of developing psychotic disorders (relative risk (RR) = 7.54, 95% confidence interval (CI) 4.02, 14.13; 33 studies).[36] Psychotic symptoms also emerge at different ages in males and females. The mean age of onset for males is 18-25,[37] whereas females have a bimodal onset profile – after puberty and over the age of 40.[38,39] Furthermore, several studies have demonstrated that incidence of schizophrenia is higher in those from low-socioeconomic classes or materially-deprived areas.[40–42] Black Caribbean and African groups have a three to six times higher incidence of schizophrenia

and other psychotic disorders compared to White groups.[43,44] Migrant status and ethnic background may also interact to influence risk of psychosis, with immigrants from the Caribbean and Bermuda (Incidence Rate Ratio (IRR) = 1.60, 95% CI 1.29, 1.98) and refugees from East Africa (IRR = 1.95, 95% CI 1.44, 2.65) shown to have higher incidence of psychotic disorders than those from Europe or Asia.[45] Given the early age of onset for the condition, adolescence and young adulthood is a risk period for psychosis. It is thought that high levels of depression, long duration of psychotic symptoms, and family history of psychosis in youth are associated with onset of psychosis.[46] Furthermore, heavy cannabis use among youth is associated with onset of psychotic symptoms,[47] as demonstrated by a recent meta-analysis across 35 studies (adjusted odds ratio (OR) = 1.41, 95% CI 1.20, 1.65).[48]

2.1.3 Incidence, Prevalence and the Impact of Psychotic Disorders

A meta-analysis of 177 studies estimated the pooled incidence of all psychotic disorders at 26.6 per 100,000 person-years (95% CI 22.0, 31.7),[49] whereas the lifetime prevalence of schizophrenia across 46 countries is estimated to be 0.4% (90% CI 0.18%, 1.16%).[50]

Schizophrenia was ranked the 16th leading cause of disability worldwide in 2012[51] due to its impact on patients, caregivers, and health systems. People with psychosis often feel stigma and shame[52] and chronic sufferers of the condition may also experience work-related absences and unemployment.[53] Additionally, they are often cared for by family members or other caregivers, which places a significant burden on the caregivers.[54] Caregivers often experience constraints in leisure time, social isolation, and lower physical and mental health-related quality of life.[55–58] Chronic psychosis also results in morbidity and mortality; as such, treatment of those with psychotic disorders comprises 3% of the budget in Ontario,[59] and schizophrenia alone costs the Canadian health system $6.85 billion CAD (*2004 dollars*).[26,60]

2.2 Physical Health of People with Psychosis: An Overview

The following section provides an overview of the physical health of people with psychosis and potential reasons for physical health ailments among this clinical population.

2.2.1 Chronic Conditions: Definition and Prevalence

Chronic conditions are physical or mental health issues which require long-term ongoing management.[61] Both *non-communicable* diseases which cannot be transmitted between people (e.g. cardiovascular disease or cancer), and *communicable diseases* which can be transmitted between people (e.g. Human Immunodeficiency Virus, HIV) may be regarded as chronic conditions.[61,62] Common features of chronic conditions include: multiple risk factors, long development periods, prolonged course of illness which may result in other health issues, and functional impairment and disability.[62,63] Chronic conditions are regarded as the leading cause of death worldwide, responsible for 38 million deaths in 2012, and projected to be responsible for 52 million deaths in 2030.[64,65] In Canada alone, one in three Canadians lives with one or more major chronic disease.[66]

2.2.2 Psychosis and Physical Health

Psychotic disorders have been associated with a reduced life expectancy of 10-25 years,[67] with findings from a systematic review and meta-analysis demonstrating that people with psychotic disorders have a reduced life expectancy of 14.5 years (95% CI 11.2, 17.8) compared to the general population.[68] This premature mortality is primarily due to differences in physical health and chronic conditions experienced by people with schizophrenia and other psychotic disorders.[2,3,69,70] A population-based repeated cross-sectional study conducted using Canadian data found that people with schizophrenia had mortality rates which were three times higher than controls (mortality rate ratios (MRR) = 3.12, 95% CI 3.06, 3.17).[71] The following sub-sections will discuss potential reasons for these differences in physical health, and common chronic conditions experienced by people with psychosis will be detailed in Section 2.3.

2.2.3 Second-Generation Antipsychotic Medications and Physical Health Consequences

People with schizophrenia and other psychotic disorders are commonly treated using second-generation antipsychotic (SGA) medications. Commonly-used SGAs include clozapine, olanzapine, risperidone, and quetiapine.[72,73] SGAs are prescribed for their efficacy in reducing acute symptoms commonly associated with psychosis, i.e. positive and negative symptoms. A Bayesian meta-analysis found a significant reduction of overall acute symptoms in people with schizophrenia (adjusted standardized mean difference (SMD) of 0.38, 95% CI 0.33, 0.43) across 105 studies.[74] SGAs were developed in the 1990s to address the limitations of first-generation antipsychotics (FGAs).[75] The use of FGAs, commonly known as neuroleptics or conventional/typical antipsychotics,[76] resulted in extrapyramidal side effects and tardive dyskinesia.[77] SGAs are associated with a lower incidence of these aforementioned unintended consequences,[72,75] but also result in other side effects that serve as risk factors for several chronic conditions and are discussed in Sections 2.2.3.1 and 2.3.

2.2.3.1 Side Effects of SGAs

Use of SGAs are associated with cardiometabolic and other unintended side effects. Common cardiometabolic side effects of SGA use include weight gain, impaired ability to metabolize glucose, insulin resistance, and dyslipidemia[4–7] which in turn, serve as risk factors for cardiovascular disease (CVD) and Type 2 diabetes.[8–10] It is postulated that SGAs increase oxidative stress, which triggers pathways leading to glucose dysregulation, dyslipidemia, and insulin resistance, and weight gain.[78] Weight gain is the most significant cardiometabolic outcome associated with use of SGAs[79,80] due to its association with a host of chronic cardiometabolic conditions. A Bayesian network meta-analysis (NMA) across 212 randomized controlled trials (RCTs) found that SGAs result in significantly greater weight gain compared to placebos, with SMDs ranging from 0.10 (95% credible interval (CrI) -0.02, 0.22) to 0.74 (95% CrI 0.67, 0.81).[81] A frequentist meta-analysis also found that use of SGAs results in significantly greater weight gain than FGAs (RR = 2.26, 95% CI 1.33, 3.69, 7 RCTs).[82] Use of SGAs may also result in impaired glucose metabolization, with dose-response associations demonstrated between

increasing SGA dosage and increased hemoglobin A1C (HbA1C) levels.[83–85] Furthermore, SGA use is associated with increased secretion of insulin from β-islet cells in the pancreas, thereby resulting in insulin resistance.[86,87] Lastly, imbalances in serum cholesterol, including decreased HDL-cholesterol and increased LDL-cholesterol and triglyceride levels may result from SGA use, as evidenced by findings from several prospective cohort studies.[8,9,88–90]

Although SGA use is primarily associated with cardiometabolic side effects, there are other unintended consequences which merit consideration. Anticholinergic effects may result from SGA use and include: impaired cognition and memory, constipation, and erectile dysfunction.[79,91] Additionally, SGAs may lead to increased prolactin synthesis and secretion through blocking dopamine receptors, thereby resulting in hyperprolactinaemia. A Bayesian NMA assessing prolactin elevation from use of antipsychotic agents compared to placebos across 90 RCTs found that several SGAs were associated with elevated prolactin levels, with weighted mean differences (WMDs) ranging from -4.47 ng/mL (95% CrI 1.60, 7.38) to 48.51 ng/mL (95% CrI 43.52, 53.51).[92] Increased prolactin levels may lead to menstrual disturbances and loss of bone mineral density.[79,93–97]

2.2.4 Behavioural Risk Factors for Chronic Physical Health Conditions Among People with Psychotic Disorders

Behavioural risk factors associated with an increased risk of various chronic conditions are also highly prevalent among people with schizophrenia and other psychotic disorders. These include smoking, sedentary behaviour, poor nutrition, disrupted sleep patterns, and substance use.

Firstly, smoking is highly prevalent among people with psychotic disorders, who may use nicotine to self-medicate and manage the negative symptoms of psychosis.[11,12,98,99] A meta-analysis of 42 studies across 20 countries found that people with schizophrenia have a five-times higher odds of being smokers compared to the general population (OR=5.3, 95% CI 4.9, 5.7).[100] Smoking has been shown to be a risk factor for a range of chronic

disease including cancer, cardiometabolic conditions, such as CVD and diabetes,[16,17,19,101] and respiratory conditions such as asthma.[18]

Secondly, people with psychosis are more likely to engage in sedentary behaviour or low levels of physical activity, relative to those without psychotic disorders, potentially due to the side effects of SGAs and the negative symptoms of psychosis.[102] Findings from a meta-analysis demonstrated that people with psychosis spend 2.8 (95% CI 1.5, 4.1) more hours per day engaging in sedentary behaviours, as compared to the general population.[13] Sedentary behaviour is associated with cardiometabolic conditions both independently[103] and through the mediating effects of high body mass index (BMI) and obesity.[104,105]

Thirdly, people with psychosis engage in poor nutritional habits more often than members of the general population, both in terms of composition of dietary macronutrients and caloric intake.[14,15] Scoping and systematic reviews have found that people with schizophrenia often have a higher intake of saturated fat and lower consumption of fruit and fibre.[106,107] Another study demonstrated that people with psychosis made similar dietary choices but had a higher caloric intake than members of the general population.[108] Diets high in saturated fat are associated with obesity, insulin resistance and increased LDL-cholesterol,[109] and low intake of fruit and fibre is associated with higher overall caloric intake and reduced control of plasma lipid levels.[110] These, in turn serve as risk factors for CVD and Type II diabetes.[8–10]

Fourthly, a systematic review suggests that people with schizophrenia and other psychotic disorders often have a disrupted sleep patterns and other comorbid sleep disorders, the latter of which include insomnia, obstructive sleep apnea, and restless leg syndrome.[111] These sleep abnormalities are often present during the prodromal period of psychotic illness and may exacerbate symptoms associated with psychotic disorders.[112] Findings from a meta-analysis suggest that both the quantity (<5-6 hours of sleep a night: RR= 1.28, 95% CI 1.03, 1.60) and quality (difficulty initiating sleep: RR=1.57, 95% CI 1.25, 1.97) of sleep are associated with a higher incidence of Type II diabetes.[113]

Lastly, damage to organs and tissue systems are consequences of misusing alcohol, cocaine, and other substances, and may lead to several chronic physical conditions.[114] For

instance, frequent users of alcohol suffer from reduced bone density and overall skeletal frailty,[115] which are risk factors for osteoporosis.[116] Furthermore, cocaine use is associated with increased risk of cardiovascular and pulmonary conditions, such as myocardial infarctions[117–119] and asthma.[120,121] There is an overlap of risk factors for psychotic disorders and substance abuse, including younger age, male sex, and low SES.[122–126] Additionally, people with psychotic disorders may use alcohol and other substances to cope with both the symptoms of psychosis and the side effects associated with using antipsychotic medications.[127–129] Thus, it is unsurprising that substance use is highly prevalent among people with psychosis.[126,130–132] A large population-based study found that people with severe psychotic disorders had increased odds of both alcohol (OR=4.0, 95% CI 3.6, 4.4) and recreational drug use (OR=4.6, 95% CI 4.3, 5.0).[133]

2.3 Common Chronic Health Conditions Experienced by People with Psychosis

As the previous section indicates, use of SGAs may result in cardiometabolic and other consequences, thereby increasing the risk of chronic health conditions experienced by people with psychotic disorders. This section is not an exhaustive list, but outlines several chronic conditions commonly experienced by this clinical population.

2.3.1 Diseases of the Cardiovascular and Circulatory Systems

People with psychosis and psychotic disorders may develop several diseases of the cardiovascular and circulatory systems, such as CVD, congestive heart failure (CHF), stroke/ transient ischemic attack, and hypertension. There is an interplay between these conditions, both with respect to common cardiometabolic risk factors, as well as these conditions serving as predictors of each other, which has been summarized below.

2.3.1.1 Hypertension

High blood pressure or *hypertension* describes the pressure from the force of blood against arterial walls. Hypertension is a chronic condition in itself, but is also a risk factor for other chronic cardiometabolic conditions, including CVD, stroke, and Type II diabetes. Risk factors for hypertension include: obesity, increased age, chronic stress, and

family history of disease.[134] Excess body fat, especially central adiposity, has been shown to be one of the primary risk factors associated with development of hypertension through the Minnesota Health Survey, China Stroke Primary Prevention trial, and the National Health and Nutrition Examination Survey.[135–137] Weight gain is the most pertinent cardiometabolic consequence associated with SGAs; as such, people with psychotic disorders have an increased risk of developing hypertension.[138] A meta-analysis found that the prevalence of hypertension is higher among people with chronic schizophrenia who receive treatment with SGAs (39.7%, 95% CI 36.4%, 43.1%), compared to people with a first episode of psychosis (30.4%, 95% CI 21.3%, 40.3%) or unmedicated people with psychosis (24.3%, 95% CI 11.2%, 40.5%).[139] These findings were corroborated by another meta-analysis across 28 studies which demonstrated increased odds of hypertension among people who had experienced multiple episodes of schizophrenia, compared to age-, sex- and cohort-matched controls from the general population (OR = 1.36, 95% CI 1.21, 1.53).[140]

2.3.1.2 Cardiovascular Diseases

Cardiovascular disease (CVD) is a term given to a wide range of conditions affecting the cardiovascular system, including coronary heart disease, peripheral artery disease, arrythmias, congenital heart defects, angina, and myocardial infarction (MI).[4,79,141] Risk factors for CVDs are a combination of genetic and lifestyle factors, which include but are not limited to: obesity, hypertension, lack of physical activity and low SES.[16,17] Given that the use of SGAs results in several cardiometabolic consequences that are known risk factors for CVDs, the most pertinent of which is weight gain, it is unsurprising that people with schizophrenia have a marked increase in the incidence of CVDs. A systematic review demonstrated that risk for CVDs is not different between untreated patients after a first episode of psychosis, but that this risk increases after first exposure to SGAs.[142] A comprehensive meta-analysis of cross-sectional studies demonstrated that people with schizophrenia had greater odds of coronary heart disease (adjusted OR = 1.52, 95% CI 1.48, 1.56; 8 studies, 187,359 patients, 4,086,191 controls). This review also pooled hazards ratios (HRs) from longitudinal studies and found that people with

schizophrenia have an increased risk of developing CVD (adjusted HR = 1.95, 95% CI 1.41, 2.70; 16 studies, 361,294 patients, 16,096,125 controls).[143]

2.3.1.3 Congestive Heart Failure

Congestive heart failure (CHF) is a chronic condition affecting the circulatory system. It develops from weakening of the heart muscle, and characterizes the heart's inability to pump blood, particularly under duress, e.g. exercise or stressful conditions. The most common risk factor for heart failure is a heart attack or myocardial infarction (MI), after which patients' hearts are weakened and damaged.[144] Narrowing of the arterial walls through conditions such as coronary heart disease may restrict blood flow and result in CHF. Since people who use SGAs have an increased incidence of developing coronary heart disease and experiencing MIs, they are also at increased risk for developing CHF. A meta-analysis across 5 cross-sectional studies which included 40,984 patients and 3,743,431 controls found that people with schizophrenia have an increased odds of CHF (adjusted OR = 1.60, 95% CI 1.06, 2.40).[143] These findings were also consistent with the findings of a meta-analysis of 3 cohort studies (RR = 1.80, 95% CI 1.15, 2.79; 85,290 patients, 9,050,272 controls).[143]

2.3.1.4 Stroke/Transient Ischemic Attack

Cerebrovascular disease is a broad grouping which characterizes conditions that impede blood flow to the brain. When a blood vessel in the brain is prevented from receiving oxygen and nutrients, this is known as a cerebrovascular accident or *stroke*.[145–147] A *transient ischemic attack* is the term given to a mini-stroke which lasts for a shorter period of time and does not result in permanent damage. It may also be a warning sign and eventually lead to the occurrence of a stroke.[148] Risk factors for both strokes and transient ischemic attacks include: obesity, hypertension, diabetes and high cholesterol levels, which may result from use of SGAs among people with psychosis.[145–147] A comprehensive meta-analysis of cross-sectional studies demonstrated that people with schizophrenia had greater odds of cerebrovascular disease (adjusted OR = 2.05, 95% CI 1.59, 2.64; 5 studies, 41,071 patients and 3,777,039 controls).[143] A more recent meta-

analysis found that SGA use was associated with an increased risk of stroke (adjusted HR = 1.71, 95% CI 1.16, 2.53).[149]

2.3.2 Type II Diabetes

Diabetes mellitus characterizes the body's impaired ability to use glucose or blood sugar, and includes both Type I and Type II sub-types. The causes of Type I diabetes remain unclear, but insulin resistance, obesity, hypertension and abnormal serum cholesterol and triglyceride levels are known to be associated with Type II diabetes.[150] Treatment with SGAs results in an increased incidence of these aforementioned cardiometabolic consequences. As such, people with schizophrenia and other psychotic disorders have an increased risk of developing Type II diabetes. A meta-analysis of 25 studies across 145,718 patients and 4,343,407 controls found that people with schizophrenia have an 82% increased risk of developing this chronic condition (RR = 1.82, 95% CI 1.56, 2.13).[151] Another meta-analysis found that the prevalence of diabetes was lower among people with first episode psychosis (1.3%, 95% CI 0.5%, 2.4%) relative to those with chronic schizophrenia (12.8%, 95% CI 8.44%, 17.9%), as may be expected by increasing use of SGAs by the latter group.[139]

2.3.3 Cancer

Cancer is the term given to diseases which result from abnormal cell proliferation and subsequent destruction of body tissue. Given that cancer may affect several body systems and tissues, there are several types of cancer, such as breast, prostate, lung, colorectal, thyroid, and liver cancers.[152] Risk factors for cancer include both lifestyle factors (e.g. smoking and lack of physical activity), and family history.[152,153] There is mixed evidence regarding the incidence of cancer for people with psychosis and other psychotic disorders. Meta-analyses have demonstrated a slight decreased overall risk (RR = 0.90, 95% CI 0.81, 0.99)[154] or no difference in risk (standardized incidence ratio (SIR) = 1.05, 95% CI 0.95, 1.15)[155] of developing any type of cancer among this clinical population, while a population-based register study found an increased risk of cancer across both sexes for people with schizophrenia, as compared to controls.[156] There are two conflicting hypotheses that support these sets of results, and involve elucidation of risk factors that

may underlie specific types of cancer.[157] People with psychosis are at risk of developing breast, colorectal and other obesity-related cancers, for which weight gain is a significant determinant and may result from use of SGAs. This has been supported by reviews demonstrating increased risk of breast cancer (SIR = 1.12, 95% CI 1.02, 1.23) among people with psychosis compared to controls.[155] Furthermore, use of SGAs result in increased prolactin levels, which further increases risk for breast cancer.[158,159] Additionally, smoking is more common among people with psychotic disorders[11,12,98,99] and serves as a risk factor for cervical, lung and other types of cancers,[101,160] which may explain why those with psychosis are at increased risk of developing cancer. Alternately, SGAs may have anti-proliferative effects on cells[161] or schizophrenia itself may have a protective effect against cancer, due to increased natural killer cell activity[162] or its association with a tumour suppressor gene.[163] This is supported by findings from other meta-analyses which demonstrate a decreased risk of even obesity-related cancers, such as colorectal (RR = 0.82, 95% CI 0.69, 0.98)[154] and liver cancer (SIR = 0.76, 95% CI 0.61, 0.96)[164] among patients compared to controls. Another review found that people with schizophrenia do not necessarily have an increased risk of developing cancer, but increased cancer-related mortality (HR = 1.51, 95% CI 1.13, 2.03),[165] which may be explained by delays in cancer screening and treatment initiation among this clinical population.[166–169]

2.3.4 Diseases of the Respiratory System

People with psychosis may also experience diseases affecting the respiratory system such as asthma, chronic obstructive pulmonary disease, and bronchitis. These have been summarized below.

2.3.4.1 Asthma

Extra production of mucus resulting from narrowed airways in the respiratory tract is called *asthma*. Risk factors for asthma include lifestyle factors (e.g. smoking, being overweight, and exposure to air pollution), as well as family history and respiratory infections.[18] Given that the use of SGAs results in weight gain, and people with psychosis have a higher prevalence of smoking compared to the general population,[11,12] they also

have an increased risk of developing asthma. A nation-wide cohort study using data from the National Health and Nutrition Examination Survey (NHANES) found that people with schizophrenia had a higher odds of developing asthma compared to age-, sex-, and race-matched controls, after adjustment for smoking (OR = 2.23, 95% CI 1.25, 3.97).[170]

2.3.4.2 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease resulting in reduced airflow to the lungs.[171] Risk factors for COPD include smoking and exposure to air pollution and other irritants. Given that people with psychosis have a higher prevalence of smoking compared to the general population,[11,12] which is considered the primary cause of developing COPD,[172] it is unsurprising that prevalence of COPD is higher among this clinical population.[4,141,173] A long-term follow-up study of health care billings in the United States found an 88% higher odds of people with schizophrenia developing COPD compared to controls (OR = 1.88, 95% CI 1.51, 2.32).[174] These findings were also supported by a population-based study evaluating the odds of developing various respiratory illnesses, including COPD, among people with psychosis compared to controls (COPD-specific OR adjusted for age and sex = 4.23, 95% CI 1.61, 11.10).[175]

2.3.4.3 Bronchitis

Bronchitis characterizes an inflammation of the bronchial tube lining, resulting in expelling of mucous, and can be a chronic condition. Primary risk factors for bronchitis include smoking and exposure to air pollution.[176] People with psychosis have a higher prevalence of smoking compared to the general population[11,12] and consequently experience a higher odds of developing chronic bronchitis compared to controls (chronic bronchitis-specific OR adjusted for age and sex = 3.75, 95% CI 1.64, 8.55), as demonstrated by a population-based study.[175]

2.3.5 Diseases of the Musculoskeletal System

People with schizophrenia and other psychotic disorders are also prone to developing diseases which affect the musculoskeletal system, such as arthritis and osteoporosis. These have been briefly summarized below.

2.3.5.1 Arthritis

Arthritis refers to swelling of the body's joints, resulting in joint pain and stiffness, and includes both rheumatoid arthritis and osteoarthritis. Risk factors for both sub-types include: obesity, family history, increased age, and the female sex.[177–181] The body's immune system attacks the joint lining, and may eventually destroy cartilage through an auto-immune condition known as *rheumatoid arthritis*,[182] whereas *osteoarthritis* results from wear and tear of the body's cartilage.[183] There is mixed evidence on the association between schizophrenia and rheumatoid arthritis,[184] with some studies suggesting a reduced risk for the condition among this clinical population (HR = 0.69, 95% CI 0.59, 0.80),[185] whereas others suggest no significant association (OR = 1.88, 95% CI 0.79, 4.49, compared to age-, sex-, and race-matched controls).[170] Research suggests that the relationship between these two chronic conditions may be the result of an overlap between genetic factors for both diseases which are located in the Human Leukocyte Antigen (HLA) region,[186] as polymorphisms in HLA-C may be associated with a decreased risk of rheumatoid arthritis and an increased risk of schizophrenia.[187–189] A recent meta-analysis found that people with schizophrenia have a lower odds of rheumatoid arthritis as compared to those without schizophrenia (OR = 0.48, 95% CI 0.34, 0.67).[190] Conversely, the weight gain caused by SGA use may lead to more strain on the body's joints and an increased risk of osteoarthritis (OR = 1.40, 95% CI 1.04, 1.89).[174]

2.3.5.2 Osteoporosis

Weakening of bones which may lead to fractures is characterized as *osteoporosis*. Risk factors for this condition include: increased age, female sex, and low calcium intake.[191,192] Given that use of SGAs is associated with elevated prolactin levels[92] which may result in loss of bone mineral density,[79,93–97] it is biologically plausible that people

with psychosis could have an increased incidence of this chronic condition. This is supported by a recent meta-analysis which found a significant greater odds of people with schizophrenia developing osteoporosis, as compared to controls (OR = 2.86, 95% CI 1.27, 6.42).[193]

2.3.6 Neurological and Other Mental Health Conditions

People with schizophrenia and other psychotic disorders are also prone to developing diseases which affect neurological systems (e.g. dementia) and other mental health conditions (e.g. mood and anxiety disorders). These have been briefly summarized below.

2.3.6.1 Dementia

Dementia is characterized by a cluster of symptoms which includes memory loss and difficulty in tasks involving coordination, problem-solving, and communication. Damage to nerve cells in the brain and increased age may result in dementia.[194,195] The association between psychosis and dementia is unclear, but two hypotheses have been postulated. Firstly, people with schizophrenia have a higher incidence of several cardiometabolic comorbidities, including diabetes[196] and CHF,[197] which are known risk factors for dementia.[198] Secondly, those with chronic schizophrenia, in particular geriatric populations, show cognitive decline,[199–202] which may be the result of cumulative exposure to the anti-cholinergic effects of SGAs.[203] Although further elucidation of this association is necessary, findings from a meta-analysis, which included 4 prospective and 2 retrospective cohort studies, highlight the increased risk of dementia among people with schizophrenia (RR = 2.29, 95% CI 1.35, 3.88).[204]

2.3.6.2 Mood and Anxiety Disorders

Mood disorders (e.g. depression, bipolar disorders) characterize one's mood being lowered or elevated, whereas *anxiety disorders* describe persistent feelings of fear or worry.[205,206] These two types of mental disorders often occur concurrently.[207,208] Blunted affect characterizes the negative symptoms of psychosis, and is also associated with depression and other mood disorders.[209] Alternately, changes in mood may also be a

consequence of a diagnosis of psychotic disorder, or both conditions may be rooted in historical childhood trauma.[210] It is postulated that anhedonia, a feature of schizophrenia, results in associated anxiety.[211] People with schizophrenia and other psychotic disorders often have comorbid mood and anxiety disorders. Meta-analyses have demonstrated pooled prevalence of depressive and anxiety disorders were respectively 26.0% (95% CI 22.1, 30.3)[212] and 10.9% (95% CI 2.9, 18.8)[213] among those with schizophrenia, whereas reviews have found that the prevalence of these conditions among the general population are as high as 6.7% (95% CI 4.2, 10.1)[214] and 4.0% (95% CI 3.7, 4.2).[215]

2.3.7 Other Chronic Conditions

People with schizophrenia and other psychotic disorders may also develop other chronic conditions, such as HIV, inflammatory bowel disease, chronic kidney disease, chronic liver disease, and urinary incontinence.

HIV is spread by contact with infected bodily fluids and characterizes the damage caused to the body's immune system and subsequent impaired ability to fight infections.[216] A meta-analysis found that people with psychotic disorders have a high prevalence of HIV infection (6.0%, 95% CI 4.3%, 8.3%),[217] which may be explained by risky sexual behaviours and reduced knowledge about HIV transmission.[218,219]

Inflammatory bowel disease (IBD) characterizes chronic inflammation of the digestive system and includes ulcerative colitis and Crohn's Disease.[220,221] Genetic overlap of alleles that give rise to both schizophrenia and Crohn's Disease may explain the strong association between the two conditions.[222] Two population-based Canadian studies using administrative health data found an increased risk of schizophrenia among people with IBD (IRR = 1.64, 95% CI 0.95, 2.84;[223] IRR = 1.51 95% CI 0.99, 2.30[224]).

Gradual loss of kidney function or kidney failure is known as *Chronic Kidney Disease* (CKD)[225,226] whereas *Chronic Liver Disease* (CLD) characterizes the slow destruction of the liver.[227] Use of SGAs are associated with an increased risk of developing cardiometabolic comorbidities such as diabetes, hypertension and CVD, which are risk factors for both CKD and CLD.[228,229] People with schizophrenia therefore have a marked

increase in the odds or risk of CKD compared to controls, as demonstrated by population-based studies in Israel (OR = 1.62, 95% CI 1.45, 1.82)[230] and Taiwan (HR = 1.25, 95% CI 1.04, 1.50).[231] A Taiwanese-based national cohort study found that people with schizophrenia also have increased risk of developing CLD as compared to controls (RR = 1.15, 95% CI 1.07, 1.24).[232]

Loss of bladder control is formally known as *urinary incontinence*. Risk factors for this condition include: female sex, increased age, smoking, obesity, and diabetes.[233–235] Detrusor overactivity resulting from use of SGAs[236,237] may explain why people with schizophrenia have an increased odds of urinary incontinence, as compared to controls, as shown in a recent population-based study (OR adjusted for comorbidity and SGA type = 1.78, 95% CI 1.26, 2.50).[238]

2.4 Multimorbidity

Chronic conditions may co-occur - the definition, measurement, prevalence, and risk factors for this phenomenon will be discussed in this section.

2.4.1 Multimorbidity: Overview and Definition

The existence of multiple co-occurring chronic conditions is formally known as *multimorbidity*.[65,239–241] There is confusion regarding the use of the term *multimorbidity* versus *comorbidity* across academic, public health, and clinical settings, as well as extensive heterogeneity in its operational definition with respect to the number and types of conditions included, the cut-offs and tools used to measure multiple co-occurring conditions, and prevalence estimates for multimorbidity. These issues will be discussed below.

2.4.1.1 Comorbidity vs. Multimorbidity

There are two terms used to refer to people with multiple co-occurring chronic conditions. Use of the term *multimorbidity* indicates no priority or precedence of any single chronic condition for the patient, clinician, or researcher, whereas comorbidity is used to describe the combined effects of additional chronic conditions when considering

one index condition.[239,241,242] For instance, we may state that a patient with multimorbidity has diabetes mellitus, cancer, and HIV, or that a patient with diabetes mellitus has the comorbid conditions cancer and HIV, the latter of which is in reference to diabetes mellitus as the index condition. Given the extensive research published on multiple chronic conditions in the last two decades[239] and previous confusion regarding interchangeable use of these terms, there are now separate designated Medical Subject Headings (MeSH) for *comorbidity* and *multimorbidity*.[243]

It is also important to note that the term *multimorbidity* has not been used extensively to-date. In 1996, van den Akker and colleagues formally documented the inconsistency and ambiguity used to describe the existence of multiple chronic conditions, and called for a conceptual organization and distinction from *comorbidity*.[241] A bibliometric analysis of publications indexed in the MEDLINE database from 1970 to 2012 demonstrated that only 434 publications mentioned *multimorbidity*, as compared to the 67,557 articles which referenced *comorbidity*.[244] The motivation behind its increased use in recent years is thought be a response to a call for more holistic, person-centered care in contrast to the existing single-disease approach.[245,246] Nonetheless, relatively few studies formally mention this term in their titles and abstracts,[244] including those included in our systematic review and meta-analysis (Chapter 3). Authors may be reluctant to use this term due to its inability to capture patients' symptoms and functionality due to chronic conditions beyond disease counts, in addition to the heterogeneity associated with its definition,[245] the latter of which is described below.

2.4.1.2 Heterogeneity in Operational Definition

There is extensive heterogeneity with respect to defining the types of chronic conditions which constitute multimorbidity, as well the number of conditions required to be considered multimorbidity.

A systematic review on multimorbidity indices[247] found that the number of different conditions included in various definitions of multimorbidity ranged from four[248] to 102.[249] It is postulated that variation in included conditions arises due to different data sources and study populations. Data sources may pose limitations due to availability of

information on particular conditions.[250] Furthermore, definitions of multimorbidity often fail to differentiate between diseases (e.g. diabetes) and risk states (e.g. obesity) or symptoms (e.g. urinary incontinence) of chronic conditions, thereby creating even greater discrepancies in the types of included conditions.[251]

In addition to the aforementioned heterogeneity, the cut-offs used to determine multimorbidity are also unclear across study contexts. For instance, a person may be considered to have multimorbidity with cut-offs ranging from two or more (2+) to five or more (5+) co-occurring conditions. This variation may be due to concern about prevention and management for research conducted to inform capacity planning and use of health services, which warrants a cut-off at 2+ conditions, whereas health care providers who are focussed on providing care to patients with more complex needs may only consider co-occurrence of conditions as multimorbid after the third, fourth, or fifth diagnosis.[252–254] However, 2+ and three or more (3+) conditions are the most widely used cut-offs when measuring multimorbidity.[250,255,256]

2.4.1.3 Operational Definitions of Multimorbidity in Canada

Definitions of multimorbidity vary both across and within jurisdictions due to differences in data sources and target audience, i.e. public health vs. clinical. Fortin and colleagues (2010) evaluated multimorbidity using Canadian Community Health Survey (CCHS) data for the general population and data abstraction of electronic medical records (EMRs) from primary care practices, and compared these prevalence estimates in Quebec for adults aged 25 and older. This study found that prevalence estimates of multimorbidity were higher in primary care practices, due to the greater number of conditions considered and due to patients seeking care for chronic health needs.[257]

Primary care definitions of multimorbidity include a greater number of conditions, as providers examine a wider number of chronic conditions due to:

1. The impact of chronic conditions on patients;
2. The relevance of chronic conditions to health services for primary care;

3. The prevalence of chronic conditions among patients who present to primary care providers.[250]

Conversely, public health professionals, who are concerned about population-level impact select conditions based on their duration, population prevalence in the region in question, impact on society and the economy, and ability to be targeted by primary prevention strategies.[65,258,259]

As such, we have several definitions of multimorbidity across Canadian contexts, which are detailed in the table below, along with a definition of multimorbidity used by studies to assess the burden of multiple co-occurring chronic conditions the province of Ontario across different data sources.[260,261]

Table 2.1: Included chronic conditions in definitions of multimorbidity across Canadian contexts

Feature	Context			
	Public Health Agency of Canada (PHAC)	**PHAC – Canadian Chronic Disease Surveillance System**	**Primary care context**	**ICES *(Ontario)***
Data Source	CCHS[65]	Administrative data from 7 provinces, 3 territories[262]	n/a (scoping review)[250]	ICES data holdings[260]
Number of conditions	9	5	20	17
Included conditions	Arthritis	-	Arthritis and/or rheumatoid arthritis	Rheumatoid arthritis, Osteoarthritis
	Mental disorders	Mental illness (omnibus)	Depression or anxiety	Mood disorder (depression, anxiety, phobia, bipolar disorder)
	Asthma	Respiratory (Asthma, COPD)	Asthma, COPD or chronic bronchitis	Asthma
	COPD			COPD including bronchitis
	Heart disease	Cardiovascular (Ischemic heart disease, heart failure)	Cardiovascular disease (angina, MI, atrial fibrillation, poor circulation in lower limbs)	Cardiovascular disease (coronary artery disease, MI, angina, peripheral vascular disease, arrythmia)
	-		Heart failure	Congestive heart failure
	Diabetes mellitus	Diabetes	Diabetes	Diabetes
	Cancer	-	Cancer	Cancer
	Stroke	-	Stroke/ transient ischemic attack	Stroke/ transient ischemic attack
	Alzheimer's and related dementias	-	Dementia or Alzheimer's	Dementia
	-	Hypertension	Hypertension	Hypertension
	-	-	Chronic musculoskeletal conditions	-
	-	-	Osteoporosis	Osteoporosis
	-	-	Stomach problems	--
	-	-	Colon problems (IBS, Crohn's, ulcerative colitis, diverticulosis)	IBD
	-	-	Chronic hepatitis	-
	-	-	Thyroid disorder	-
	-	-	Kidney disease or failure	Chronic kidney disease
	-	-	Chronic urinary problem	Urinary incontinence
	-	-	Hyperlipidemia	-
	-	-	Obesity	-
	-	-	-	HIV
	-	-	-	Chronic liver disease

As Table 2.1 illustrates, although there is variation in the types of chronic conditions across definitions of multimorbidity, conditions which appear across all contexts include: diabetes, mental illness of some form, asthma, COPD, and CVD, owing to their prevalence and impact on the Canadian population. There are also broad groupings of chronic conditions for disease categories; for example, CVD refers to angina, MI, atrial fibrillation, and poor power limb circulation in the definition of Fortin and colleagues (2017), and includes coronary artery disease, MI, angina, peripheral vascular disease, and arrythmia in the definition of Ryan and colleagues (2018). *Mental disorders* or *mental illness* also broadly captures a range of mental health conditions in both definitions of multimorbidity used by the Public Health Agency of Canada (PHAC).[65,262]

2.4.2 Tools used to Measure Multimorbidity

The variation across definitions of multimorbidity also extends to differences in measurement tools or instruments. Systematic reviews of the literature on measures of multimorbidity across primary care and community health settings revealed that as many as 35 different tools may be employed.[263–265] Measures include: disease counts, Adjusted Clinical Groups (ACG) System, the Charlson Comorbidity Index, and administrative data. The use of different measures reflects variation in the outcome of interest. For instance, the Charlson Comorbidity Index or disease counts are best used to assess health care utilization and quality of life, whereas the ACG system is best suited for health care utilization and costs.[263] Furthermore, health administrative data, e.g. medical billings, is best used to provide information about large numbers of people.[266] Although measures may also be combined to increase validity, simple disease counts, complex measures, and billings from administrative data are considered accurate in predictive value.[263,267] Four of these measures are briefly described below.

Disease counts can be derived from patient self-reports to questionnaires or interviews. Alternately, they may reflect clinician diagnoses or disease counts from EMRs and health administrative data.[263] Fortin and colleagues (2017) developed a questionnaire for patients to document 20 self-reported chronic conditions or categories in primary care settings. The Charlson Comorbidity Index is another tool used to measure multiple co-

occurring chronic conditions, and is often considered the most widely-studied validated measure of multimorbidity.[263] It was intended to evaluate prognosis based on age and weight for specific comorbid conditions.[268] Alternately, the ACG System is an adjustment system which groups diagnosed conditions from EMRs or insurance billings. Its development was intended for prediction of morbidity and health care resource utilization.[269] Finally, health administrative data, e.g. medical billings, are collected for administrative and billing purposes, but may be utilized to inform healthcare decision-making on chronic diseases and risk factors.[270,271] A Canadian study found that as many as 30 chronic conditions could be identified using health administrative data with moderate to high validity.[272]

2.4.3 Prevalence of Multimorbidity

It is difficult to compare prevalence estimates of multimorbidity across settings due to the heterogeneity in the types, included conditions, and cut-offs and tools used for measurement, as discussed above. As such, estimates of multimorbidity which have been presented below are considered with note to their definition, data sources, and populations.

The pooled global prevalence of multimorbidity was estimated as 33.1% (95% CI 30.0–36.3%) in a systematic review and meta-analysis which evaluated patients of varying ages (mean age ranging from 36-75 years) in community-based settings across 18 high-income countries (HICs) and 31 low-income countries.[273] A report from the Academy of Medical Sciences, which identifies multimorbidity as a priority for global health research, further details that its prevalence is the norm among HICs, but is also becoming increasingly prevalent across low- and middle-income countries (LMICs) due to the aging population and increasing prevalence of non-communicable diseases.[104]

In Canada, the PHAC found that 12.9% and 3.9% of Canadians aged 20 and older had 2+ and 3+ chronic conditions, respectively, from a list of 9 conditions and utilizing data from the CCHS.[65] Another Canadian analysis by the PHAC found that 26.5% and 10.2% of Canadians aged 40 and older had 2+ and 3+ chronic conditions, respectively from a list of 5 conditions and utilizing provincial and territorial health administrative data holdings

in accordance with Canadian Chronic Disease Surveillance System (CCDSS) methodology (see Table 2.1 for list of included conditions).[262]

Here in Ontario, a retrospective cohort study utilizing ICES data holdings across all age groups found that the prevalence of 2+ chronic conditions from a list of 16 increased from 17.4% to 24.3% in 2003 and 2009 respectively.[274] A more recent cross-sectional study using the same data source and a list of 17 conditions revealed an overall prevalence of 15.2% (3+ conditions) among Ontario residents of all age groups.[260]

2.4.4 Risk Factors for Multimorbidity

Factors associated with the development of multiple chronic conditions include both behavioural and sociodemographic factors. Prior research has demonstrated that behavioural risk factors including tobacco use, diet, and physical activity, and sociodemographic characteristics such as sex, age, and SES or material deprivation may be associated with multimorbidity.[104] Lifestyle factors are particularly important in influencing risk for developing multiple co-occurring chronic conditions. Although various studies have found conflicting evidence on the association between tobacco use and multimorbidity,[21,22,275] smoking remains a risk factor for several chronic conditions, including CVD and diabetes.[19] Low rates of physical activity have also been found to be associated with multimorbidity[20,21] due to the mediating effects of high BMI and obesity,[104] which are in turn risk factors for cardiometabolic conditions.

Sex is a known risk factor for multimorbidity, as demonstrated across studies in both LMICs[276–278] and HICs[279–282]. It is postulated that females are more likely than males to experience income inequality and be of low SES, and are consequently at higher risk for developing multimorbidity.[104] Mental-physical comorbidity is also more prevalent among females than males.[281] Alternately, sex may serve as a proxy for the differential recognition of physical symptoms across males and females by health care providers, in particular for coronary heart disease[283–285] and/or comparatively greater health-seeking behaviour by females.[281,286–289]

A systematic review and meta-analysis found that age is a significant determinant of multimorbidity, with ORs ranging from 1.26 to 227.46 across 39 studies.[290] This finding has been replicated by several observational studies where increasing age is associated with greater prevalence or increased odds of developing multiple co-occurring chronic conditions.[65,279,291]

SES or material deprivation has also been identified as a risk factor for multimorbidity, but it has a differential impact on the development of multimorbidity in HICs compared to LMICs. An inverse relationship between SES and multimorbidity has been demonstrated in HICs, with multimorbidity being more prevalent among those of low SES or high deprivation.[246,279,291] This may be due to the fact that SES underlies access to health care, environmental exposure to risk factors for chronic conditions (e.g. smoke and pollution), and health behaviours.[292] Conversely, affluent residents of LMICs have greater access to substances such as tobacco and alcohol and high-calorie foods, which contribute to increased risk for developing multiple co-occurring chronic conditions. Alternately, they may also have increased access to healthcare and be more likely than those from lower income brackets to be diagnosed with chronic diseases.[104]

Multimorbidity may also be associated with other sociodemographic characteristics, including: ethnicity, level of education, and migration status. A long-term follow-up study analyzing data from the Health and Retirement Study found that Non-Hispanic Blacks had higher initial chronic disease counts than non-Hispanic Whites (IRR = 1.28, 95% CI 1.20, 1.36).[293] Another US population-based study found that non-Hispanic Blacks had greater odds of developing multimorbidity compared to non-Hispanic Whites, after adjustment for family income level, employment status, and home ownership.[294] Another risk factor for multimorbidity is level of education. People who did not complete high school (OR = 1.58, 95% CI 1.50, 1.66) and those who completed high school or college (OR = 1.32, 95% CI 1.27, 1.37) had a higher odds of developing multiple chronic conditions compared to those who had at least a baccalaureate degree.[294] Lastly, migrant status is also associated with developing multiple chronic conditions. Refugees and immigrants may experience deteriorations in their health status after arrival in their host countries, due to barriers in accessing health care services, and poorer education and

employment prospects. As such, migrant status may be a proxy for other social determinants, including education level and SES.[295–297] A cohort study found that Danish refugee groups were at 20% higher risk of developing multimorbidity as compared to native Danes (HR = 1.20, 95% CI 1.15, 1.25).[298]

2.4.5 Impact of Multimorbidity

A recent study called multimorbidity "the most common chronic condition worldwide" [299], due to its impact on patients, clinicians, and health care systems. Findings from a recent systematic review and meta-analysis demonstrate that multimorbidity is significantly associated with a decrease in both mental (−1.55%, 95% CI −2.97, −0.13) and physical (−4.37%, 95% CI −7.13, −1.61) health-related quality of life with each added disease.[300] Clinicians who care for patients with multiple chronic conditions experience difficulties in adjusting treatments based on other conditions.[104] They also face challenges in navigating healthcare services and systems which are fragmented by specialty, and in collaborating with other health care providers in shared-decision making.[301] People with multimorbidity use health care services at a disproportionately high rate, contributing to increased use of primary care and hospital admissions.[279,280,286] Furthermore, the cost of care for people with multimorbidity is exponentially greater than that for those with individual chronic conditions, as found by a systematic review evaluating health care costs across HICs.[302]

2.5 Study Rationale and Objectives

Findings from several studies indicate that there is a widening mortality gap between people with schizophrenia and the general population[69,303–305] and that these people experience longer hospital stays and increased healthcare costs,[2,306,307] both of which are due to other chronic health conditions. There has been extensive research conducted on the types of conditions experienced by people suffering from psychotic disorders,[2,3,69,70] and estimation of the prevalence of multiple co-occurring chronic conditions across the general population in global,[104,273] Canadian,[65,262] and Ontario contexts.[260,274] However, there is a paucity of research on the excess prevalence of multimorbidity experienced by those with psychotic disorders, despite the presence of common risk factors which

underlie both psychosis and multimorbidity, such as low SES, ethnic background, and migrant status. These shared risk factors may be interrelated and form a unique pattern of conditions associated with psychotic disorders.[3]

2.5.1 Study Objectives

There is a gap in research and a need to evaluate the burden of multimorbidity among people with psychotic disorders. The overall objective of this thesis was to quantify the excess risk or prevalence of multimorbidity experienced by people with psychotic disorders. This was achieved through a systematic review and meta-analysis of the existing literature (Chapter 3), as well as an analysis of data from a retrospective cohort study. The latter assessed whether there was an excess prevalence of multiple chronic health conditions 10-years after a first episode of psychosis, compared to people without psychotic disorders (Chapter 4). To meet these objectives, our thesis answered the following questions:

1. Is there a significant difference between the risk of multimorbidity for people with psychotic disorders and the general population? (Chapter 3)
2. What is the prevalence of multimorbidity 10-years after a first diagnosis of psychotic disorder for people treated by an early intervention program? Do people with psychosis have a higher prevalence of multimorbidity as compared to those without psychotic disorders? (Chapter 4)
3. Are increased severity of psychotic symptoms and persistence of impaired functioning associated with increased prevalence of multimorbid conditions? (Chapter 4)
4. What are common risk factors for multimorbid health conditions among people with psychotic disorders (e.g. age, sex, neighbourhood income level, SES)? (Chapter 4)

We hypothesized that people with psychotic disorders would have a higher risk of multimorbidity after first diagnosis, and that certain socioeconomic, lifestyle, and clinical factors may have rendered particular subgroups of people more susceptible to the development of multiple chronic health conditions. We hope that the findings from this

study will facilitate increased surveillance and recognition of the common chronic conditions faced by people with psychotic disorders, including those contributing to premature mortality. This information will assist decision-makers in creating tailored intervention plans to improve the physical health of people with psychotic disorders, and integrate care across multiple specialties to reduce the growing burden of disease on the Canadian health system.

2.6 Thesis Format

This thesis was written in integrated-article style and consists of two independent studies in Chapters 3 and 4.

Chapter 3 presents a systematic review and meta-analysis to summarize the relationship between psychotic disorders and multimorbidity. It specifically examines the excess risk of multimorbidity experienced by people with psychosis, compared to those without psychotic disorders, and presents pooled prevalence estimates of multimorbidity for people with psychosis.

Chapter 4 assesses the excess prevalence of multimorbidity experienced by people with psychotic disorders, compared to those without psychosis, using health administrative data in Ontario, Canada.

Chapter 5 summarizes the findings from the integrated articles and describes the implications of these findings for patients, clinicians, and policy-makers. It concludes with a brief discussion of areas for future research.

Chapter 3

3 The Risk of Physical Multimorbidity in People with Psychotic Disorders: A Systematic Review and Meta-Analysis

3.1 Abstract

Background*:* The occurrence of multiple co-occurring chronic health conditions, known as multimorbidity, is associated with decreases in quality of life for patients and poses unique challenges for healthcare systems. Since people with psychotic disorders have an excess of physical health conditions compared to the general population, they may also be at a higher risk for multimorbidity. We conducted a systematic review and meta-analysis to quantify the prevalence and excess risk of multimorbidity among people with psychotic disorders, relative to those without psychosis. ***Methods****:* We searched the MEDLINE, EMBASE, and PsycINFO databases, and conducted forward and backward citation tracing of included studies. Studies published after 1990 were included if they reported the prevalence of multiple chronic physical health conditions among people with psychotic disorders. Data on the prevalence and relative risk of multimorbidity were meta-analyzed using random effects models. ***Results****:* Fourteen studies met the inclusion criteria, and eight were included in the meta-analysis. Each study used a different operational definition of multimorbidity, both for the number and types of chronic conditions, which resulted in a wide range in prevalence estimates (16% to 91%). People with psychotic disorders had an increased risk of multimorbidity (RR=1.69, 95%CI=1.37, 2.08), relative to those without psychosis. ***Conclusions****:* People with psychotic disorders are more likely to experience multimorbidity than those without psychotic disorders. Clinicians treating people with psychosis should closely monitor for a range of physical health conditions. Future research examining multimorbidity among people with psychiatric illness should employ consistent definitions to better enable cross-study comparisons.

Keywords**:** comorbidity, multimorbidity, multiple chronic conditions, physical health, psychotic disorders, systematic review

3.2 Introduction

Chronic conditions are those that require long-term ongoing management,[61] and the co-existence of multiple co-occurring chronic conditions is known as multimorbidity.[65] There is currently no consensus on what constitutes the appropriate number of co-existing conditions, nor which particular conditions are to be considered in the operational definition of multimorbidity. Across the literature, there is considerable variation in the types of included conditions, and cut-offs include two (2+), three (3+), and four (4+) or more co-occurring conditions.[252,253] This heterogeneity is perceived to be the result of contextual variation in the consideration of multimorbidity across clinical and public health settings; whereas clinical management of multiple diagnoses is considered challenging only after the third diagnosis, concerns about prevention and management for public health professionals warrants a cut-off of two co-occurring conditions.[239,252,253,257,308]

Despite these inconsistencies, however, it is clear that the prevalence of multimorbidity has increased. One-third of Canadians live with at least one chronic condition, with 2+ and 3+ conditions affecting over 12% and 3% of Canadians, respectively.[65,66] The prevalence of multimorbidity is expected to increase with the aging population and increased exposure to risk factors for chronic conditions.[309] The co-occurrence of multiple chronic conditions poses a unique set of challenges for healthcare systems, clinicians, and patients. People with multimorbidity contribute to exponentially greater costs for health care systems as compared to those with individual chronic conditions due to increased use of primary care and hospital admissions. [302] Furthermore, health care providers must make adjustments to treatments based on other conditions, and liaise with other clinicians for shared decision-making in healthcare systems that are fragmented by specialty.[301] Findings from a recent systematic review and meta-analysis also show that multimorbidity is significantly associated with a decrease in mental and physical health-related quality of life with each additional chronic condition.[300]

People with psychotic disorders have a reduced life expectancy of 14.5 years (95% CI=11.2, 17.8) compared to the general population.[68,310] This premature mortality is

primarily due to differences in physical health and preventable physical conditions.[2,3] Prior systematic reviews suggest that people with schizophrenia and other psychotic disorders have a higher prevalence of several chronic physical health conditions, including HIV, diabetes mellitus, as well as gastrointestinal, cardiovascular, and respiratory diseases.[4,141] There is also evidence of an three-fold gap in standardized all-cause mortality rates (SMR) between people with schizophrenia and the general population (SMR=3.0%, 95%CI=0.1,6.0).[71,303]

The increased risk of chronic health conditions among people with psychosis may be due to ongoing treatment with second-generation antipsychotic medications, which are associated with cardiometabolic side effects such as weight gain and impaired glucose metabolism.[4–7] These side effects may predispose patients to chronic physical health conditions, including cardiovascular disease and diabetes mellitus.[8–10] People with psychotic disorders also have a higher prevalence of smoking,[11,12] poor nutritional habits,[14,15] disrupted sleep patterns,[111] and sedentary behaviour[13] compared to the general population. These lifestyle factors are particularly important in influencing the risk of various chronic conditions,[19–21] including cardiometabolic[8–10,16,17,109,110,113] and respiratory[18] diseases. Moreover, sociodemographic characteristics, including ethnic background and socioeconomic status (SES) are associated with psychosis and multimorbidity;[33] people from non-White backgrounds and materially-deprived areas experience a higher incidence of both psychotic disorders[40–44] and multimorbidity.[246,279,291,293,294]

Despite extensive evidence on the increased risk of chronic physical conditions among people with psychotic disorders, there has been a paucity of research on the risk of multimorbidity[3] and no prior systematic review and meta-analysis on this topic. The objective of our review was to quantify the prevalence of multimorbidity among people with psychotic disorders, and to assess the risk of multimorbidity relative to people without psychotic disorders.

3.3 Methods

3.3.1 Protocol

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[311] (*Supplementary Appendix 3A*). The protocol for our review was registered in PROSPERO (CRD42019112512).[312]

3.3.2 Search Strategy and Study Selection

We searched the MEDLINE, EMBASE, and PsycINFO electronic databases in September 2019 using the Ovid platform. An academic librarian assisted with the development of the search strategy, which involved a combination of keywords and controlled vocabulary that were specific to each database (*Supplementary Appendix 3B*). We limited the search to human subjects, and restricted records to the English language and to those published after 1990, which was the year when second-generation antipsychotic medications came onto the market.[75] Forward and backward citation tracing of included articles was also used to identify relevant studies that may have been missed by the main search strategy.

Both level 1 (title and abstract) and level 2 (full-text) screening were performed independently by two reviewers (MR & JCW), with discrepancies resolved by discussion and consensus, and conflicts resolved by a third reviewer (KKA) as necessary. Studies of all designs, including both experimental and observational, were considered for inclusion. Studies were included if: (i) the study population was limited to people with psychotic disorders, or stratified data were presented for people with psychosis; and (ii) the study assessed the prevalence of multimorbidity, defined as the presence of 2+ and/or 3+ conditions from a defined list of chronic physical health conditions; or (iii) the study presented proportions or data which enabled computation of proportions of multimorbidity among people with psychotic disorders. The cut-offs for the number of conditions was based on commonly-used definitions of multimorbidity in public health and clinical settings, respectively.[252,253,257] We excluded studies that focused exclusively

on co-morbid mental and substance use disorders, due to our principal focus on physical health conditions among people with psychosis.

3.3.3 Data Extraction and Risk of Bias Assessment

Data extraction was completed independently by two reviewers (MR & JCW) using standardized tools developed *a priori*. We extracted data on characteristics of the study (e.g. design, country) and sample (e.g. case composition), ascertainment of exposure (i.e., psychosis) and outcome (i.e., multimorbidity), the considered risk factors for multimorbidity, and the proportions of people with 2+ and 3+ chronic conditions among the exposed group and comparison group. Risk of bias assessments were also conducted independently by two reviewers using the CLARITY tools for case-control[313] and cohort[314] studies, which we adapted for cross-sectional studies (*Supplementary Appendix 3C*).

3.3.4 Data Synthesis

We synthesized the characteristics and findings of included studies in a summary table, including the number and types of conditions across the multimorbidity definitions, as well as findings regarding the prevalence and risk of multimorbidity for people with psychotic disorders.

All meta-analyses were conducted using Stata version 13.0[315] with random effects models to account for heterogeneity in the study methodology (e.g. number and type of chronic conditions) and sample characteristics.[316,317] We stratified the analyses by study design where applicable, and also computed a common pooled effect estimate. For both stratified and pooled estimates, we assessed statistical heterogeneity using the I^2 statistic, which can be interpreted as low (>25%), moderate (>50%), or high (>75%) heterogeneity.[317,318]

First, we conducted meta-analyses to compute a pooled estimate of the prevalence of multimorbidity among people with psychotic disorder using the *metaprop* command; study-specific confidence intervals (CIs) were computed using the exact method to yield the most conservative estimates.[319] The analysis for the prevalence of multimorbidity (2+

and 3+ chronic conditions) was stratified by study design, and then combined to obtain a common pooled estimate with 95% CI.

Second, we pooled study effect estimates to assess the risk of multimorbidity (2+ chronic conditions) among people with psychotic disorder (exposed group), relative to those without psychosis (unexposed group), using the *metan* command.[320] We pooled prevalence ratios (PR) with 95% CI for cross-sectional studies where incidence could not be assessed, and risk ratios (RR) with 95% CIs for cohort studies where the incidence of multimorbidity was estimated. PRs can be pooled with RRs to obtain a common risk estimate,[321] which may be interpreted as a RR, when the exposure (i.e. psychosis) does not impact the duration of the outcome (i.e. multimorbidity). We used this approach rather than a pooled odds ratios (OR), given that the OR overestimates the RR when the outcome is common (i.e. prevalence of multimorbidity > 5% to 10%).[318,322–325]

We conducted sensitivity analyses to assess: (i) the excess risk of 3+ chronic conditions among those with psychotic disorders; and (ii) the impact of study quality on estimates, after removing studies that scored 'intermediate' or 'high' on any risk of bias domains. We also performed an exploratory analysis to assess the impact of excluding substance use disorders and mental health conditions from multimorbidity definitions by separately pooling studies that only examined physical health conditions. Given that we had fewer than 10 studies for our meta-analysis, we were unable to perform meta-regression to explore sources of heterogeneity or assess publication bias through funnel plots.[318]

3.4 Results

Our search strategy retrieved 4,141 records, and we reviewed 81 full-text studies for inclusion (*Figure 3.1*). Fourteen studies met our inclusion criteria, and a detailed list of reasons for exclusion is presented in Figure 1. The included studies reported data on the proportion of people with psychosis who had 2+ and/or 3+ chronic physical conditions, or enabled us to calculate the prevalence or risk of multimorbidity (2+ and 3+ conditions) for patients with psychosis.

The characteristics of included studies are summarized in *Table 3.1*. Studies were conducted in various settings, including the UK (*n*=2),[326,327] USA (*n*=4),[174,328–330] Europe (*n*=5),[331–335] and Middle East/South Asia (*n*=2),[336,337] with one study[338] reporting data on 48 low- and middle-income countries. Studies also varied in methodological design, including cross-sectional (*n*=6),[326–328,332,337,338] case-control (*n*=1),[336] and both prospective (*n*=1)[334] and retrospective (*n*=6)[174,329–331,333,335] cohort studies. The presence of a psychotic disorder was determined through administrative data, chart reviews, and patient self-reports, whereas the multimorbidity outcome was ascertained through administrative data, patient self-reports, physician claims, pharmacy records, and various comorbidity indices. Case definition of psychosis was restricted to people with non-affective psychotic disorders (e.g. schizophrenia, schizoaffective disorder) in twelve[174,326,328–337] studies, and was not reported in the remaining two[327,338] studies. The mean age of people with psychotic disorders ranged from 28 to 52 years across the studies, and the percentage of males ranged from 16% to 76%.

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

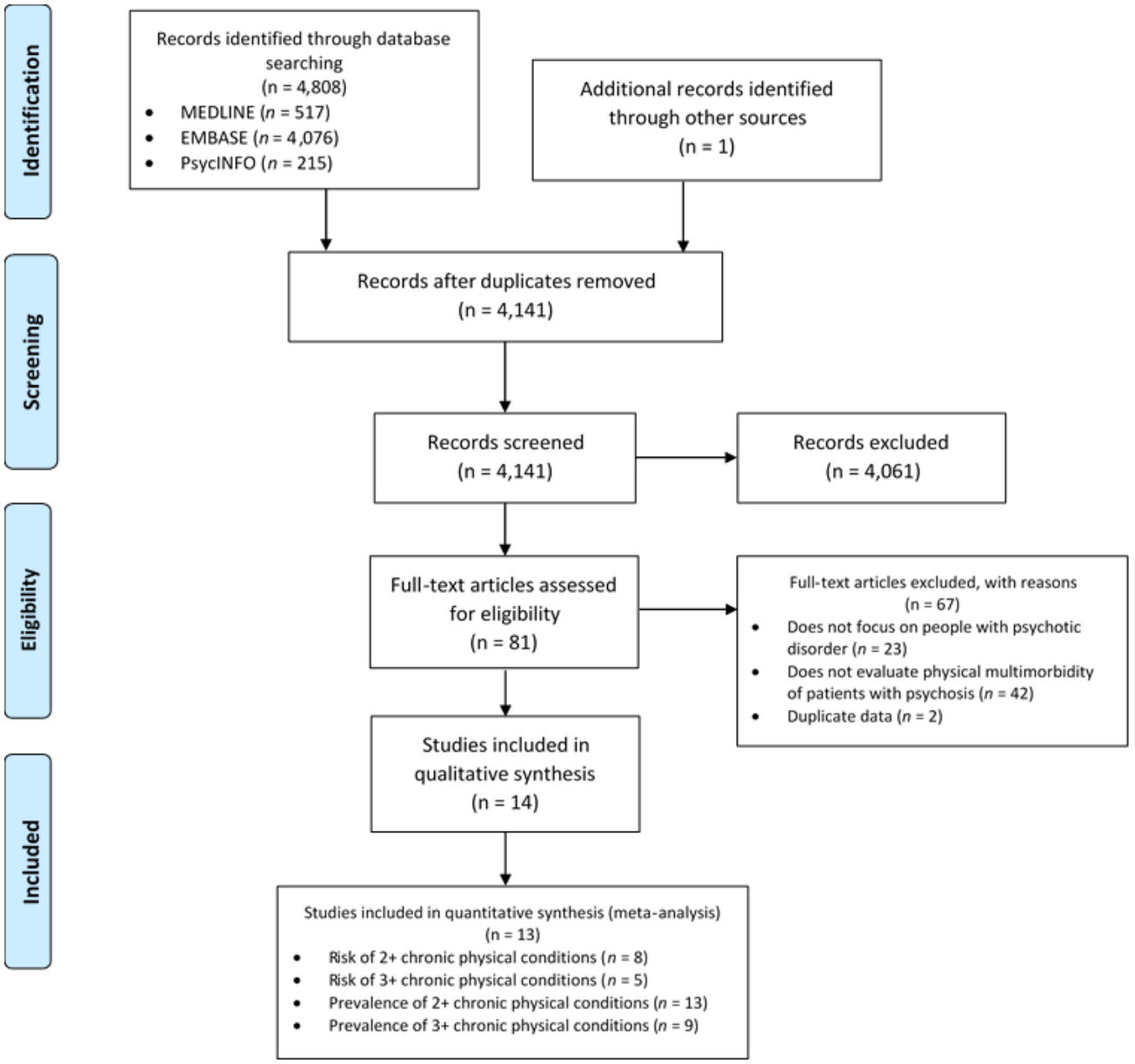


Table 3.1: Summary of the characteristics of included studies (*n*=14)

Study	Country	Study Design	Sample Size	Mean Age of Cases in years (sd)	Number of Males in Case Sample (%)	Diagnostic Criteria for Psychosis	Source of Psychosis Diagnosis	Multimorbidity definition: number of included conditions	Inclusion of mental health in definition of multimorbidity	Source of Multimorbidity conditions
Bhalla et al., 2018	USA	Cross-Sectional	843,583	NR	NR	ICD-9	Registry/Admin data	40	✓	Charlson Comorbidity Index
Bouza et al., 2010	Spain	Retrospective Cohort	16,776	43.5 (16)	10,952 (65%)	ICD-9	Registry/Admin data	12 (clusters)	☒	ICD-9 Codes
Carney et al., 2006*	USA	Retrospective Cohort	727,336	40.2 (11.9)	505 (47%)	ICD-9	Registry/Admin data	46	✓	Elixhauser Comorbidity Index
Correll et al., 2017*	USA	Retrospective Cohort	182,309	49.8 (NR)	103,916 (57%)	ICD-9 CM codes	Registry/Admin data	6	☒	ICD-9 CM codes
Domino et al., 2014	USA	Retrospective Cohort	188,531	stratified results presented only	stratified results presented only	Claims Diagnoses	Registry/Admin data	6	☒	Claims diagnoses
Filipcic et al., 2019	Croatia	Cross-Sectional	1,166	NR	184 (16%)	None described	Self-Reports	15	☒	Self-reports
Gabilondo et al., 2017	Spain	Retrospective Cohort	2,255,406	48.6 (NR)	4,429 (60.4%)	None described	Registry/Admin data	47	☒	Diagnoses in chart reviews - not specified
Islam et al., 2017*	Netherlands and Belgium	Prospective Cohort	2,584	27.8 (8.2)	1,951 (75.50%)	ICD-10	Chart Reviews	121	✓	Self-reports + Pharmacy records
Jahrami et al., 2017	Bahrain	Case-Control	240	41.69 (13)	66 (55%)	None described	Registry/Admin data	4	☒	National Health Information System Bahrain
Kugathasan et al., 2019	Denmark	Retrospective Cohort	5,432,821	32.59 (11.42)	17,288 (57%)	ICD-8 or ICD-10	Registry/Admin data	10 (clusters)	☒	ICD-10 codes
Nishanth et al., 2017	India	Cross-Sectional	100	35.12 (10.7)	55 (55%)	DSM-IV	Not Described	Not Described	Not described	Not described
Smith et al., 2013	UK	Cross-Sectional	1,424,378	51.6 (16.5)	4,961 (51.5%)	Read codes	Registry/Admin data	32	☒	Not described
Stubbs et al., 2016	International	Cross-Sectional	207,146	NR	NR	WHO Composite International Diagnostic Interview	Self-Reports	9	☒	Self-reported
Woodhead et al., 2014*	UK	Cross-Sectional	308,643	48.7 (NR)	2,432 (56%)	None described	EHRs	12	☒	Binary (Y/N) variables in EHRs

Notes:

*Baseline characteristics for these studies are based on the sample sizes reported in this table, and do not account for loss to follow-up. Meta-analyses have been conducted on the observed number of cases and controls, accounting for loss to follow-up.

Abbreviations:

DSM = Diagnostic and Statistical Manual of Mental Disorders; EHR = electronic health record; ICD = International Classification of Diseases; NR = not reported; SD = standard deviation; Y/N = yes/no variables

Legend:

✓Mental health condition(s) included in study definition of multimorbidity

☒ No mental health condition(s) included in study definition of multimorbidity

The studies varied with respect to the number (range: 6 to 121) and types of chronic conditions included in definitions of multimorbidity (see *Supplementary Appendices 3D-3E* for the conditions examined by individual studies). All studies included both diabetes mellitus and some form of chronic cardiovascular disease, such as hypertension, coronary heart disease, myocardial infarction, ischemic stroke, or atrial fibrillation. Eleven studies counted individual conditions,[174,326–330,332–334,336,338] whereas two studies organized conditions into disease clusters (e.g. infectious diseases, respiratory diseases) and conditions within the same cluster counted as one chronic condition.[331,335] Three studies considered substance use and/or mental disorders in their definitions of multimorbidity, and counted each distinct type of substance use or mental disorder as a separate condition. Psychotic disorder was not included in these definitions, as it was considered the exposure variable.[174,328,334]

Studies investigated sociodemographic (e.g. age, sex, SES), clinical (e.g. healthcare use, medication use), and lifestyle (e.g. smoking, alcohol use, body mass index (BMI)) factors associated with multimorbidity. Five studies investigated age as a risk factor for multimorbidity,[331,332,334,337,338] and three of these studies found older age to be significantly associated with multimorbidity.[331,334,337] One of the studies noted an interaction between age and sex, where female cases under 35 years of age had a higher prevalence of multimorbidity compared to same-aged female controls.[332] Five of six[326,331–334,337] studies which examined sex as a risk factor found that females with psychotic disorders were significantly more likely to experience multimorbidity than males. One study investigated quality of care metrics for people with schizophrenia who had other co-occurring chronic health conditions, and observed a positive association between adherence to antipsychotic medications and number of medical conditions.[330] Both studies that investigated smoking and alcohol consumption found that alcohol was associated with multimorbidity, and that smoking accounted for excess physical morbidity related to specific chronic conditions (e.g. heart failure, COPD, epilepsy).[327,336] Findings for other risk factors for multimorbidity among people with psychotic disorders are summarized in *Table 3.2* and *Supplementary Appendix 3F.*

The findings from the risk of bias assessment for included studies are presented in *Figure 3.2* and *Supplementary Appendix 3C*. We found that only two studies completely satisfied all domains.[329,330] Common issues included: selection of the source population and exposed or unexposed cohorts; assessment of exposure, outcome, and confounding factors; and missing data.

Table 3.2: Brief summary of findings from included studies on factors associated with multimorbidity among people with psychosis (*n*=14)

Study	Case Sample	Low SES	Homelessness	High BMI or Excessive Dietary Intake	Increased Age	Female Sex	Rural Settings	Healthcare Use	Mortality	Medication Use and Adherence	Smoking and Alcohol Use[3]
Bhalla et al., 2018	Veterans in mental health specialty clinics	✓	✓	✓	-	-	-	-	-	-	-
Bouza et al., 2010[1]	Inpatients in hospitals across country	-	-	-	✓	☒	-	-	-	-	-
Carney et al., 2006	Outpatients in practices across state	-	-	-	-	-	☒	✓	-	-	-
Correll et al., 2017[1]	Inpatients in hospitals across country	-	-	-	-	-	-	↓	✓	-	-
Domino et al., 2014[2]	Outpatients and inpatients among Medicaid enrollees	-	-	-	-	-	-	-	-	✓	-
Filipcic et al., 2019	Stable outpatients who were once treated as inpatients at 1 academic psychiatric institution	-	-	-	☒	✓	-	-	-	-	-
Gabilondo et al., 2017	Outpatients and inpatients in practices across county	-	-	-	-	✓	-	-	-	-	-
Islam et al., 2017	Outpatients of academic psychiatric institutions across country	-	-	-	✓	✓	-	-	-	-	-
Jahrami et al., 2017	Outpatients of 1 academic psychiatric institution	-	-	✓	-	-	-	-	-	-	✓
Kugathasan et al., 2019[1]	Outpatients and inpatients of psychiatric hospitals across country	-	-	-	-	-	-	-	✓	-	-
Nishanth et al., 2017	Outpatients of 1 academic psychiatric institution	-	-	-	✓	✓	-	-	-	✓	-
Smith et al., 2013	Outpatients of primary care practices across country	-	-	-	-	✓	-	-	-	-	-
Stubbs et al., 2016	Persons with psychosis across 48 low- and middle-income countries	-	-	-	↓	-	-	-	-	-	-
Woodhead et al., 2014	Outpatients of family physicians' practices across borough	-	-	✓	-	-	-	-	-	-	✓

Notes:

[1]Studied factors related to mortality among patients with schizophrenia due to 2+/3+ physical health conditions

[2]Studied quality care metrics among patients with schizophrenia with co-occurring 2+/3+ physical health conditions

[3]Smoking and alcohol use studied as a risk factor for multimorbidity, not included in counts of chronic conditions

Legend:

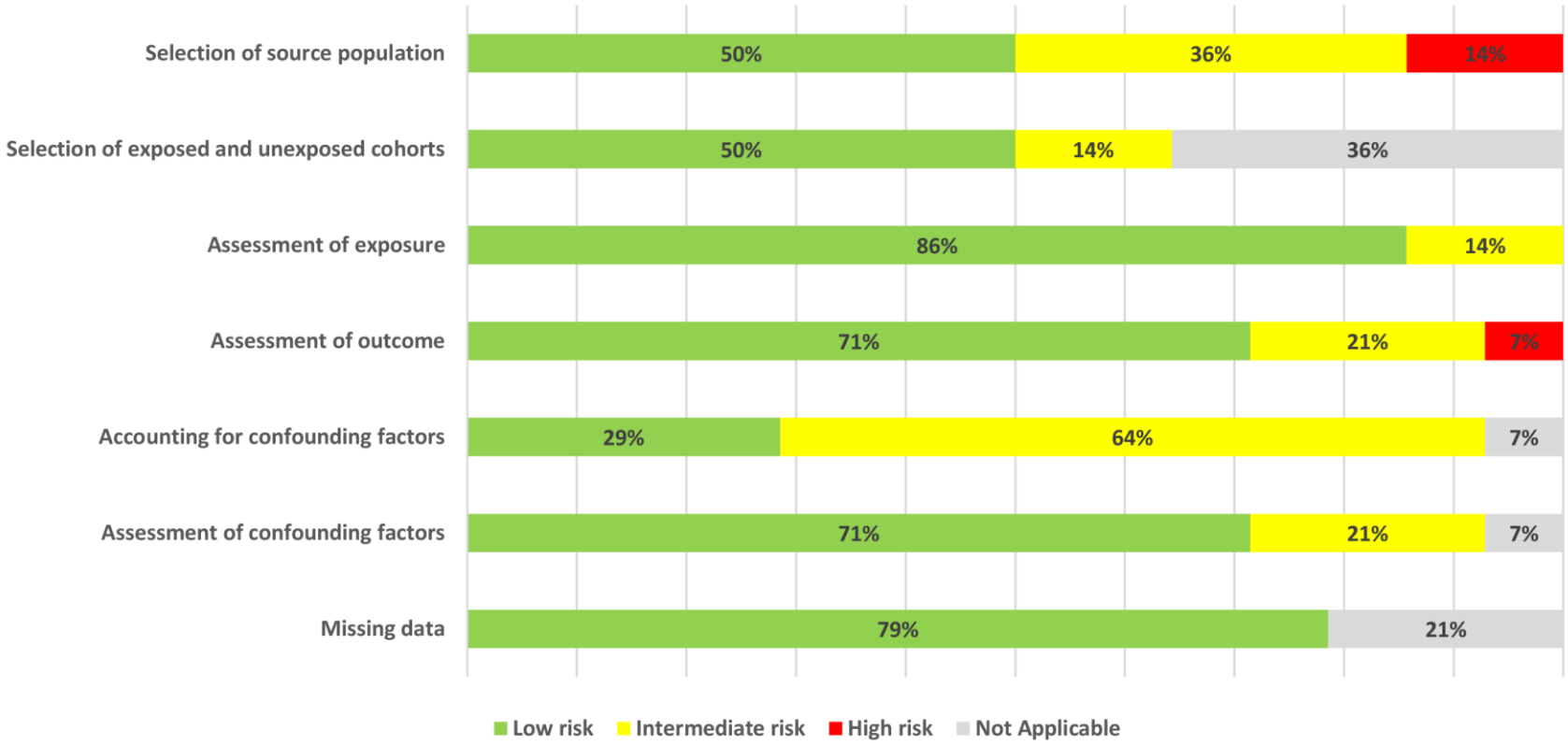
✓Positive association between risk factor and prevalence/ odds/ incidence of multimorbidity

↓Inverse association between risk factor and prevalence/ odds/ incidence of multimorbidity

☒ No significant association between risk factor and prevalence/ odds/ incidence of multimorbidity

- Association not studied

Figure 3.2: Risk of bias assessment across included studies (*n*=14)



3.4.1 Meta-Analyses

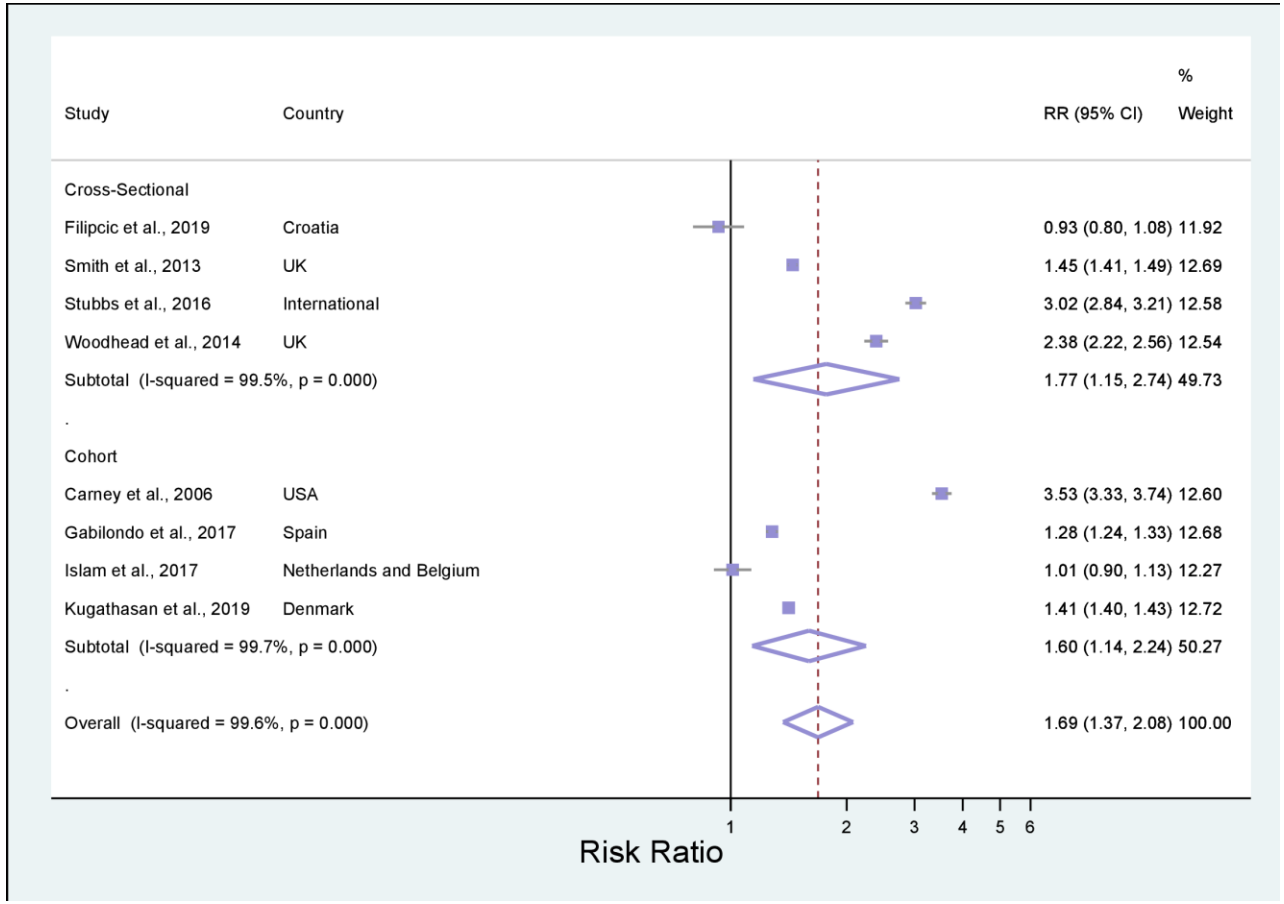
Across the thirteen studies included in our quantitative synthesis of 2+ chronic physical health conditions (pooled *n*=211,093), the pooled prevalence of multimorbidity among people with psychotic disorders was 43% (95%CI=25%,60%; I^2=99.9%). Prevalence estimates across individual studies varied with the number of conditions included in multimorbidity definitions, ranging from 16% to 91% (*Supplementary Appendix 3G*). Across the nine studies reporting data on 3+ chronic physical health conditions (pooled *n*=142,568), the pooled prevalence among people with psychotic disorders was 22% (95%CI=14%,30%; I^2=99.9%; *Supplementary Appendix 3H*).

Our meta-analysis of eight studies (pooled *n*=10,253,920) reporting risk of 2+ chronic conditions found that the risk of multimorbidity was 69% higher among people with psychotic disorders, relative to people without psychosis (RR=1.69, 95%CI=1.37,2.08; I^2=99.7%). The magnitude of effect was similar for the pooled estimates from the four cross-sectional studies (pooled *n*=1,915,810; PR=1.77, 95%CI=1.15,2.74; I^2=99.5%) and the four cohort studies (pooled *n*=8,338,110; RR=1.60, 95%CI=1.14,2.24; I^2=99.7%) (*Figure 3.3*).

3.4.1.1 Sensitivity Analyses

We found a larger magnitude of effect for our sensitivity analysis of 3+ chronic conditions, where people with psychotic disorders had a nearly three times greater risk of multimorbidity (RR=2.68, 95%CI=1.45,5.10; I^2=99.9%) relative to those without psychosis (*Supplementary Appendix 3I*). Sensitivity analyses restricted to studies which met all criteria in our risk of bias assessment yielded similar effect estimates as the main analysis (*Supplementary Appendix 3J*). An exploratory analysis of six studies (pooled *n*=9,604,037) which only considered physical health conditions in their definitions of multimorbidity also yielded similar findings as the main analysis (RR=1.62, 95%CI=1.36,1.94; I^2=99.4%; *Supplementary Appendix 3K*).

Figure 3.3: Risk of multimorbidity (2+ conditions) for people with psychosis compared to people who do not have psychotic disorders (*n*=8)



Abbreviations:
CI = confidence interval; RR = risk ratio

3.5 Discussion

The findings from our systematic review and meta-analysis suggest an increased risk of multimorbidity among people with psychotic disorders. The excess risk of having 2+ chronic health conditions was found to be 69% higher among people with psychotic disorders, relative to people without psychosis. Furthermore, people with psychosis had a nearly three times greater risk of developing 3+ chronic conditions. This finding may potentially be due to the cardio-metabolic disturbances caused by antipsychotic medications, as well as behavioural risk factors such as smoking, physical inactivity, and poor dietary patterns, which increase the risk of several chronic health conditions.[4,141] Our exploratory analysis of studies which did not consider substance use and other mental health conditions in definitions of multimorbidity found similar effect sizes. We expected to see a smaller magnitude of effect for this analysis due to the comorbidity between mental health conditions, but this may be explained by diagnostic overshadowing of psychosis over other mental health conditions with psychotic-like symptoms.[339,340]

Factors associated with multimorbidity among people with psychotic disorders included sociodemographic characteristics such as female sex and older age, and behavioural risk factors such as substance use, sedentary behaviour, high caloric intake, and high BMI. Several studies of the general population have documented higher risk of multimorbidity among females,[246,257,341–343] potentially owing to lower healthcare utilization by men and consequent under-recognition of chronic medical conditions.[288,289] Primary studies in our review found that older age was a risk factor for development of multiple chronic conditions, but two studies noted high odds or prevalence of multimorbidity among younger persons with psychosis relative to those without psychotic disorders. Other population-based studies have also found that although older cohorts have the highest risk of developing multiple chronic conditions,[246,260] there is a high prevalence of multimorbidity across all age groups, including those in the youngest cohorts.[274] Excessive dietary intake, low physical activity, and substance use are risk factors for several cardiometabolic conditions such as diabetes and hypertension.[344] These lifestyle

factors are prevalent among both younger people[345,346] and those with psychosis,[11–13] which may explain the high prevalence of multimorbidity observed among younger people with psychotic disorders.

Our systematic review and meta-analysis findings also highlight the extensive heterogeneity associated with operational definitions of multimorbidity across the literature, both in the number and types of included chronic conditions, which is a common issue in multimorbidity research.[252,253] The implications of this issue were evident in the wide range of prevalence estimates (16% to 91%) across studies included in our review. The variation in the number of conditions stems from considerations for the prevention and management of chronic conditions across public health (2+) and clinical (3+) settings,[252,253,257] but may also reflect regional differences regarding chronic conditions which merit consideration.[257,300] However, conditions in the metabolic syndrome, such as diabetes and cardiovascular disease were included in the definition for all studies owing to the high prevalence of these conditions, both among the general population and people with psychotic disorders.[4,141,347–349] Furthermore, the majority of studies in our review (n=11/14) did not consider substance use or mental health conditions in their definitions of multimorbidity. This raises important questions regarding the inclusion of mental health conditions generally, and psychotic disorders specifically, in the definitions of multimorbidity when attempting to assess the risk among people with psychosis. The Public Health Agency of Canada considers mental health conditions as a broad category,[65,262] such that people with any number of mental disorders are counted only once according to their definition of multimorbidity. Although this approach takes into account the high degree of comorbidity among diverse mental health conditions,[339] effect estimates would be of even greater magnitude if we were to consider each psychiatric disorder separately in defining multimorbidity. Further, if we were to consider the exposure condition of psychotic disorder in definitions of multimorbidity, such that people with schizophrenia and other psychotic disorders already have one chronic health condition, effect estimates for the observed excess risk of multimorbidity would be even higher.

Our risk of bias assessment indicated that several studies failed to consider confounding factors beyond age, sex, and SES. In the future, studies should account for notable confounders such as duration of antipsychotic medication use[139] and common behavioural risk factors (e.g. smoking, low physical activity),[19–21] which is a limitation of using health administrative data.[350] Future studies should also use similar operational definitions for multimorbidity, in terms of both the number and types of chronic conditions included, in order to better enable cross-study comparisons. Moreover, further investigation of specific clusters of chronic conditions commonly experienced by this clinical population is warranted.

3.5.1 Limitations

Our findings should be interpreted with consideration of the limitations of included studies. Several studies were cross-sectional, which makes it challenging to establish temporality between psychosis and multimorbidity,[351] as people with psychotic disorders may have chronic health conditions prior to the onset of psychosis.[352] Assessment of chronic conditions also occurred by self-report in some studies. Although this method has been shown to have a high degree of reliability in ascertaining chronic health conditions among patients with mental illness,[353] it is a potential source of misclassification for the studies included in our review.

The methodological limitations of our review should also be noted. First, most included studies were not designed with a primary objective of examining the risk of multimorbidity among people with psychotic disorders, and our search strategy may have missed studies that did not use the terms “multimorbidity” or “comorbidity” in their titles or abstracts. Second, risk of bias assessment was conducted using the CLARITY tools, which were originally designed for case-control[313] and cohort[314] studies, but were adapted for the cross-sectional studies in our review. Third, we pooled PR and RR into a common estimate under the assumption that psychotic disorders do not impact the duration of multimorbidity,[321] which may not be valid for conditions where the presence of psychotic symptoms may impact illness duration. Fourth, we cannot rule out systematic underreporting by studies with null findings, as we had fewer than the number of studies

required to assess this publication bias.[318] Finally, we found a high degree of statistical heterogeneity in our pooled estimates, which made it difficult to compare prevalence estimates across studies. This heterogeneity may be partially explained by the wide variation in definitions of multimorbidity and different compositions of samples. Neither the severity of illness nor the subsequent duration of antipsychotic treatment were considered when evaluating the risk of multimorbidity, which may differ greatly among people with more severe psychoses, affective psychotic disorders, or longer duration of treatment with antipsychotic medications.[139] However, we were unable to examine the sources of heterogeneity using meta-regression, given that we had fewer than 10 studies for our meta-analysis.[318]

3.5.2 Conclusions

Our systematic review and meta-analysis highlight a greater risk of physical multimorbidity among people with psychotic disorder. This burden of illness is likely to reflect both exposure to antipsychotic medications as well as a higher prevalence of behavioural risk factors. Clinicians who care for patients with psychosis should routinely assess for risk of physical health conditions and work to integrate care across medical specialties to better manage the unique needs of this population.

3.6 Declaration of Interests

Declaration of interest: none.

3.7 Role of the Funding Source

Role of the funding source: none.

3.8 Acknowledgements

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Chapter 4

4 The Prevalence of Multimorbidity among People with Non-Affective Psychotic Disorders 10-Years after First Diagnosis

4.1 Abstract

Background: An excess risk of physical health conditions among people with psychotic disorders may result in a reduced life expectancy, as compared to those without psychosis. It is unknown whether those with psychotic disorders also have a higher risk of multiple co-occurring chronic health conditions, known as multimorbidity. We conducted a retrospective matched cohort study to quantify the prevalence of multimorbidity and associated factors among people with psychotic disorders over the 10-year period following first diagnosis, relative to those without psychosis. ***Methods:*** Data from the Prevention and Early Intervention Program for Psychoses in London, Canada were linked to population-based health administrative data to identify patients with first-episode of psychosis (*n*=439), and a comparison group from the general population (*n*=1,759) matched on age, sex, and neighbourhood. We followed the cohort for ten years to ascertain the prevalence of multimorbidity. We compared people with and without psychosis using modified Poisson regression models, and explored risk factors for multimorbidity among those with psychotic disorder. ***Results:*** People with psychotic disorders may have a 26% higher prevalence of multimorbidity ten years following first diagnosis, although our findings include the possibility of a null effect (PR=1.26, 95%=CI 0.96,1.66). Twenty-six to thirty-year olds with psychosis had a higher prevalence of multimorbidity than those aged 16-20 years (PR=1.77, 95%CI=0.98,3.21). People with psychotic disorders living in areas with the highest levels of material deprivation had a three-fold higher prevalence of multimorbidity as compared to those in the lowest areas of material deprivation (PR=3.09, 95%CI=1.21,7.90). ***Conclusions:*** More research is needed to better understand multimorbidity among people with serious mental illness, particularly studies using larger sample sizes and longer follow-up periods.

***Keywords*:** comorbidity, multimorbidity, multiple chronic conditions, physical health, psychotic disorders

4.2 Introduction

People with schizophrenia and other psychotic disorders have a reduced life expectancy of up to 20 years compared to the general population,[1] primarily due to differences in physical health and preventable physical illnesses.[2,3] Several studies have found that people with schizophrenia experience longer hospital stays and increased healthcare costs for chronic health conditions, relative to the general population.[2,306] Furthermore, mortality gaps are widening between those with and without psychotic disorders,[303,305] largely due to presence of chronic health conditions. Diabetes mellitus, infection with human immunodeficiency virus (HIV), and cardiovascular and respiratory diseases are several chronic conditions found to be highly prevalent among people with psychosis.[4] The differences in the risk of chronic conditions for this clinical population may be explained by ongoing treatment with second-generation antipsychotic medications. These interventions may result in metabolic side effects such as weight gain and impaired glucose metabolism,[4–7] which are associated with an increased risk of cardiovascular disease and diabetes mellitus.[8–10] Furthermore, the high prevalence of lifestyle factors such as risky sexual behaviours[218] and smoking[11–13] among people with psychotic disorders may explain why the relative risk of HIV infection and respiratory illness is higher among this clinical population.[4]

Although there is a vast body of evidence on the increased risk of individual chronic physical conditions among people with schizophrenia and other psychotic disorders, research on the co-existence of multiple co-occurring chronic conditions – known as multimorbidity – is more limited.[3] Operational definitions of multimorbidity vary extensively across studies with respect to the types of chronic conditions included and cut-offs for the number of co-existing conditions, ranging from two to four co-occurring conditions.[252] Considerations of multimorbidity across public health and clinical settings

may explain this heterogeneity, as prevention and management of chronic diseases is concerning for public health professionals at two co-occurring conditions, whereas clinical management of multiple diagnoses typically pose a challenge for clinicians after the third diagnosis.[252,253]

Evidence to date suggests that both psychosis and multimorbidity share common risk factors. Lifestyle factors, such as smoking and sedentary behaviour, influence risk for cardiometabolic,[16,17] respiratory,[18] and other chronic conditions[19–21] and are more prevalent both among people with multimorbidity[20–22] and those with psychotic disorders.[11–13] Furthermore, studies indicate that people from non-White ethnic backgrounds and materially-deprived areas experience a higher incidence of both psychosis[33,40–44] and multimorbidity.[246,279,291,293,294] Risk factors underlying the co-existence of multiple chronic conditions and psychotic disorders may be interrelated and form unique clusters of conditions.[3]

There have been few large-scale studies to date quantifying the excess prevalence of multimorbidity experienced by people with schizophrenia and other psychotic disorders. The objective of our study was to estimate the excess prevalence of multiple chronic conditions 10-years after a first episode of psychosis, compared to people without psychotic disorders matched on age, sex, and neighbourhood. Although psychosis is a chronic condition,[61] we excluded it as a count towards multimorbidity in our main model, given that it was the exposure of interest and it is not typically included in standard multimorbidity definitions.[250,260]

We sought to: (i) estimate the prevalence of multimorbidity 10-years after a first diagnosis of non-affective psychotic disorder, and assess whether it was significantly different relative to people without psychotic disorders; (ii) evaluate the effect of age, sex and material deprivation on the prevalence of multimorbidity separately for people with and without psychotic disorders; and (iii) investigate whether severity of psychotic symptoms and persistence of functioning impairments were associated with a higher prevalence of multimorbidity among people with psychotic disorders. We hypothesized that people with psychotic disorders would have a higher prevalence of multimorbidity,

and that sociodemographic and clinical factors may render subgroups of this clinical population particularly susceptible to the development of multiple chronic health conditions.

4.3 Methods

We followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines for observational studies (see *Supplementary Appendix 4L*).[354] We obtained approval using an existing Health Sciences Research Ethics Board application at Western University (protocol #112446) to link the primary data from the early psychosis intervention program, described below.

4.3.1 Data Sources

We used the following population-based databases housed at ICES, which compiles health administrative data for the province of Ontario:[355] According to Ontario's Personal Health Information Privacy Act,[356] ICES is a prescribed entity, and permitted to collect personal health information on Ontario's patients from physicians, hospitals and long-term care homes without prior patient consent. Information used by ICES is for evaluation and monitoring of Ontario's health care system and approved research. Data sharing agreements between ICES and data partners who access ICES data detail security measures which ensures privacy of sensitive patient health data.[357]

- Demographic information about people registered for the Ontario Health Insurance Plan (OHIP), such as date of birth, sex, and neighbourhood-level indicators of deprivation, is collected and stored in the Registered Persons Database by the Ontario Ministry of Health and Long-Term Care. Nearly the entire population of Ontario (98.5%) is covered for medically necessary health services by OHIP.[358–361]
- The Ontario Mental Health Reporting System (OMHRS), which contains standardized information on clinical and administrative mental health data for all patients admitted to designated adult psychiatric inpatient beds.

- The Discharge Abstract Database (DAD) maintains administrative, clinical, and demographic information from acute care settings for people discharged from other hospital inpatient units, and for psychiatric hospitalization not covered by OMHRS.
- The OHIP Claims Database contains data on physician billing claims, including information on the type, date, and the diagnosis made during the provision of services.[362]
- The National Ambulatory Care Reporting System (NACRS) stores administrative, clinical, and demographic information for emergency departments, day surgeries, and hospital and community-based ambulatory care.[362]
- Information about prescription drugs issued under the Ontario Drug Benefit (ODB) program is routinely collected and stored in the ODB Claims Database, which excludes the majority of drugs prescribed in Ontario that are not issued under this program.[362] The ODB covers Ontario residents with a valid health card who are either below 25 or over 65 years of age, or those who live in a Long-Term Care Home, are enrolled in the Home Care Program, are low income residents registered in the Trillium Drug Program due to inability to pay for prescription drugs, or receive governmental social assistance.[363]

These ICES databases were also linked to primary data from the Prevention and Early Intervention Program for Psychoses (PEPP) using health insurance numbers (96% of clinical sample). This primary data linkage was needed to identify PEPP clients within the health administrative data holdings. Unique encoded identifiers were used to link all datasets by analysts at ICES, and remote data access was made available through the ICES Data & Analytic Services division.[364]

4.3.2 Study Design and Sample

We used a retrospective cohort design to investigate the association between psychosis and multimorbidity over a ten-year follow-up period, the duration for which we had follow-up data.

People with first-episode psychosis treated at PEPP in London, Ontario between April 1, 1997 and March 31, 2007 formed our exposed group.[45] PEPP provides early psychosis intervention services for young people with psychosis (aged 16 to 50) in London and the

surrounding catchment area,[365–368] including tailored treatment plans consisting of pharmacological and psychosocial interventions.[367–369] The index date was defined as the date when exposed participants were admitted to the PEPP program.

We randomly selected an unexposed comparison group from the general population, matched to exposed participants with psychosis on age (±3 years), sex, and postal code. Up to four unexposed participants were selected for each exposed participant, and those who were unexposed assumed the same index date as the exposed participant to whom they were matched. We excluded people from the comparison group who had a diagnosis of schizophrenia, schizoaffective disorder, or psychotic disorder not-otherwise-specified at any point in their medical records. Both exposed and unexposed participants were followed up for ten years in the health administrative data to ascertain the onset of chronic health conditions.

4.3.3 Definition of Multimorbidity

Our primary outcome of interest – multimorbidity – was defined as the co-occurrence of two or more (2+) chronic health conditions from a list of 17 conditions, which included 16 physical conditions and 1 mental health condition (comprised of either of two mental disorders). Multimorbidity has been previously identified using ICES databases,[260] and we used the same definitions and time frames for chronic conditions which were used by this prior study. These conditions were also selected based on a research tool developed to document the presence of chronic conditions.[250] The conditions included: arthritis (either osteoarthritis or rheumatoid arthritis), asthma, cancer, congestive heart failure, chronic obstructive pulmonary disease, cardiovascular disease, dementia, diabetes, HIV, hypertension, inflammatory bowel disease, chronic kidney disease, chronic liver disease, osteoporosis, stroke/ transient ischemic attack, urinary incontinence, and either mood or anxiety disorder.

All conditions included in our definition have been validated for use in health administrative data, and the presence of these conditions was ascertained from predefined cohorts where available, or with the use of standardized algorithms. We identified

conditions present at the index date using a lookback window of 5, 8, or 10 years (condition-dependent), as well as the presence of conditions that developed over the 10-year follow-up period. Both the predefined cohorts as well as the algorithms use diagnostic codes from the International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10), and a complete list of the relevant codes and lookback windows is presented in *Supplementary Appendix 4M*.

For all physical health conditions, we included both prevalent conditions (present before study entry) and incident conditions over the 10-year follow-up period (i.e. within 3,650 days of follow-up) in our definition of multimorbidity. We chose to employ this approach due to the long-standing nature of chronic conditions,[62] and the fact people with psychotic disorders may have a higher burden of chronic health conditions even prior to the onset of psychosis.[352] For mental health conditions included in the multimorbidity definition, specifically mood and/or anxiety disorders, we excluded diagnoses that were present before cohort entry given that changes in mood and anxiety symptoms (e.g. depression, anxiety, mood swings) often characterize the prodrome to psychosis,[370] which we did not want to capture in our outcome definition.

We first created a summary variable to capture the sum of all chronic conditions in each person. We then created binary variables to capture presence or absence of multimorbidity using two ore more (2+) and three or more (3+) chronic conditions as cut-offs, in line with public health and clinical definitions of multimorbidity, respectively. For exploratory analyses, we also created a binary variable aligned with the Public Health Agency of Canada's (PHAC) definition,[65,262] which considers psychosis as a "count" towards multimorbidity due to its chronic nature.[61] For this variable, we used an omnibus mental health condition that included both psychotic and mood/anxiety disorders, in keeping with the PHAC definition, such that people with psychotic disorders were required to have only 1 or more (1+) chronic physical condition from our list to meet the definition for multimorbidity.

4.3.4 Factors associated with Multimorbidity

We examined sociodemographic factors potentially associated with multimorbidity separately among people with and without psychotic disorders. These included sex, age at index date, and neighbourhood-level indicators of material deprivation. Sex was used as a binary variable (*Male, Female*), whereas age was captured through ordinal variables representing distinct age groups (*26 to 30, 31 to 35, 36 to 40, 41 to 45, 46 to 50* years of age). We used the Ontario Marginalization Index (ON-Marg) to obtain information on neighbourhood-level material deprivation.[371] ON-Marg is a multi-dimensional scale based on census data that captures components of marginalization and has been validated as a geographically-based index.[372,373] Material deprivation broadly encompasses the inability to access and attain basic material needs, and includes indicators of income, educational attainment, family structure, and quality of housing.[371,374] Neighbourhood-level material deprivation scores were divided into quintiles based on the provincial distribution ranging from one (least marginalized) to five (most marginalized).

Among people with psychotic disorders, we used proxy measures as indicators of the severity of psychotic symptoms and persistence of impaired functioning. Total psychiatric hospital days over the follow-up period was used as a proxy measure to assess psychosis severity, which has been validated in a recent study which found a dose-response association between psychosis severity and total days spent in the hospital.[375] For persistence of impaired functioning, we used the length of time on the Ontario Drug Benefit Program (ODB) as a proxy measure, as people who experience psychosis for prolonged periods may be unable to partake in gainful employment and consequently depend on social assistance for their income.[376–378] The face validity of our measure has been demonstrated in a study where length of time on social assistance programs increased with poorer functioning of psychotic patients.[379] Social assistance is provided by the Ontario government through either Ontario Works for people in temporary financial need, or through the Ontario Disability Support Program as a form of long-term income support for people with disabilities.[380] We used the ODB program as a proxy measure of social assistance in our study, given that the ODB is a comprehensive public drug funding program which covers Ontario residents with a valid health card who

receive social assistance through these programs.[363] We used a continuous measure of length of time a patient has received ODB over the follow-up period, calculated as the time between the earliest and latest prescription dispensing date.

4.3.5 Data Analysis

All analyses were conducted using Stata MP version 16.1.[315] Descriptive statistics were summarized using frequencies and proportions for categorical data.

First, we estimated the proportion of people who experienced multimorbidity within 10-years of a first diagnosis of psychotic disorder. We also estimated the proportion of people without psychotic disorders who experienced multimorbidity within this time period. Second, we compared these proportions using modified Poisson regression models with robust variance estimators through the *xtpoisson* command in Stata MP version 16.1. This command enabled us to produce a prevalence ratio with an associated 95% confidence interval conditioned on the matched study design where cohort members of the same set were identified by a common group identification number.[381,382]

Third, we limited the sample to those with psychotic disorders in order to examine the effect of sociodemographic and clinical factors (age, sex, neighbourhood-level material deprivation, psychosis severity, persistence of impaired functioning) on the prevalence of multimorbidity among people with psychotic disorders, computing prevalence ratios (PRs) with associated 95% confidence intervals for each variable. To explore the association between psychosis severity and multimorbidity, we used the proxy measure of total hospital days (number of days in 30-day intervals) for severity. We used length of time on ODB in years as a proxy measure for persistence of impaired functioning to explore its association with prevalence of multimorbidity in our Poisson regression model. We also explored the effect of age, sex, and neighbourhood-level material deprivation on prevalence of multimorbidity among people without psychotic disorders.

We conducted complete-case analyses given our small to moderate sample size and limited missingness (<4%) of data.[383,384] We also performed sensitivity analyses for all objectives using 3+ conditions as a cut-off for our definition of multimorbidity, which is

in line with clinical definitions. Lastly, we performed exploratory analyses that included psychosis as a "count" towards multimorbidity, meaning that 1+ physical health condition would be the cut-off for multimorbidity among our exposed group, whereas 2+ conditions would be the cut-off for the unexposed comparison group. Further details describing our methods can be found in *Supplementary Appendices 4M-4N*.

4.4 Results

Out of 455 people with first-episode psychosis and 1,783 controls, we excluded 16 exposed participants and their unexposed matched counterparts from our final sample due to missing information for neighbourhood-level deprivation as a result of missing postal codes. Thus, our final sample consisted of 439 people with psychotic disorders and 1,759 age-, sex-, and neighbourhood-matched comparisons (total n = 2,198). The sociodemographic characteristics of the cohort are presented in *Table 4.1*.

Table 4.1: Sociodemographic characteristics in people with and without psychotic disorders at baseline (*n*=2,198)

Sociodemographic characteristics	People with Psychotic Disorders (*n*=439) N (%)	People without Psychotic Disorders (*n*=1,759) N (%)
Age group		
16-20 years	172 (39.2)	677 (38.5)
21-25 years	128 (29.2)	525 (29.9)
26-30 years	139 (31.7)	557 (31.7)
Sex		
Males	330 (75.2)	1,322 (75.2)
Females	109 (24.8)	437 (24.8)
Material Deprivation[1]		
Quintile 1	82 (18.7)	324 (18.4)
Quintile 2	77 (17.5)	332 (18.9)
Quintile 3	66 (15.0)	313 (17.8)
Quintile 4	114 (26.0)	393 (22.3)
Quintile 5	100 (22.8)	397 (22.6)

Notes:

[1]Material deprivation was assessed in quintiles ranging from one (least marginalized) to five (most marginalized).

Two hundred and fifty-five people with psychosis were admitted to the hospital for psychiatric reasons over the follow-up period, with hospital stays ranging from one to fifteen (median = 2 counts; Interquartile Range, IQR = 1, 3 counts). The total number of hospital days ranged from 0 to 735 days, with a median of 40 days (IQR = 16, 68 days). The ODB was administered to 304 people with psychosis over the follow-up period, and the length of coverage ranged from 100 to 3650 days. The median length of time on ODB was 3622 days (IQR = 2879, 3644 days).

The number of chronic conditions for people with and without psychotic disorders is presented in *Supplementary Appendix 4O*, and range from 0 to 7 counts, with a median count of 1 condition. Nearly 75% of people with psychotic disorders were already living with one chronic condition prior to study entry (see *Supplementary Appendix 4P*). Over 14.1% of people (95%CI = 11.2%, 17.7) with psychosis had 2+ chronic conditions, compared to 11.2% (95%CI = 9.8%, 12.8) of the matched comparison group. The prevalence ratio suggests that people with psychotic disorders may have a 26% higher prevalence of multimorbidity, although the 95% CI includes the possibility of a null effect (PR=1.26, 95% CI 0.96, 1.66).

Prevalence ratios summarizing the effect of sociodemographic and clinical factors on the prevalence of multimorbidity (2+ conditions) at 10-year follow-up for those with psychotic disorders are presented in *Tables 4.2 and 4.3*. People with psychotic disorders aged 21-25 at first diagnosis had a 33% higher prevalence of 2+ chronic conditions at 10-year follow-up (PR=1.33, 95%CI = 0.72, 2.46), and those aged 26-30 years had a 77% higher prevalence of multimorbidity (PR=1.77, 95%CI = 0.98, 3.21), as compared to people with psychosis aged 16-20 years, although our 95% CI for both estimates included the null value. Females with psychotic disorders did not have a higher prevalence of 2+ chronic conditions as compared to males (PR=1.01, 95%CI = 0.59, 1.73). There was also evidence of a gradient effect for neighbourhood-level material deprivation, with exposed participants in the second-highest level of deprivation having a two-fold greater prevalence of multimorbidity (PR=2.46, 95%CI = 0.99, 6.12), and exposed participants at the highest deprivation level having a three times greater prevalence of multimorbidity,

when compared to those with psychotic disorders at the lowest deprivation level (PR=3.09, 95%CI = 1.21, 7.90). We observed similar findings for the effects of age, sex and material deprivation on prevalence of 2+ chronic conditions among people without psychotic disorders (see *Supplementary Appendix 4Q*). The prevalence of multimorbidity among people with psychotic disorders increased by 5% for each 30-day increase in total length of psychiatric hospitalization (PR = 1.05, 95%CI=0.96, 1.13), although this included the possibility of a null effect. Furthermore, the prevalence of 2+ chronic conditions among people with psychotic disorders increased by 6% for each year spent receiving social assistance through ODB (PR = 1.06, 95%CI=1.00, 1.12).

Table 4.2: Prevalence ratios of sociodemographic factors and their association with multimorbidity among people with psychotic disorders at 10-year follow-up (*n*=439)

Sociodemographic characteristics	2+ conditions PR (95% CI)[1]
Age group[2]	
26-30 years	*Reference*
31-35 years	1.33 (0.72, 2.46)
36-40 years	1.77 (0.98, 3.21)
Sex	
Males	*Reference*
Females	1.01 (0.59, 1.73)
Material Deprivation	
Quintile 1 (Least Deprived)	*Reference*
Quintile 2	1.69 (0.57, 5.07)
Quintile 3	2.14 (0.76, 6.05)
Quintile 4	2.46 (0.99, 6.12)*
Quintile 5 (Most Deprived)	3.09 (1.21, 7.90)**

Abbreviations:

CI = confidence interval; PR = prevalence ratios

Notes:

[1]Prevalence ratios have been adjusted for total hospital days (severity of psychotic symptoms) and length of time on the Ontario Drug Benefit (proxy measure of social assistance; persistence of impaired functioning).

[2]Age categories at follow-up reflect age of participants 10 years after baseline.

*Prevalence ratio may be considered significant at α=0.05

**Prevalence ratio is significant at α=0.05

Table 4.3: Severity of psychotic symptoms and persistence of impaired functioning, and their association with multimorbidity among people with psychotic disorders at 10-year follow-up (*n*=439)

Psychotic Symptoms	2+ conditions PR (95% CI)[1]
Severity	
Total hospital days (30-day intervals)	1.05 (0.96, 1.13)
Persistence	
Length of time on ODB (365-day intervals)	1.06 (1.00, 1.12)*

Abbreviations:
CI = confidence interval; ODB = Ontario Drug Benefit; PR = prevalence ratio
Notes:
[1]Prevalence ratios have been adjusted for age, sex and material deprivation.
*Prevalence ratio is significant at α=0.05.

4.4.1 Sensitivity Analyses

When using 3+ conditions as the cut-off for multimorbidity, in keeping with clinical definitions, 3.0% (95%CI = 1.7%, 5.0) of people with psychosis had multiple co-occurring chronic conditions, compared to 2.7% (95%CI = 2.1%, 3.6) of those without psychotic disorders. People with psychotic disorders did not have a higher prevalence of 3+ co-occurring chronic conditions as compared to those without psychotic disorders (PR=1.08, 95%CI = 0.60, 1.96). The findings from our other sensitivity analyses were similar to those from our main analysis (see *Supplementary Appendices 4R-4T*).

4.4.2 Exploratory Analyses

Our exploratory analyses which considered psychosis and mood and anxiety disorders as an omnibus mental health chronic condition, as used in the PHAC definition, found that 33.7% of people with psychosis had multimorbidity (95%CI = 29.4%, 38.3) compared to 11.2% (95%CI = 9.8%, 12.8) of the unexposed comparison group. When including mental health disorders in the multimorbidity definition, people with psychotic disorders had a prevalence that was over three times greater than those without psychotic disorders (PR=3.01, 95%CI = 2.47, 3.67).

4.5 Discussion

Our findings suggest that people with schizophrenia and other psychotic disorders had a higher prevalence of 2+ co-occurring chronic conditions although our 95% CI also included the possibility of a null effect. This may be explained by characteristics of our cohort and study methodology. Firstly, several population-based studies have demonstrated that the onset of multiple chronic conditions peaks after 45 years of age.[65,246,279,291,385,386] Given that the oldest people in our cohort were only between 36-40 years of age at the end of the follow-up period, it is likely that we would need a longer follow-up time to see an even higher prevalence of multimorbidity among those with psychotic disorders. Additionally, our use of physician billing claims to identify chronic conditions may be subject to diagnostic overshadowing. Since physicians may only submit one diagnostic code per patient encounter, it is likely that billings for psychosis

take precedence over other conditions,[339,340] particularly mental health conditions that were included in our definition of multimorbidity, thus resulting in an underestimation of prevalence estimates. Furthermore, prior research suggests that the use of a single data source, in particular health administrative data, may result in an underestimate of the prevalence of multimorbidity as compared to studies which used multiple data sources, e.g. health administrative and self-report data.[350] Lastly, chronic health conditions are underdiagnosed among people with mental illness who navigate fragmented healthcare systems in accessing treatment,[387] which may explain why our study did not find a larger difference in the prevalence of multimorbidity between those with and without psychosis.

Our study did not find evidence that females with psychotic disorders had a greater prevalence of multimorbidity than males 10 years after a first-episode of psychosis, which may be explained by our small exposed group and relatively short follow-up period.[388] In contrast, other studies examining people with psychotic disorders have found that multimorbidity is higher among females[326,332] than males potentially due to comparatively greater help-seeking behaviour by females.[288] Although our 95% CIs included the possibility of a null effect, we found that age was associated with multimorbidity among people with psychotic disorders, particularly for people with psychotic disorders who were 36-40 years at 10-year follow-up. Other studies which examined people with psychotic disorders have also found that age is associated with a higher prevalence of multimorbidity,[331,334,337] since older age is often associated with greater prevalence of multiple co-occurring chronic conditions.[65] Additionally, we found evidence of a gradient effect for material deprivation on the prevalence of multimorbidity. Given that socioeconomic status may facilitate or hinder access to health care, health promoting behaviours, and environmental exposures (e.g. smoke, pollution),[292] it is unsurprising that the prevalence of multimorbidity increases with increasing deprivation levels, as demonstrated by findings from several studies.[246,279,291,385]

Although our findings included the possibility of a null effect, we found evidence for an association between severity of psychotic symptoms and prevalence of multimorbidity,

using the proxy measure of number of days spent in the hospital. Several meta-analyses have found that the prevalence of chronic cardiometabolic conditions, e.g. hypertension,[139] cardiovascular diseases,[142] diabetes,[139] is higher among people with chronic schizophrenia as compared to those immediately after the onset of psychosis, potentially owing to longer duration of antipsychotic medications, which may increase the risk of various illnesses[139] and consequently, multimorbidity among people with psychotic disorders. Although the face validity of our proxy measure has been demonstrated in prior research where patients with more severe psychotic symptoms spend more time in the hospital,[375] our sample may have been underpowered to reveal a stronger association between psychosis severity and prevalence of multiple chronic conditions due to our relatively small exposed group.[388] Furthermore, our study followed people treated by an early psychosis intervention program immediately after a first episode of psychosis, where the risk for developing chronic conditions may be lower as compared to later in the course of psychotic illness.[139,142] Alternately, other measures of severity to which we did not have access may have a stronger relationship with chronic health conditions. For example, prior research has found a dose-response relationship between the number of psychotic symptoms and a higher number of chronic physical conditions.[389]

We also found evidence for an association between persistence of impaired functioning and prevalence of multimorbidity, using the proxy measure of years on social assistance. The interplay between metabolic side effects associated with the use of antipsychotic medication and behavioural risk factors among people with psychotic disorders may underlie this association, which is consistent with findings from other studies.[390–393] Diminished physiological capacity which characterizes functional impairment may directly impede the ability of those with psychotic disorders to engage in physical fitness and may lead to sedentary behaviour,[390,394,395] which is known to influence risk for various cardiometabolic chronic conditions.[103] Furthermore, there is already an excess of behavioural risk factors among chronic sufferers of psychotic disorders, such as poor nutritional habits and high rates of smoking,[11–13] which are associated with respiratory and other chronic diseases.[16–21] Finally, use of antipsychotic medications is also

associated with weight gain and other metabolic side effects which influence risk for various chronic conditions.[4–7] Thus, functional impairment, when combined with poor physical fitness, behavioural risk factors, and medication use may explain the observed association between impaired functioning and prevalence of multimorbidity among those with psychotic disorders in our study.

It is important to note that variation in the type and number of chronic conditions used to define multimorbidity will affect prevalence estimates. When the cut-off was increased to 3+ conditions in our sensitivity analysis, we found a lower prevalence of multimorbidity among those with psychotic disorders, which has been demonstrated in the broader literature where higher cut-offs result in lower prevalence estimates.[253] In contrast, inclusion of psychosis as a count towards multimorbidity resulted in over a three-fold greater prevalence of multimorbidity among this clinical population, as compared to those without psychotic disorders. Using this definition, we found that over 30% of those with psychosis met the definition for multimorbidity compared to 11.2% of the comparison group. Furthermore, nearly three-quarters of people with psychotic disorders in our study had at least one other chronic condition even prior to the onset of psychosis. When we consider the presence of this condition, in addition to the burden posed by psychosis, the public health cut-offs for multimorbidity are met. This finding also illustrates the phenomenon commonly seen in multimorbidity research – that inclusion of additional risk factors, symptoms, or conditions influences prevalence estimates.[253,396] Psychotic disorders are broadly grouped with other mental health conditions in definitions of multimorbidity used by the PHAC,[65,262] and psychosis does not factor into definitions suggested for use in primary care settings[250] and ICES data holdings,[260] which only consider mood and anxiety disorders. Use of these definitions that do not include psychotic disorders may therefore result in an underestimation of the true prevalence of multimorbidity.

Our study follows people with psychotic disorders treated by an early psychosis intervention program who have been followed immediately after the onset of symptoms for 10 years, which is novel for multimorbidity research conducted on this population[309]

and enabled us to see development of multiple chronic conditions early in the course of psychotic illness. However, future studies examining multimorbidity should use larger sample sizes with longer follow-up periods to ascertain the true burden of multiple chronic conditions among those with psychotic disorders, which our study may have been underpowered to detect. We found that those with psychotic disorders have chronic conditions even prior to the onset of the study, and future research with longer follow-up periods would enable us to gauge the development of chronic conditions over the trajectory of psychotic illness. Furthermore, our study linked data from an early psychosis intervention program to health administrative databases to examine multimorbidity among people with psychotic disorders. Participants in our study therefore had access to care for psychotic symptoms through the PEPP program and furthermore access to other forms of healthcare through OHIP, as we were able to track their health outcomes. However, people with psychotic disorders often lack consistent access to care both for psychotic illness as well as physical health needs.[397] There is therefore a need for broader population-based studies to examine the association between psychosis and multimorbidity and capture people with psychotic disorders who may not have consistent access to care in order for prevalence estimates of the burden of multimorbidity to be more reflective of this clinical population.

Researchers should also consider cross-validation of multiple data sources when assessing multimorbidity – such as chart reviews, administrative data, and patient self-reports – to obtain more accurate estimates.[350] Furthermore, they should also explore how variation in definitions influences prevalence estimates.[396] Finally, they should consider the association between severity of psychotic symptoms and prevalence of multimorbidity using better proxy measures, such as the number of psychotic symptoms,[389] or a direct measurement of psychosis severity using the Positive and Negative Syndrome Scale.[25]

4.5.1 Limitations

Our use of pre-existing health administrative data limits our analyses to the variables captured by this database. In particular, we do not have information on obesity or

hyperlipidemia,[350] which were identified for inclusion in operational definitions of multimorbidity by a recent scoping review.[250] We may also be missing information on key variables integral to our analysis, such as ethnicity[293,294] and duration of treatment with antipsychotic medications,[139,142] which may serve as confounders in the association between psychosis and multimorbidity. Additionally, lack of standardization in data collection procedures across health care providers or institutions may result in missing or inconsistent data. Furthermore, we lack information on the duration of untreated psychosis (DUP) for people with psychotic disorders in our study, which is known to affect prognosis of psychotic illness.[398] The association between DUP and chronic health conditions is unknown, but DUP may serve as a confounder in our study, for which we could not account.

The use of proxy measures for psychosis severity and impaired functioning may result in the presence of residual confounding in our study. The ODB includes low-income residents of Ontario, as well as those who receive social assistance through disability support programs, which may have resulted in misclassification. Furthermore, since we used dispensing dates of prescriptions issued under only the ODB program as a proxy to calculate the length of time on social assistance, our study may be subject to measurement error in underestimating the length of time on social assistance. Use of neighbourhood-level indicators of marginalization may also have resulted in misclassification, particularly as this was assigned at baseline, and this may have changed throughout the follow-up period. Social drift is often documented among people with serious mental illness due to deteriorations in functioning over the course of psychotic illness and consequent difficulties in securing gainful employment.[399] As such, marginalization of those with psychotic disorders is likely to increase over the follow-up period. Finally, given that our sample is limited to people with psychosis treated by an early psychosis intervention program, we cannot generalize our findings to people with psychotic disorders treated elsewhere in the mental health system.[369]

4.5.2 Conclusions

Our matched retrospective cohort study highlights that people with psychotic disorders treated by an early psychosis intervention program may have a 26% higher prevalence of multimorbidity over a 10-year follow-up period from first-episode psychosis, although our findings also include the possibility of a null effect. Future studies should use larger sample sizes with longer follow-up periods to better ascertain the development of chronic conditions over the lifespan of those with psychotic disorders, and the influence of behavioural, sociodemographic and clinical risk factors on the prevalence of multimorbidity. Clinicians who care for patients with psychosis should routinely assess for risk of chronic health conditions to better capture the extent of multimorbidity among this clinical population.

4.6 Declaration of Interests

Declaration of interest: none.

4.7 Role of the Funding Source

Role of the funding source: none.

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Chapter 5

5 Synthesis and Conclusion

The overall objective of this chapter is to synthesize and contextualize the findings presented in the two manuscripts in this thesis within the larger body of literature on multimorbidity among people with psychotic disorders. The research contributions and limitations of our analyses will be noted. Finally, this chapter will discuss the implications of our findings for policy makers and clinicians, and future directions for research in this area.

5.1 Summary of Studies

The principal aim of this thesis was to contribute to the growing body of literature on multimorbidity among people with schizophrenia and other psychotic disorders using two complementary but independent analyses. First, we synthesized the existing literature to quantify the prevalence and excess risk of multimorbidity among people with psychotic disorders, relative to those without psychotic disorders, using a systematic review and meta-analysis (Chapter 3). This review provided context for the subsequent assessment of the excess prevalence of multimorbidity experienced by people with psychotic disorders, compared to those without psychosis, using health administrative data in Ontario, Canada in a retrospective matched cohort study (Chapter 4).

Our systematic review and meta-analysis found that people with psychotic disorders had an increased risk of 2+ chronic conditions (RR=1.69, 95%CI=1.37,2.08), relative to those without psychosis. Furthermore, every study used different operational definitions of multimorbidity, with respect to both the number and types of included chronic conditions, which resulted in a wide range of prevalence estimates (16% to 91%). Included studies identified older age,[331,334,337] low SES,[328] and female sex[326,331–334,337] as risk factors for multimorbidity among people with psychotic disorders.

Our retrospective cohort study found that people who were treated for psychotic disorders at an early intervention program in London, Ontario have a greater prevalence of

multimorbidity (2+ chronic conditions) (PR=1.26, 95%CI=0.96,1.66) than controls matched on age, sex, and postal code, however the confidence interval includes the possibility of a null effect. We did not find that females with psychotic disorders had a greater prevalence of multimorbidity than males. However, we found that age was associated with multimorbidity among people with psychotic disorders, although our findings included the null value. Furthermore, among people with psychosis, living in areas with the highest levels of material deprivation was associated with multimorbidity (PR=3.09, 95%CI=1.21, 7.90). Most importantly, we found that the operational definition of multimorbidity had a profound impact on prevalence estimates. When we conducted an exploratory analysis which included mental illness as an omnibus condition and 'count' towards multiple chronic conditions, we found that people with psychotic disorders had a significantly greater prevalence of 2+ chronic conditions than those without psychotic disorders (PR=3.01, 95% CI=2.47, 3.67).

5.2 Research Contributions

This thesis fits in with the growing body of literature on the increased risk of many physical health conditions experienced by people with psychosis. To our knowledge, we conducted the first systematic review and meta-analysis quantifying the excess risk of multimorbidity among people with psychotic disorders relative to those without psychosis (Chapter 3). Furthermore, our retrospective cohort study using health administrative data to assess the prevalence of multimorbidity among people treated by an early psychosis intervention program is the first Canadian data on this topic (Chapter 4). Additionally, our study is novel among research which examines the association between psychosis and multimorbidity given that we follow people with psychotic disorders immediately after the onset of psychosis, and our follow-up period is 10 years.[309] We note limitations of our retrospective cohort study and additional considerations for interpretation in the following section.

5.3 Limitations

The primary limitation of our retrospective cohort study was the small sample size,[388] which may explain why our study did not find similar trends in the prevalence of multimorbidity among people with psychotic disorders as found in prior studies.[326,327,338] Furthermore, our use of health administrative data limited our definition of multimorbidity to conditions solely captured by this database. Several studies have found that the identification of people as having "multimorbidity" increases as the outcome definition expands, i.e. as the number of included co-morbidities in operational definitions increase.[256,257,400] In particular, we used a list of 17 chronic conditions for our operational definition of multimorbidity, which may not be an exhaustive list of all chronic conditions experienced by patients in our study. For instance, we do not have access to information on hyperlipidemia or obesity,[350] which are very common conditions as well as predictors of cardiometabolic chronic conditions,[8–10] and also serve as chronic conditions on their own that were identified for inclusion in operational definitions of multimorbidity by a recent scoping review[250] (see Table 2.1). Additionally, we could not control for behavioural risk factors such as smoking and poorer nutritional habits, which may have confounded our findings, since these are known to be associated with multimorbidity[19–21] and highly prevalent among people with psychotic disorders.[11,12,14,15] Finally, health care providers may not recognize chronic health conditions among those with serious mental illness, compared to those without mental health conditions,[401] which may have resulted in an underestimation of the excess prevalence of multimorbidity in our study.

5.4 Additional Considerations

There are additional considerations which may help to contextualize our findings within the larger body of literature. First, it must be noted that our analysis of the association between age and multimorbidity among people with psychotic disorders included the possibility of a null effect. In contrast, age is a well-replicated risk factor for multimorbidity in the broader literature both among the general population[290] and in studies examining people with psychotic disorders.[331,334,337] However, a recent study by

Filipcic and colleagues (2019) found that age was not significantly associated with the prevalence of multiple chronic physical conditions among people with psychotic disorders.[332] These findings may indicate that the patterns of risk for multiple chronic conditions are different for those with and without psychotic disorders. Alterations in immune system responses have been identified in people with schizophrenia who have several chronic physical conditions, such as diabetes mellitus and cancer.[402] It is therefore possible that those with schizophrenia already have a vulnerability to developing certain chronic conditions,[403] and that the risk of multimorbidity is heightened across all age groups for this clinical population.[332]

Second, we found that females with psychotic disorders did not have a higher prevalence of 2+ co-occurring chronic conditions than males (PR=1.01, 95%CI = 0.59, 1.73. This is in contrast with studies included in our systematic review, which have found a much greater prevalence of multimorbidity among females with psychosis compared to males.[326,332–334,337] General population studies have similarly identified that females have a higher prevalence of multimorbidity,[257,282,342,404] whereas more males than females are observed to have multimorbidity in studies which focus on primary care/ family practice settings.[386] Differential patterns of help-seeking behaviour may explain these findings, as females are more likely than males to visit health care providers for concerns about potential illness.[288] Furthermore, sex may also interact with age and practice setting, such that younger males and older females have higher prevalence of multimorbidity in the general population.[405,406] Given that our study focussed on younger people with psychotic disorders, we may have been unable to find an association between female sex and multimorbidity. The association between sex and multimorbidity is unclear among people with psychotic disorders, and needs to be further studied across both family practice and general population contexts.

5.5 Implications for Policy and Practice

Although psychosis is not present in widely-used definitions of multimorbidity, our study highlights that consideration of this chronic condition merits recognition. Furthermore, our study demonstrated that people with psychotic disorders have a higher prevalence of

multimorbidity as compared to people without psychotic disorders. These findings have important implications for health policy and clinical practice.

Our exploratory analysis, which considered people with psychotic disorders and other mental health conditions to already have one 'count' towards chronic conditions found that prevalence of 2+ chronic conditions was significantly higher among this population than same age, sex, and neighbourhood-matched controls. Although our analysis was exploratory in nature, it aligns with the definitions of multimorbidity set forth by PHAC; i.e., consideration of any mental health diagnosis as one chronic condition in multimorbidity counts.[65,262] By contrast, psychotic disorders were not identified for inclusion in operational definitions of multimorbidity by a recent scoping review,[250] nor considered in the ICES definition[260] (see Table 2.1).

Using the definitions suggested by the scoping review and ICES, policy makers require people with psychotic disorders to have 2+ chronic conditions in order to meet the cut-off for multimorbidity. This is problematic because it fails to capture younger populations with psychotic disorders in counts of multimorbidity who may have one other co-occurring chronic condition, and therefore do not meet the criteria. Furthermore, it underestimates the burden of multiple co-occurring chronic conditions experienced by this clinical population, and understates the impact of psychosis as a chronic condition which in itself has a prolonged course of illness[53–58] and multiple risk factors[33,62,63] and requires long-term ongoing management.[61] Inclusion of schizophrenia and psychotic disorders in definitions of multimorbidity is pivotal to capacity planning for health services and systems. People with multimorbidity are frequent service users[279,280,286] and incur greater costs of care than those with single chronic conditions.[302] Thus, including people with psychotic disorders in conventionally-used definitions of multimorbidity would better capture the extent of service use for their chronic health conditions,[2,306,307] and assist policy-makers in planning to meet the needs of patients.

Additionally, clinicians caring for people with schizophrenia and other psychotic disorders need to routinely probe for the risk of other chronic conditions to inform treatment planning. Concerns about *polypharmacy*, or the prescription of multiple

medications used to treat more than one chronic illness,[407] are often noted among providers who care for patients with multimorbidity.[408,409] This is of particular importance for those who care for people with psychotic disorders who also have other co-occurring chronic conditions, as SGAs may interact with other medications, including those used to treat cancer, HIV, and CVD.[410] Multimorbidity should therefore be documented in patients' health records so that providers are aware of other co-existing conditions and are better able to adjust treatment planning.[104]

5.6 Future Studies

Future research is needed to better assess the extent of multimorbidity among people with psychotic disorders. Integration of health administrative records with patient-level data, such as clinical charts and pharmacy records, would provide information on behavioural risk factors such as smoking and nutritional habits,[11,12,14,15,19–21] and duration of antipsychotic use.[139,142] These aforementioned factors may have confounded the association between psychosis and multimorbidity in our study, and require adjustment in statistical models in future studies. Furthermore, the use of multiple data sources, in particular the integration of population- and patient-level data, has been demonstrated to increase accuracy when assessing the prevalence of multimorbidity.[350] Future research should also consider inclusion of schizophrenia in operational definitions of multimorbidity.

Moreover, longer term studies with larger sample sizes are needed to better estimate excess prevalence and risk of multimorbidity among this clinical population, as well as understand factors associated with occurrence of multiple co-occurring chronic health conditions. Studies with larger sample sizes and longer follow-up periods would enable us to better see trajectories of illness onset over the lifespan. It would be useful for treatment and capacity planning to assess whether there is a critical timeframe after onset of psychotic symptoms during which people with psychotic disorders develop other chronic health conditions.

5.7 Conclusions

The primary objective of this thesis was to explore the association between psychotic disorders and multimorbidity using two independent studies. Our systematic review and meta-analysis found that people with psychosis had a 69% excess risk of multiple co-occurring chronic conditions compared to those without psychotic disorders. Our retrospective cohort study found that those treated for psychotic disorders at an early intervention program in London, Ontario experienced a higher prevalence of multimorbidity than controls matched for age, sex, and postal code; however, our findings included the possibility of a null effect. Our subsequent analysis which included psychotic disorders in multimorbidity counts did find a statistically significant greater relative prevalence of multiple co-occurring chronic conditions among this clinical population. Although our main analysis did not find a statistically significant association between psychotic disorders and multimorbidity, our thesis overall echoes the findings of several studies which have evaluated multimorbidity, and reinforces the idea that multimorbidity frameworks greatly impact prevalence estimates. The findings from this thesis serve to highlight the consideration of psychotic disorders as a chronic condition in all definitions of multimorbidity, which has important implications for patients, clinicians and health systems.

Chapter 6

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Appendices

Appendix 3A: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	31
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	31
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	32-33
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	33
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	34
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	34
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	34
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Appendix 3B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	34-35
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	35
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	35
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	35
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	35-36
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	35-36

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	35
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	36
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	36, Fig 3.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	36-37, Table 3.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Appendix 3C
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	36-41, Supplementary Appendices 3D-3F, Table 3.2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	44, Fig 3.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Fig 3.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	44, Supplementary Appendices 3G-3K
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	46-48
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	48-49
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	49
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	49-50

Appendix 3B: Search Strategy

Concept	MEDLINE	EMBASE	PsycINFO	Keywords
Psychosis	1.(Psychosis OR psychotic OR psychotic disorder* OR schizophreni* OR sever* mental ill* OR sever* mental disorder*).ti,ab	1. (Psychosis OR psychotic OR psychotic disorder* OR schizophreni* OR sever* mental ill* OR sever* mental disorder*).ti,ab	1. ti,ab(Psychosis OR psychotic OR psychotic disorder* OR schizophreni* OR sever* mental ill* OR sever* mental disorder*)	1. exp schizophrenia/ or schizophreni*.ti,ab. 2. exp psychosis/ or disorders with psychotic features.ti,ab. 3. Affective Disorders, Psychotic.mp. or affective psychosis.ti,ab. 4. acute psychosis/ or schizoaffective psychosis/ or manic psychosis.ti,ab. 5. psychotic disorder.ti,ab. 6. mental disease/ or sever* mental ill*.ti,ab. 7. (sever* mental disorder* or Mental Disorders).ti,ab. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7
Comorbidity	2. (Comorbidity OR associated condition* OR associated diagnos* OR associated disease* OR associated health problem* OR associated illness* OR associated morbidit* OR associated patholog* OR coexisting condition* OR co-existing condition* OR coexisting diagnos* OR co?existing diagnos* OR coexisting disease* OR co-existing disease* OR coexisting health problem* OR co-existing health problem* OR coexisting illness* OR co-existing illness* OR coexisting pathology* OR co-existing pathology* OR comorbid condition* OR co-morbid condition* OR comorbid diagnos* OR co-morbid diagnos* OR comorbid disease* OR co-morbid disease* OR comorbid health problem* OR co-morbid health problem* OR comorbid illness* OR co-morbid illness* OR comorbid patholog* OR co-morbid patholog* OR concurrent condition* OR concurrent diagnos* OR concurrent disease* OR concurrent health problem* OR concurrent illness* OR concurrent patholog* OR cooccurring condition* OR co-occurring condition* OR cooccurring diagnos* OR co-occurring diagnos* OR cooccurring disease* OR co-occurring disease* OR cooccurring health problem* OR co-occurring health problem* OR cooccurring illness* OR co-occurring illness* OR cooccurring patholog* OR co-occuring patholog* OR comorbidities OR co-morbidity OR co-morbidities OR chronic illness* OR chronic disease*).ti,ab	2. (Comorbidity OR comorbidities OR co-morbidity OR co-morbidities OR associated condition* OR associated diagnos* OR associated disease* OR associated health problem* OR associated illness* OR associated morbidity OR associated morbidities OR associated pathology OR associated pathologies OR comorbid condition* OR co-morbid condition* OR comorbid diagnos* OR co-morbid diagnos* OR comorbid disease* OR co-morbid disease* OR comorbid health problem* OR co-morbid health problem* OR comorbid illness* OR co-morbid illness* OR comorbid patholog* OR co-morbid patholog* OR coexisting condition* OR co-existing condition OR coexisting diagnos* OR co-existing diagnos* OR coexisting disease* OR co-existing disease* OR coexisting health problem* OR co-existing health problem* OR coexisting illness* OR co-existing illness* OR coexisting patholog* OR co-existing patholog* OR concurrent condition OR concurrent conditions OR concurrent diagnos* OR concurrent disease* OR concurrent health problem* OR concurrent illness* OR concurrent morbid* OR concurrent patholog* OR cooccurring condition* OR cooccurring disease* OR cooccurring diagnos* OR co-occurring diagnos* OR cooccurring disease* OR co-occurring disease* OR cooccurring health problem* OR co-occurring health problem* OR cooccurring illness* OR co-occurring illness* OR cooccurring morbid* OR co-occurring morbid* OR cooccurring patholog* OR co-occurring pathology*).ti,ab	2. ti,ab(Comorbidity OR Comorbid disorders OR medical comorbidity)	9. comorbidit*.kw. 10. co?existing diagnos*.ti,ab. 11. comorbid condition*.ti. 12. co-morbid condition*.ti. 13. comorbid illness*.ti. 14. co-morbid illness*.ti. 15. concurrent condition*.ti,ab. 16. concurrent diagnos*.ti,ab. 17. concurrent disease*.ti,ab. 18. concurrent health problem*.ti,ab. 19. concurrent illness*.ti,ab. 20. cooccurring condition*.ti,ab. 21. co-occurring condition*.ti,ab. 22. co-occurring diagnos*.ti,ab. 23. cooccurring disease*.ti,ab. 24. co-occurring disease*.ti,ab. 25. cooccurring illness*.ti,ab. 26. co-occurring illness*.ti,ab. 27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
Multimorbidity	3. (Multimorbidit* OR multiple chronic condition* OR Multiple condition* OR multiple diagnos* OR multiple disease* OR multiple health problem* OR multiple illness* OR multiple patholog* OR multidisease* OR multi-disease* OR multi-morbidit* OR multiple chronic condition* OR multipatholog* OR multi-patholog* OR pluripatholog* OR polypatholog* OR poly-patholog*).ti,ab	3. (Multiple chronic condition OR multiple chronic conditions OR multimorbidity OR multiple chronic disease OR multiple chronic diseases OR Multiple chronic disorders OR multiple chronic illnesses OR multiple chronic health conditions OR multiple condition OR multiple conditions OR multiple diagnosis OR multiple diagnoses OR multiple disease OR multiple diseases OR multiple health problem* OR multiple illness* OR multiple morbid* OR multiple pathology OR multiple pathologies OR multidisease OR multi disease OR multi diseases OR multimorbidity OR multimorbidities OR multi morbidity OR multi morbidities OR multipathology OR multipathologies OR multi pathology OR multi pathologies OR pluripathology or pluripathologies OR polypathology OR polypathologies OR poly pathology or polypathologies).ti,ab	3. ti,ab(Multiple health conditions OR Multiple morbid conditions)	28. multimorbidity/ or multimorbidit*.ti,ab. 29. multiple chronic condition*.ti,ab. 30. multiple condition*.ti,ab. 31. multiple diagnos*.ti,ab. 32. multiple disease*.ti,ab. 33. multiple illness*.ti,ab. 34. multi-morbidit*.ti,ab. 35. multiple chronic condition*.ti,ab. 36. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
Linking Concepts	4. 1 AND 2 5. 1 AND 3 6. 4 OR 5	4. 1 AND 2 5. 1 AND 3 6. 4 OR 5	4. 1 AND 2 5. 1 AND 3 6. 4 OR 5	37. 8 and 27 38. 8 and 36 39. 37 or 38
Limits	7. limit 6 to (human and english and yr="1990 -Current")	7. limit 6 to (human and english and yr="1990 -Current")	7. limit 6 to (human and english and yr="1990 -Current")	40. limit 39 to (human and english and yr="1990 -Current")

Appendix 3C: Risk of bias assessment for individual studies (*n*=14)

Domain	Quality criteria	Assessment of included studies													
		Bhalla et al., 2018	Bouza et al., 2010	Carney et al., 2006	Correll et al., 2017	Domino et al., 2014	Filipcic et al., 2019	Gabilondo et al., 2017	Islam et al., 2017	Jahrami et al., 2017	Kugathasan et al., 2019	Nishanth et al., 2017	Smith et al., 2013	Stubbs et al., 2016	Woodhead et al., 2014
1. Is the source population representative of the general population?	Population-based roster (+) Community-based study (*) Hospital-based patient records or undefined source population (-) No description (-)	*	+	*	+	+	*	+	+	-	+	-	*	+	*
2. Was selection of exposed (people with psychosis) and non-exposed (people without psychosis) cohorts drawn from the same population?	Same roster (+) Similar roster (*) Different points of care for exposed and unexposed populations (-) No description (-)	NA	NA	+	NA	NA	*	+	+	*	+	NA	+	+	+
3. Can we be confident in the assessment of exposure (psychosis)?	Secure record or repeated ascertainment (+) Single interview or retrospective recall (*) Uncertain (-) No description (-)	+	+	+	+	+	+	+	*	+	+	+	+	*	+
4. Can we be confident in the assessment of the outcome (multimorbidity)?	Independent blind assessment or validated instrument (+) Instrument with limited validity assessment or self-report (*) Clinical interview or chart diagnoses or unvalidated instruments (-) No description (-)	+	+	+	+	+	*	+	*	-	+	+	+	*	+
5. Did the design or analysis account for important confounding factors?	Participant interview or survey, or reproducible chart review or accurate database (+) Chart review without reproducibility or database with uncertain accuracies (*) Database with no available information on accuracy of confounding factors (-) No description (-)	NA	*	+	+	+	+	*	*	*	*	*	*	*	*
6. Can we be confident in the assessment of the confounding factors?	Matching or adjustment for sociodemographic and clinical factors (+) Matching or adjustment for age, sex, and other sociodemographic factors (*) Matching or adjustment for age and sex (-) No description (-)	NA	+	+	+	+	*	+	*	+	+	*	+	+	+
7. Is there little missing data?	High responses and little missing data (+) Moderate responses and some missing data (*) Low responses and substantial missing data (-) No description (-)	+	+	+	+	+	NA	+	+	NA	+	NA	+	+	+

Legend:
+ criteria satisfied
* criteria partially met
- criteria not met
NA criteria not applicable to study design

Appendix 3D: Conditions included in multimorbidity definitions (*n*=14)

Study	Number of included conditions	Types of included conditions
Bhalla et al., 2018	40	Psychiatric; Substance Abuse; Medical disorders: hypertension, diabetes mellitus, chronic obstructive airway disease, miscellaneous
Bouza et al., 2010	12 (clusters)	Infectious Diseases; Neoplasms; Endocrine Diseases; Hematological Diseases; Neurological Diseases; Diseases of the Circulatory System; Respiratory Diseases; Diseases of the Digestive System; Diseases of the genitourinary tract; Complications of pregnancy, childbirth and the puerperium; Diseases of the musculoskeletal system and connective tissue; Injury and Poisoning
Carney et al., 2006*	46	Cardiovascular; Neurological; Pulmonary; Endocrine; Renal; Gastrointestinal; Viral/infectious; Hematology/oncology; Musculoskeletal; Other - accidents and injuries; Genital; Inflammatory disease of ovary; Drug abuse/dependence; Other – miscellaneous
Correll et al., 2017*	6	Cerebrovascular disease; Coronary or ischemic heart disease; Diabetes mellitus; Hyperglycemia; Hyperlipidemia; Hypertension
Domino et al., 2014	6	Asthma; COPD; Diabetes; Hypertension; Hyperlipidemia; Seizure disorder
Filipcic et al., 2019	15	Asthma (including allergic asthma); Chronic bronchitis, COPD and emphysema; Myocardial infarction or chronic consequences of MI; Coronary heart disease or angina pectoris; Hypertension; Cerebrovascular insult (cerebral haemorrhage, cerebral thrombosis) or chronic consequences of stroke; Arthrosis (excluding arthritis); Low back disorder or other chronic back defects; Neck disorder or other chronic neck defects; Diabetes mellitus; Allergy (rhinitis, hay fever, eye inflammation, dermatitis, food allergy or other allergy/ asthma allergy excluded); Liver cirrhosis; Urinary incontinence; Kidney disease; Obesity
Gabilondo et al., 2017	47	*Clusters:* Neurological; Cardiovascular 1 - Hypertension, diabetes, ischemic heart disease, chronic kidney disease; Cardiovascular 2 – cardiovascular disease, atrial fibrillation, heart failure; Chronic liver disease or pancreatic disease, viral hepatitis; Dementia, COPD, low back pain, cancer, asthma, osteoporosis, peripheral neuropathy; Miscellaneous: bone disorders or chromosomal abnormalities or glaucoma or gout
Islam et al., 2017*	121	*Clusters:* Mental and behavioural disorders; Diseases of the circulatory system; Endocrine, nutritional and metabolic diseases; Diseases of the respiratory system; Neoplasms; Diseases of the musculoskeletal system and connective tissue; Diseases of the digestive system; Pregnancy, childbirth and the puerperium; Diseases of the genitourinary system; Certain infectious and parasitic diseases; Diseases of the skin and subcutaneous tissue; Diseases of the eye and adnexa; Diseases of the ear and mastoid process; Diseases of the nervous system (+ due to injury); Diseases of blood & blood-forming organs and certain disorders involving the immune mechanism; Congenital malformations, deformations and chromosomal abnormalities
Jahrami et al., 2017	4	Diabetes Type 2; Hypertension; Cardiovascular disease; Musculoskeletal disorders
Kugathasan et al., 2019	10 (clusters)	Infection; Cancer; Endocrine; Neurologic; Cardiovascular; Respiratory; Digestive; Skin; Musculoskeletal; Urogenital
Nishanth et al., 2017	Not Described	Not described
Smith et al., 2013	32	Cardiovascular diseases; COPD; Cancer; Neurological; Gastrointestinal issues; Diabetes; Hypertension; Miscellaneous
Stubbs et al., 2016	9	Arthritis; Asthma; Diabetes mellitus; Angina pectoris; Chronic back pain; Tuberculosis; Visual impairment; Hearing problems; Edentulism
Woodhead et al., 2014*	12	Hypertension; Epilepsy; Diabetes mellitus; Coronary heart disease; Chronic kidney disease; COPD; Cancer (non specified); Atrial fibrillation; Heart failure; Stroke; Hypothyroidism; Asthma

Abbreviations:
COPD = chronic obstructive pulmonary disease; MI = myocardial infarction

Appendix 3E: Risk of specific chronic conditions among people with psychosis in included studies (*n*=14)

Study	Diseases of the Cardiovascular and/or Circulatory Systems	Diabetes Mellitus	Respiratory Diseases	Substance Abuse and Addiction Disorders	Endocrine Diseases	Chronic Pain or Arthritis	Obesity	Infectious Diseases	Neuropsychiatric Diseases	Digestive Diseases
Bhalla et al., 2018	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Bouza et al., 2010	↑	↑	↑	↑	☒	☒	☒	☒	☒	↑
Carney et al., 2006	☒	↑	↑	↑	↑	☒	☒	↑	☒	☒
Correll et al., 2017	↑	↑	☒	☒	☒	☒	☒	☒	☒	☒
Domino et al., 2014	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Filipcic et al., 2019	↑	☒	☒	☒	☒	↑	↑	☒	☒	☒
Gabilondo et al., 2017	↓	↑	☒	☒	☒	☒	☒	↑	↑	☒
Islam et al., 2017	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Jahrami et al., 2017	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Kugathasan et al., 2019	↑	☒	↑	☒	☒	☒	☒	☒	☒	↑
Nishanth et al., 2017	↑	↑	☒	☒	☒	☒	☒	☒	☒	☒
Smith et al., 2013	↓	☒	☒	☒	☒	☒	☒	↑	↑	↑
Stubbs et al., 2016	↑	↑	☒	☒	☒	↑	☒	☒	☒	☒
Woodhead et al., 2014	↑	↑	☒	☒	☒	☒	☒	☒	☒	☒

Legend:

↓ Decreased prevalence, incidence or odds among persons with psychosis relative to those without psychosis

↑ Increased prevalence, incidence or odds among persons with psychosis relative to those without psychosis

☒ Study did not examine prevalence, incidence or odds of specific condition experienced by persons with psychosis

Appendix 3F: Detailed summary of findings from included studies on factors associated with multimorbidity among people with psychosis (*n*=14)

Study	Summary of Findings
Bhalla et al., 2018	Veterans with multimorbidity had a substantial increase in all examined risk factors (low SES, homelessness, BMI >30)
Bouza et al., 2010[1]	Age >53 years was significantly related to in-hospital mortality among cases with multimorbidity
Carney et al., 2006	Persons with schizophrenia were only slightly more likely to live in urban settings than controls; Cases had significantly more months of follow-up and healthcare visits than controls
Correll et al., 2017[1]	Inverse association between cardiometabolic comorbidity burden and length of stay for patients; Patients with schizophrenia had twice the rate of mortality due to cardiometabolic multimorbidities as compared to patients with bipolar disorder
Domino et al., 2014[2]	Positive association between adherence to antipsychotic medications and number of medical conditions
Filipcic et al., 2019	Age was not significantly associated with multimorbidity among cases; Female cases had a higher prevalence of multimorbidity than males; Interaction between age and sex – female cases under 35 years of age had a higher prevalence of multimorbidity than same-aged controls
Gabilondo et al., 2017	Female cases had a higher prevalence of multimorbidity than males
Islam et al., 2017	Sex (females > males) and age (older adults > 40 years) were significantly associated with multimorbidity independently, but interaction was not significant
Jahrami et al., 2017[3]	Cases with multimorbidity had excessive dietary intake, decreased physical activity and higher prevalence of smoking and alcohol intake, as compared to controls
Kugathasan et al., 2019[1]	Patients with schizophrenia had an increased mortality rate compared to controls, independent of the number of somatic diseases; Cases had more than double hazard rate for all individual disease categories
Nishanth et al., 2017	Cases with multimorbidity were older, married, and female, and had longer duration of illness and longer duration of treatment
Smith et al., 2013	Higher proportions of female cases had multimorbidity (2+ and 3+ conditions) as compared to male cases
Stubbs et al., 2016	Multimorbidity present across all age groups; Highest odds of multimorbidity in younger age groups (those aged 18-44 years) for those with psychosis
Woodhead et al., 2014[3]	Smoking and high BMI accounted for excess physical morbidity among cases

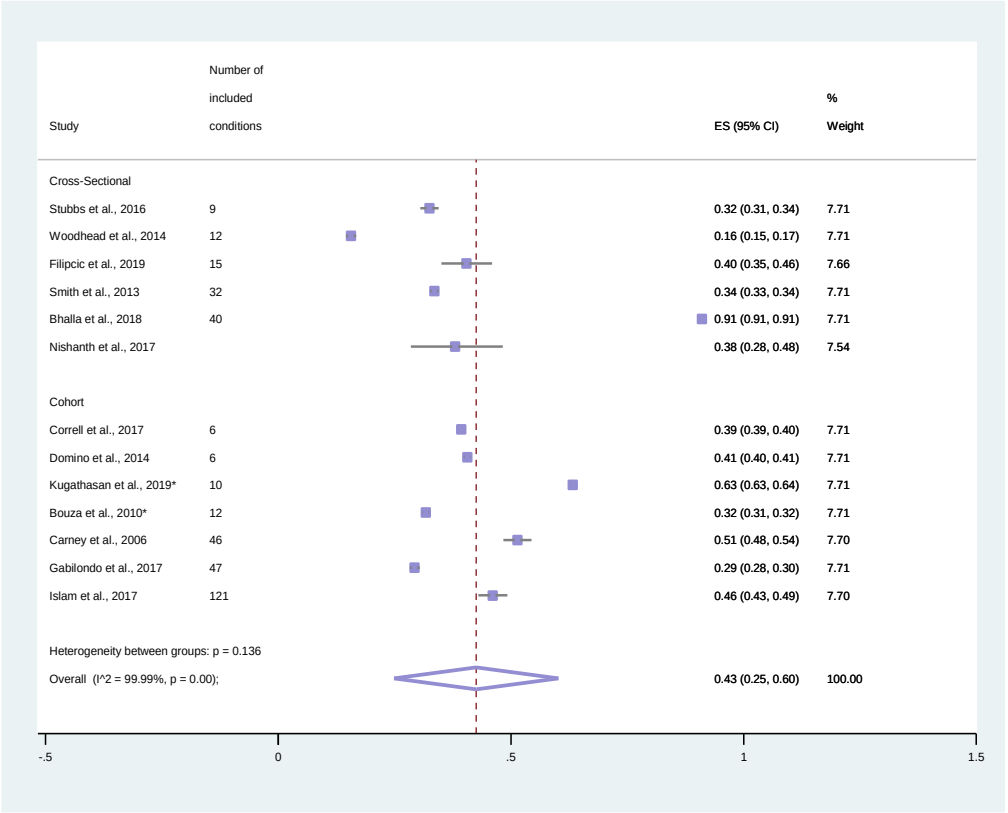
Notes:

[1]Studied factors related to mortality among patients with schizophrenia due to 2+/3+ physical health conditions

[2]Studied quality care metrics among patients with schizophrenia with co-occurring 2+/3+ physical health conditions

[3]Smoking and alcohol use studied as a risk factor for multimorbidity, not included in counts of chronic conditions

Appendix 3G: Prevalence of multimorbidity (2+ conditions) among people with psychosis (*n*=13)



Notes:

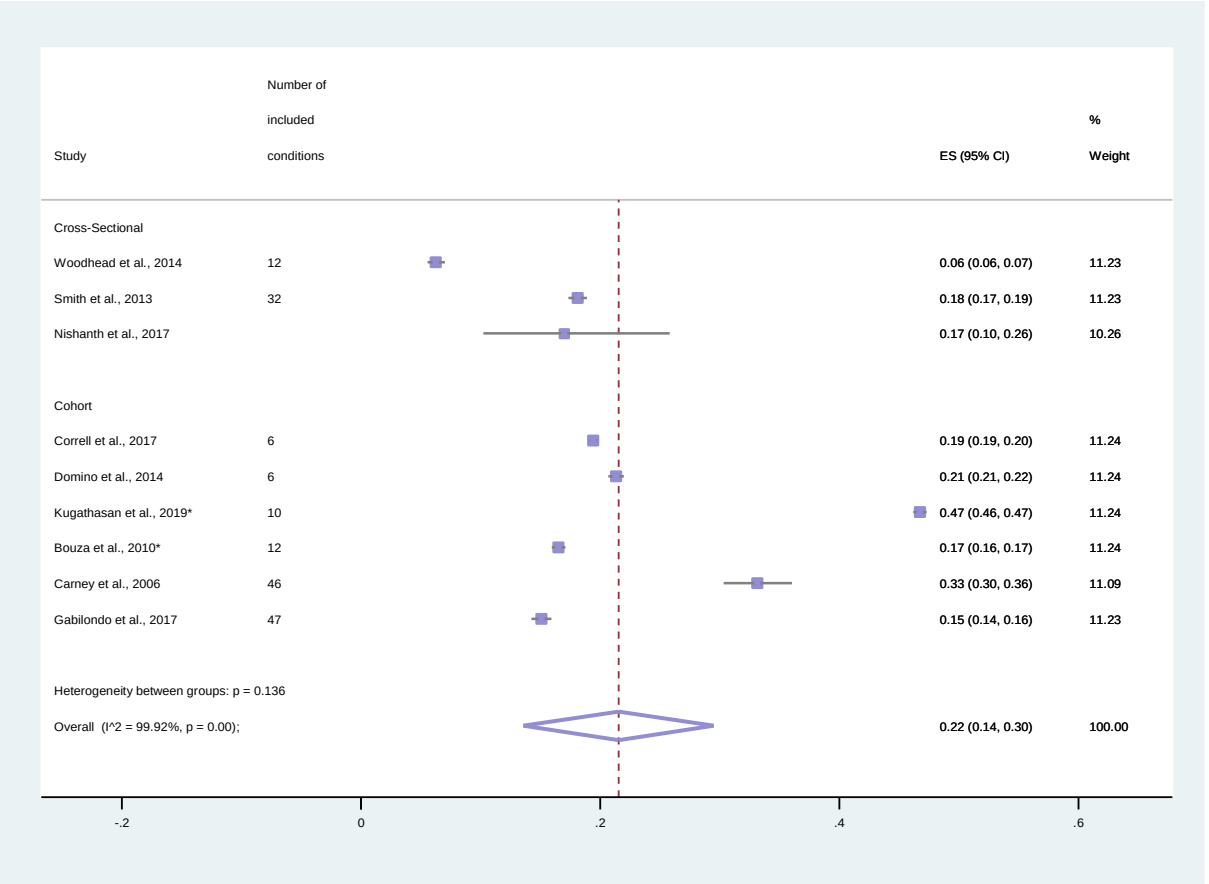
*Studies which examined clusters of conditions

Nishanth et al. (2017) did not describe included conditions in the definition of multimorbidity

Abbreviations:

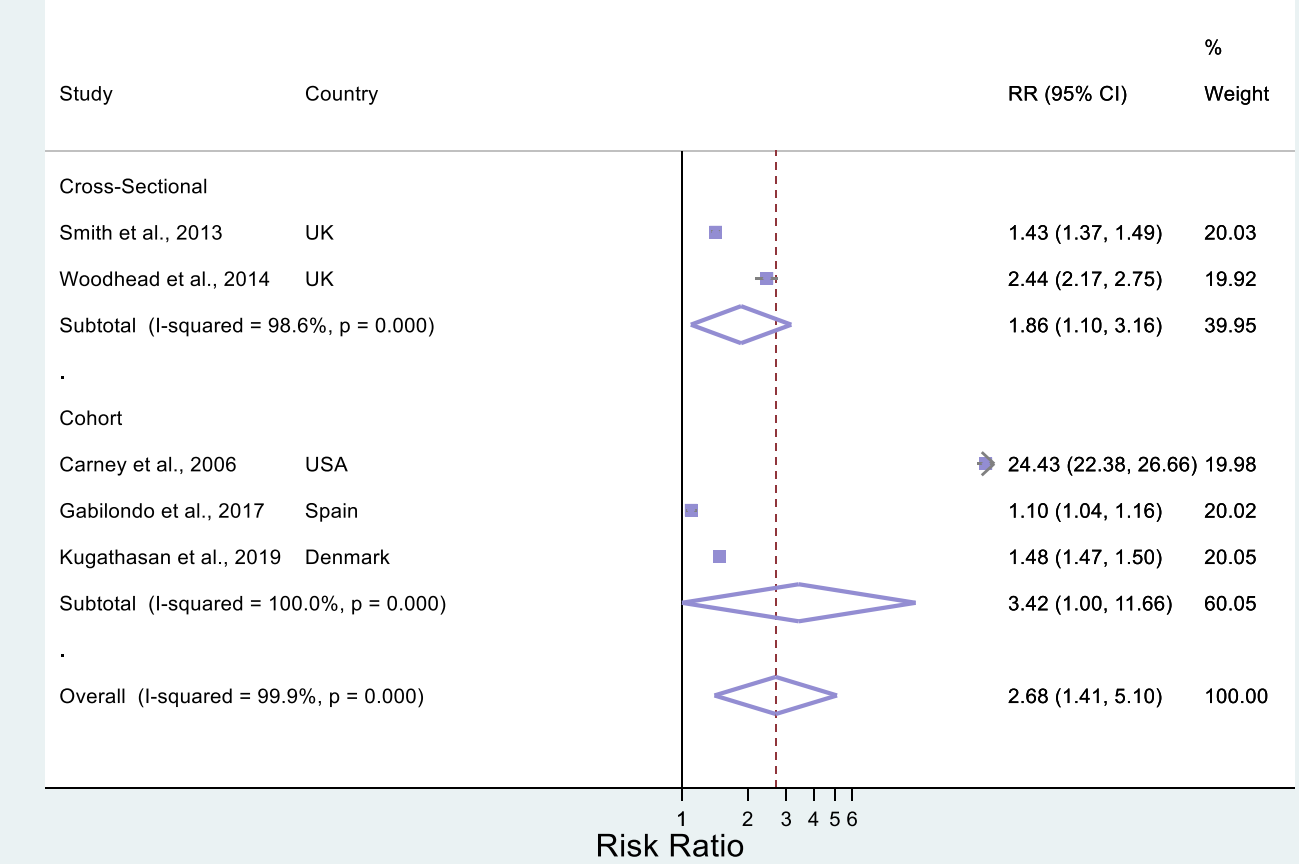
CI = confidence interval; ES = effect size

Appendix 3H: Prevalence of multimorbidity (3+ conditions) among people with psychosis (*n*=9)



Notes:
*Studies which examined clusters of conditions
Nishanth et al. (2017) did not describe included conditions in the definition of multimorbidity
Abbreviations:
CI = confidence interval; ES = effect size

Appendix 3I: Sensitivity analysis: Risk of multimorbidity (3+ conditions) for people with psychosis compared to people who do not have psychotic disorders (*n*=5)



Abbreviations:
CI = confidence interval; RR = risk ratio

Appendix 3J: Sensitivity analyses for risk of bias assessment

Risk of multimorbidity (2+ conditions) for people with psychosis compared to those who do not have psychotic disorders

Domain	Cross-sectional Studies				Cohort Studies				Pooled Estimate			
	Number of Studies	Sample Size	RR (95%CI)	I^{2*}	Number of Studies	Sample Size	RR (95%CI)	I^2	Number of Studies	Sample Size	RR (95%CI)	I^2
Representativeness of source population	1	181,653	3.02 (2.84,3.21)	N/A	3	7,689,817	1.24 (1.11,1.40)	96.7%	4	7,871,470	1.54 (1.16,2.03)	99.5%
Selection of exposed and non-exposed cohorts	3	1,914,644	2.18 (1.33,3.59)	99.6%	4	8,338,110	1.60 (1.14,2.24)	99.7%	7	10,252,754	1.83 (1.46,2.28)	99.7%
Assessment of exposure	3	1,734,157	1.48 (0.99,2.23)	99.0%	3	8,336,520	1.85 (1.25,2.76)	99.8%	6	10,070,677	1.66 (1.35,2.05)	99.6%
Assessment of outcome	2	1,732,991	1.86 (1.14,3.03)	99.4%	3	8,336,520	1.85 (1.25,2.76)	99.8%	5	10,069,511	1.85 (1.48,2.32)	99.7%
Accounting for confounding factors	1	1,166	0.93 (0.80,1.08)	N/A	1	648,293	3.53 (3.33,3.74)	N/A	2	649,459	1.81 (0.49,6.71)	99.6%
Assessment for confounding factors	3	1,914,644	2.18 (1.33,3.59)	99.6%	3	8,336,520	1.85 (1.25,2.76)	99.8%	6	10,251,164	2.01 (1.58,2.55)	99.7%
Missing Data	4	1,915,810	1.77 (1.15,2.74)	99.5%	4	8,338,110	1.60 (1.14,2.24)	99.7%	8	10,253,920	1.69 (1.37,2.08)	99.6%

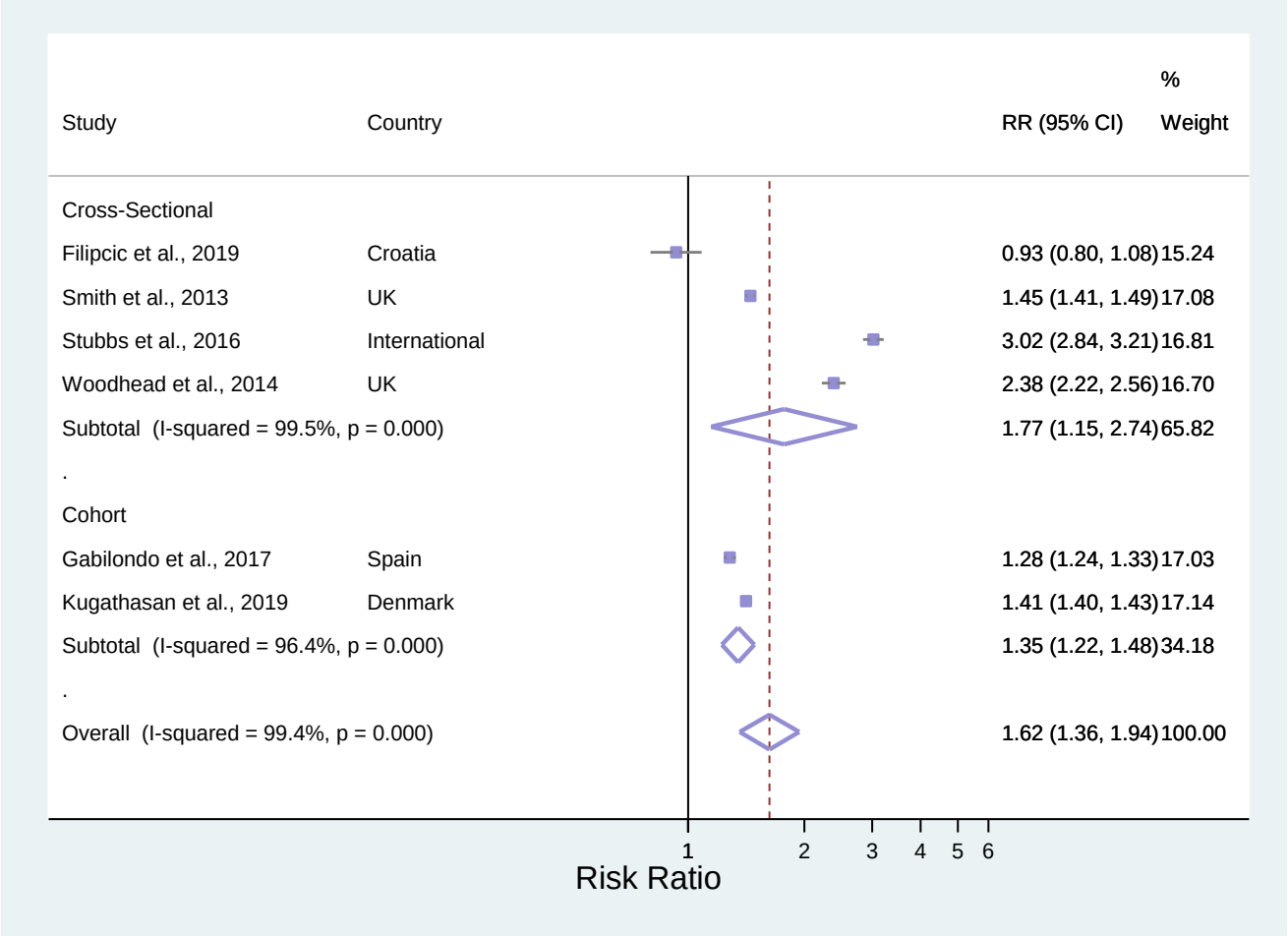
Notes:

*I^2 (heterogeneity) values are not applicable for sub-group analyses with only one study

Abbreviations:

CI = confidence interval; RR = risk ratio

Appendix 3K: Exploratory analysis: Risk of physical health multimorbidity (2+ conditions) for people with psychosis compared to people who do not have psychotic disorders (*n*=6)



Abbreviations:
CI = confidence interval; RR = risk ratio

Appendix 4L: The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data

	Item No.	STROBE items	Location in manuscript where items are reported *(page numbers)*	RECORD items	Location in manuscript where items are reported *(page numbers)*
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	a. 51 b. 51	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.	51
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	52-53		
Objectives	3	State specific objectives, including any prespecified hypotheses	53-54		
Methods					
Study Design	4	Present key elements of study design early in the paper	54-56		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	55-56		
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	55-56	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.	Supplementary Appendix 4M, 55-56
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	56-58	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.	Supplementary Appendix 4M
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	56-58		
Bias	9	Describe any efforts to address potential sources of bias	59		

Study size	10	Explain how the study size was arrived at	59		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	56-60		
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	59-60		
Data access and cleaning methods		..	54. 59	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.	54. 59
Linkage		..	54-55	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.	54-55
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	60	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.	60
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)	Table 4.1, 62		
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	62-63		
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	Tables 4.2 and 4.3, 62-63		

		(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	66		
Discussion					
Key results	18	Summarise key results with reference to study objectives	66-69		
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	70-71	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.	70-71
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	70-71		
Generalisability	21	Discuss the generalisability (external validity) of the study results	70-71		
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	71		
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.	N/A

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Appendix 4M: Chronic conditions included in definition of multimorbidity

Conditions in Multimorbidity Definition	Variables in administrative data holdings	Database[260]	Diagnosis of condition		Lookback Window	Source
Arthritis[1]	**Rheumatoid arthritis**	ORAD2016 database[3]	≥1 Hospitalization with RA diagnosis code (ICD-9 or ICD-10), or ≥3 OHIP visits with RA diagnosis code within 2 years with ≥1 of the claims made by musculoskeletal specialist **Only patients over the age of 15 included*		**DAD:** 28 years; **OHIP:** 24 years, 9 months *5-year washout/lookback for incidence*	CIHI-DAD, OHIP, RPDB
	Osteoarthritis	Algorithm	Diagnosis of OA based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		10 years	CIHI-DAD, OHIP, RPDB
Asthma	**Asthma**	ASTHMA2016 database[3]	≥1 Hospitalization or ≥2 OHIP visits within 2 years		**DAD:** 25 years; **OHIP:** 24 years, 9 months; **SDS:** 25 years *5-year washout/lookback for incidence*	CIHI-DAD, OHIP, CIHI-SDS, RPDB
Cancer	**Cancer**	OCR database	1 acute care diagnosis present on admission in the look-back window, or 2 OHIP visit diagnoses within two years, with the first of the two visit dates defined as the diagnosis date, in the look-back window		5 years	CIHI-DAD, OHIP, RPDB
Congestive heart failure	**Congestive heart failure**	CHF2016 database[3]	≥1 Hospitalization or ≥1 OHIP/ED visit, followed by ≥1 Hospitalization/ ED/ OHIP visit within 1 year **Only patients over the age of 40 included*		**DAD:** 28 years; **OHIP:** 25 years; **SDS:** 25 years; **OMHRS:** 11 years *3-year washout/lookback for incidence*	CIHI-DAD, OHIP, NACRS, OMHRS, RPDB
COPD (including bronchitis)	**COPD (including bronchitis)**	COPD2016 database[3]	≥1 Hospitalization or ≥1 OHIP visit within 2 years **Only patients over the age of 35 included*		**DAD:** 25 years; **OHIP:** 24 years, 9 months; **SDS:** 25 years *5-year washout/lookback for incidence*	CIHI-DAD, OHIP, CIHI-SDS, RPDB
Cardiovascular disease	**Cardiovascular disease**	Algorithm	Flag if diagnosis of any of these conditions:		5 years	CIHI-DAD, OHIP, RPDB
			Coronary Artery Disease (including MI and angina)	1 acute care diagnosis present on admission or 2 OHIP visit diagnoses within 2 years, with the first of the two visit dates defined as the diagnosis date		
			Peripheral vascular disease	1 acute care diagnosis present on admission in the lookback window (5 years), or 2 OHIP visit diagnoses within 2 years, with the first of the two visit dates defined as the diagnosis date in the look-back window (5 years)		
			Arrhythmia	1 acute care diagnosis present on admission in the lookback window (5 years), or 2 OHIP visit diagnoses within 2 years, with the first of the two visit dates defined as the diagnosis date in the look-back window (5 years)		
Dementia	**Dementia**	DEMENTIA2016 database	≥1 Hospitalization, or ≥1 ODB claim for cholinesterase inhibitors, or ≥3 OHIP visits at least 30 days apart within 2 years **Only patients over the age of 40 included*		10 years	CIHI-DAD, OHIP, ODB, RPDB
Diabetes	**Diabetes**	ODD2016 database[3]	≥2 OHIP diagnosis 250 within 2 years, or ≥1 Hospitalization within 2 years, or ≥1 OHIP fee code (Q040/K020/K030) within 2 years **Patients over 19 years of age*		**DAD:** 28 years; **OHIP:** 24 years, 9 months; **SDS:** 25 years *3-year washout/lookback for incidence*	CIHI-DAD, OHIP CIHI-SDS, NACRS, RPDB
HIV	**HIV**	HIV2016 database[3]	≥3 OHIP visits within 3 years **Only patients over the age of 18 included*		**DAD:** 25 years; **OHIP:** 24 years *2-year washout/lookback for incidence*	OHIP, RPDB
Hypertension	**Hypertension**	HYPER2016 database[3]	≥1 Hospitalization or ≥2 OHIP visits within 2 years, or 1 OHIP visit followed by Hospitalization/ OHIP visit within 2 years, or Hospitalization (<1991) followed by 1 Hospitalization (>1991) **Only patients over the age of 20 included*		**DAD:** 28 years; **OHIP:** 24 years, 9 months; **SDS:** 25 years *3-year washout/lookback for incidence*	CIHI-DAD, OHIP, RPDB
Inflammatory Bowel Disease	**Inflammatory Bowel Disease**	OCCC2016 database[3]	2 Years of OHIP eligibility and ≥5 Hospitalization/ OHIP visits within 4 years, or ≥3 Hospitalization/ ED/ OHIP visits within 4 years with no 2-year OHIP eligibility **Patients between 18 and 64 years of age*		8 years	CIHI-DAD, OHIP, NACRS, ODB, RPDB
Chronic kidney disease	**Chronic kidney disease**	Algorithm	Diagnosis of CKD based on one of the ICD-9 or ICD-10 codes in DAD or two in OHIP within a 2-year period		10 years	CIHI-DAD, OHIP, RPDB
Chronic liver disease	**Chronic liver disease**	Algorithm	Diagnosis of CLD based on 1 hospitalization or 2 OHIP visit diagnoses or fee codes within 2 years		10 years	CIHI-DAD, OHIP, RPDB
Mood or Anxiety Disorder[2]	**Anxiety**	Algorithm	Diagnosis of anxiety based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		5 years	CIHI-DAD, OHIP, OMHRS, RPDB
	Mood disorder	Algorithm	Diagnosis of MD based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		5 years	CIHI-DAD, OHIP, OMHRS, RPDB
Osteoporosis	**Osteoporosis**	Algorithm	Diagnosis of osteoporosis based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		10 years	CIHI-DAD, OHIP, RPDB
Stroke/ transient ischemic attack	**Stroke/ transient ischemic attack**	Algorithm	Diagnosis of stroke based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		10 years	CIHI-DAD, OHIP, RPDB
Urinary incontinence	**Urinary incontinence**	Algorithm	Diagnosis of UI based on 1 hospitalization or 2 OHIP visit diagnoses within 2 years		5 years	CIHI-DAD, OHIP, RPDB

Notes:

[1]Rheumatoid arthritis and osteoarthritis were captured by two variables in the administrative data holdings, but presence of either condition counted as one chronic condition for our definition of multimorbidity.

[2]Mood and anxiety disorders were captured by two variables in the administrative data holdings, but presence of one or both conditions counted as one chronic condition for our definition of multimorbidity.

[3]ICES-derived cohort

Abbreviations:

CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database; CIHI-SDS: Canadian Institute for Health Information Same Day Surgery Database; NACRS: National Ambulatory Care Reporting System; ODB: Ontario Drug Benefit Claims; OHIP: Ontario Health Insurance Plan Claims Database; OMHRS: Ontario Mental Health Reporting System; RPDB: Registered Persons Database

References:

Ryan BL, Jenkyn KB, Shariff SZ, et al. Beyond the grey tsunami: a cross-sectional population-based study of multimorbidity in Ontario. *Can J Public Heal*. 2018;109(5-6):845-854.

Appendix 4N: Detailed methods

PEPP program

Suspected cases are screened by a psychiatric nurse or social worker within 24 hours of referral, and are followed up by a full psychiatric assessment within one week, as needed. Patients between the ages of 16 and 50 who reside in the defined catchment area, have been diagnosed with nonaffective psychotic disorder, have not received treatment with antipsychotic medications for over 1 month, do not have a developmental disability or organic psychosis, and do not have ongoing criminal charges potentially resulting in contact with the criminal justice system are accepted into the PEPP program.[367–369] The PEPP program is similar to its US counterpart, the National Institute of Mental Health Recovery After an Initial Schizophrenia Episode-Early Treatment Program (NAVIGATE RAISE-ETP).[411]

Severity of psychotic symptoms and persistence of impaired functioning

Typically, the severity of psychosis is assessed using an eight-item Likert-type scale in the DSM-V which measures the severity of symptoms which define schizophrenia spectrum disorders (e.g. hallucinations, disorganized speech, abnormal psychomotor behaviour, negative symptoms, delusions), and cognitive, depressive, and manic symptoms from 0 (absent) to 4 (severe).[25] However, this information is not available to us in the health administrative data, therefore we will use a proxy measure of total number of hospital days to assess psychosis severity. A recent study demonstrated the validity of this proxy measure through a dose-response association between psychosis severity and number of hospital days.[375]

People who experience psychosis for prolonged periods may face impairment in activities of daily living. This includes inability to partake in gainful employment, and consequently, these people may depend on social assistance for their income.[376,377] A recent study in the U.S. found that time to receipt of social assistance benefits for patients with psychosis treated by the NAVIGATE RAISE-ETP could be significantly predicted by higher positive symptom scores (on the Positive and Negative Syndrome Scale

(PANSS) used to measure psychosis severity) (HR= 1.06, 95% CI 1.01, 1.11, *p*= 0.021).[379] In other words, patients who had impaired functioning, as identified by PANSS, received income from social assistance earlier. Because we lack information on persistence of impaired functioning, we will use a proxy measure of time on social assistance, i.e. length of time a patient has received the Ontario Drug Benefit (ODB) over the follow-up period. This measure has been calculated from the time between the earliest and latest prescription dispensing date for patients receiving ODB. Furthermore, as noted above, the NAVIGATE RAISE-ETP and PEPP programs are similar in the provision of early intervention services for young people with psychosis.

Poisson regression model

We used the *xtpoisson* command in Stata MP version 16.1 to compute prevalence ratios. This command is appropriate for producing estimates from matched-cohort data.[382] We specifically used a robust variance estimator given that use of conventional variance estimators may produce standard errors, p-values, and confidence intervals which are too large. Furthermore, the robust variance estimator results in more accurate coverage,[381,382,412,413] and may account for the outcome being a poor fit for the Poisson distribution.[414]

Appendix 4O: Counts of chronic conditions for people with and without psychotic disorders at 10-year follow-up (*n*=2,198)

Number of Chronic Conditions	People with Psychotic Disorders (*n*=439) N (%)	People without Psychotic Disorders (*n*=1,759) N (%)
0	207 (47.2)	1,032 (58. 7)
1	170 (38.7)	530 (30.1)
2	49 (11.2)	149 (8.5)
3+*	13 (3.0)	48 (2.7)

Notes:

*The number of chronic conditions in this category range from 3 to 7. Exact counts have been suppressed due to ICES privacy regulations.

Appendix 4P: Counts of chronic conditions for people with psychotic disorders before study entry and during the follow-up period (*n*=439)

Number of Chronic Conditions	Before study entry N (%)	During the follow-up period N (%)
0	53 (12.1)	242 (55.1)
1	327 (74.5)	161 (36. 7)
2+*	59 (13.4)	36 (8.2)

Notes:

*The number of chronic conditions in this category range from 2 to 7. Exact counts have been suppressed due to ICES privacy regulations.

Appendix 4Q: Prevalence ratios of sociodemographic factors and their association with multimorbidity among people without psychotic disorders at 10-year follow-up (*n*=1,759)

Sociodemographic characteristics	2+ conditions PR (95% CI)
Age group[1]	
26-30 years	*Reference*
31-35 years	0.81 (0.54, 1.20)
36-40 years	1.86 (1.34, 2.57)*
Sex	
Males	*Reference*
Females	2.03 (1.59, 2.73)*
Material Deprivation	
Quintile 1 (Least Deprived)	*Reference*
Quintile 2	1.00 (0.64, 1.58)
Quintile 3	1.02 (0.68, 1.52)
Quintile 4	0.86 (0.57, 1.29)
Quintile 5 (Most Deprived)	1.10 (0.74, 1.67)

Abbreviations:
CI = confidence interval; PR = prevalence ratios
Notes:
[1]Age categories at follow-up reflect age of participants 10 years after baseline.
*Prevalence ratio is significant at α=0.05

Appendix 4R: Prevalence ratios of sociodemographic factors and their association with multimorbidity among people with psychotic disorders at 10-year follow-up (*n*=439)

Sociodemographic characteristics	3+ conditions PR (95% CI)	1+ condition[1] PR (95% CI)[2]
Age group[3]		
26-30 years	*Reference*	*Reference*
31-35 years	1.20 (0.15, 9.37)	1.25 (0.89, 1.76)
36-40 years	3.72 (0.59, 23.41)	1.54 (1.11, 2.13)*
Sex		
Males	*Reference*	*Reference*
Females	1.82 (0.59, 5.60)	1.17 (0.88, 1.55)
Material Deprivation		
Quintile 1 (Least Deprived)	*Reference*	*Reference*
Quintile 2	0.78 (0.02, 26.4)	1.60 (0.94, 2.74)
Quintile 3	2.42 (0.24, 24.6)	1.32 (0.74, 2.35)
Quintile 4	3.20 (0.50, 20.5)	1.80 (1.11, 2.93)*
Quintile 5 (Most Deprived)	3.13 (0.38, 25.6)	2.08 (1.28, 3.37)*

Abbreviations:
CI = confidence interval; PR = prevalence ratios
Notes:
[1]1+ physical health condition for people with psychosis and mood/anxiety disorders (an omnibus mental health condition).
[2]Prevalence ratios have been adjusted for total hospital days (severity of psychotic symptoms) and length of time on the Ontario Drug Benefit (proxy measure of social assistance; persistence of impaired functioning).
[3]Age categories at follow-up reflect age of participants 10 years after baseline.
*Prevalence ratio is significant at α=0.05

Appendix 4S: Prevalence ratios of sociodemographic factors and their association with multimorbidity among people without psychotic disorders at 10-year follow-up (*n*=1,759)

Sociodemographic characteristics	3+ conditions PR (95% CI)
Age group[1]	
26-30 years	*Reference*
31-35 years	1.19 (0.41, 3.42)
36-40 years	5.35 (2.31, 12.34)*
Sex	
Males	*Reference*
Females	2.03 (1.06, 3.89)*
Material Deprivation	
Quintile 1 (Least Deprived)	*Reference*
Quintile 2	0.48 (0.16. 1.42)
Quintile 3	0.60 (0.22, 1.68)
Quintile 4	1.06 (0.50, 2.24)
Quintile 5 (Most Deprived)	1.13 (0.50, 2.55)

Abbreviations:
CI = confidence interval; PR = prevalence ratios
Notes:
[1]Age categories at follow-up reflect age of participants 10 years after baseline.
*Prevalence ratio is significant at α=0.05

Appendix 4T: Severity of psychotic symptoms and persistence of impaired functioning, and their association with multimorbidity among people with psychotic disorders at 10-year follow-up (*n*=439)

Psychotic Symptoms	3+ conditions PR (95% CI)	1+ conditions[1] PR (95% CI)[2]
Severity		
Total hospital days (30-day intervals)	1.17 (0.95, 1.44)	1.01 (0.95, 1.07)
Persistence		
Length of time on ODB (365-day intervals)	0.98 (0.87, 1.10)	1.06 (1.02, 1.09)*

Abbreviations:
CI = confidence interval; ODB = Ontario Drug Benefit; PR = prevalence ratio
Notes:
[1]1+ physical health condition for people with psychosis and mood/anxiety disorders (an omnibus mental health condition).
[2]Prevalence ratios have been adjusted for age, sex, and material deprivation.
*Prevalence ratio is significant at α=0.05.

Appendix U: ICES Dataset Creation Plan

Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation		
Project Title:	Long-Term Outcomes of First-Episode Psychosis: 10-Years After Admission to an Early Psychosis Intervention Program	
Project TRIM number:	2018 0906 327 000 (ICES Western), 2018-465 (DAS)	
Research Program:	MHA	
Site:	DAS	
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA*	
	1.) To identify socio-demographic and clinical factors at admission that are associated with long-term trajectories of mental health service use among people with first-episode psychosis, including mental health related emergency department visits, psychiatric hospitalizations, and involuntary admissions	
	2.) To identify socio-demographic and clinical factors at admission that are associated with other outcome indicators at 10-year follow-up, including use of social assistance programs, contact for alcohol- and substance-use problems, self-harm attempts, and mortality	
	3.) To describe the incidence of physical co-morbidities and multimorbidity after a first episode of psychosis	
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)*	
	2018-Mar-22	
Principal Investigator (PI):	Kelly Anderson	
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*	
	N/A	
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*	
		yyyy-mon-dd
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*	
		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 ☒	2018-Aug-13
	Responsible ICES Scientist or Second ICES Scientist/Lead ☐	yyyy-mon-dd
	ICES Research and Analysis Staff Creating the DCP ☐	yyyy-mon-dd
	ICES Analytic Staff ☐	yyyy-mon-dd

Designated ICES Research and Analysis Staff accountable for Project Documentation:	*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 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***
	2018-Aug-01	Kelly Anderson

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)***
CCRS	1997 – 2016
CIHI DAD	1992 – 2016
CIHI SDS	1992 – 2016
CONTACT	1997 – 2016
NACRS	1992 – 2016
ODB	1997 – 2016
OHIP	1992 – 2016
OMHRS	1992 – 2016
General Use Datasets – Population	
RPDB	1997 – 2016
General Use Datasets - Other	
ASTHMA	2016
CHF	2016
COPD	2016
HIV	2016
HYPER	2016
MOMBABY	2016
OCCC	2016
ODD	2016
OMID	2016
ONMARG	2006
ORAD	2016
Controlled Use Datasets	
OCR	2016
Other Datasets	

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		

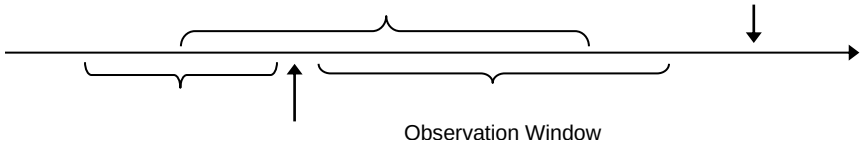
Project Cohort

Study Design	☒ Cohort study ☐ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	All patients admitted to the Prevention and Early Intervention Program for Psychoses (PEPP) between fiscal years 1997 and 2006, identified through a primary data linkage (previously linked on TRIM #2016 0900 300 010). Cohort members can be identified by the variable EPI_user (1). The index date from the linked dataset is admit_date (NOT the index date defined in the original database).
Estimated Size of Cohort (if known)	Approximately 450 people

Exclusions (in order)

Step	*Description*
1	Invalid IKN
2	Admission date (admit_date) occurs after March 31 2007

Project Time Frame Definitions



Accrual Start/End Dates	April 1 1997 to March 31 2007 (ie. fiscal years 1997 to 2006 inclusive)
Max Follow-up Date	March 31 2017
When does observation window terminate?	Index date + 10 years – censor people at date of last contact, loss of OHIP eligibility, death, or end of follow-up period
Lookback Window(s)	Identification of Control Group: 10 years prior to the index date Physical Comorbidities: 10 years prior to the index date

Cohort Build- Unexposed Group	
Index Event / Inclusion Criteria for unexposed group	General population comparison group
Estimated Size of Cohort (if known)	~1800 controls
Exclusions (in order)	*Step* *Description*
	1 Age < 16 or > 50 on index date
	2 Non-Ontario resident (first 2 characters of PRCDDA is NE '35' - use %GETDEMO) on index date
	3 Patient in exposed group
	4 Presence of a diagnostic code for schizophrenia, schizoaffective disorder, or psychosis NOS at any point in the medical records • OMHRS: AXIS1_DSM4CODE_DISCH1-3 code for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [October 2005] up to March 31, 2017, inclusive) • DAD: DXCODE or DX10CODE (dxtype=alldx) for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [April 1988]-March 31, 2017, inclusive) • OHIP: DXCODE for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [July 1991]-March 31, 2017, inclusive) • NACRS: DXCODE or DX10CODE (dxtype=alldx) for schizophrenia, schizoaffective disorder, or psychosis NOS (lookback from database inception [July 2000]-March 31, 2017, inclusive) NOTE 1: Diagnostic codes listed in Appendix A.
Matching Criteria	Match on age, sex, forward sortation area (FSA). Choose 4 unexposed patients for every exposed patient (1-4 matching exposed:unexposed). The control assumes the same index date as the matched case.

Variable Definitions (add additional rows as needed)	
Variable/Concept	**Definition**
Main Comparison Groups	
fep	People with first-episode psychosis, defined based on linked database from TRIM #2016 0900 300 010. All cases from the linked databasee are classified as fep = 1, and people from the matched comparison group are classified as fep = 0
censor_date	Date that the person was censored – occurs at date of last contact, end of OHIP elibigility, death, or end of follow-up period
Baseline Characteristics	
NOTE: These are already defined for the exposed group (fep = 1) but will need to be pulled for the comparison group	
sex	Sex from RPDB
age	Age on the index date, calculated based on date of birth from RPDB
age_cat	Categories for variable age, classified as follows: 1 = age 16 to 20 2 = age 21 to 25 3 = age 26 to 30 4 = age 31 to 35

Variable Definitions (add additional rows as needed)	
	5 = age 36 to 40 6 = age 41 to 45 7 = age 46 to 50
income	INCQUINT from %GETDEMO (1 = lowest income quintile, 5 = highest incomes quintile)
rural	RURAL from %GETDEMO (1 = rural, 0 = non-rural)
dependency	DEPENDENCY_Q_CSD from ONMARG (1 = least marginalized, 5 = most marginalized)
deprivation	DEPRIVATION_Q_CSD from ONMARG (1 = least marginalized, 5 = most marginalized)
ethnic	ETHNICCON_Q_CSD from ONMARG (1 = least marginalized, 5 = most marginalized)
instability	INSTABILITY_Q_CSD from ONMARG (1 = least marginalized, 5 = most marginalized)
odb	Flag if patient covered by ODB on index date (1)

Variables for Exposed Group Only

NOTE: These are already defined and just need to be pulled from the original dataset

pepp_dx	Diagnosis at time of admission to the PEPP program, obtained from the linked database
index_dx	Classify index diagnosis as follows: 1 = Schizophrenia & Schizoaffective Disorder (ICD-9 = 295.X; ICD-10 = F20, F25) 2 = Delusional Disorder (ICD-9 = 297.X; ICD-10 = F22, F24) 3 = Other Psychoses (ICD-9 = 298.X; ICD-10 = F23, F28, F29)
source_dx	Source of the index diagnosis (1 = DAD or OMHRS, 2 = OHIP and/or ED)
source_ohip	If source OHIP/ED, then type of physician who made the diagnosis (1 = GP, 2 = Psychiatrist, 3 = GP + Psychiatrist, 4 = Other)
psychiatrist_index	Flag if patient had a psychiatrist involved at the index diagnosis, defined as source_dx = 1 OR source_ohip = 2 or 3 (1 = psychiatrist involved, 0 = no psychiatrist involved)
year	Fiscal year of index diagnosis
prior_alcohol	Flag if patient had prior history of contact with services for alcohol-related disorders (Appendix D)
prior_substance	Flag if patient had prior history of contact with services for substance-related disorders (Appendix E)
primcare_pre6m	Number of primary care visits for a mental health reason, defined as all mental health service codes and general service codes with a mental health diagnostic code (Appendix F)
psych_pre6m	Number of visits with a psychiatrist
edtotal_pre6m	Number of ED visits with a main diagnosis - mental health diagnostic code (ICD-9 291.x,292.x,and 294.x-319.x, ICD-10 F codes), by triage category (CTAS 1-3 vs. 4-5). Use %GETNACRS, INCLscheduled=T. Exclude transfers (FROM_TYPE='E').
edharm_pre6m	Number of ED visits from edtotal_pre6m that were for self-harm (ICD 10 codes X60-X84). Use %GETNACRS, INCLscheduled=T. Exclude transfers (FROM_TYPE='E').
edmh_pre6m	Number of ED visits from edtotal_pre6m that were not for self-harm (ie. edtotal_pre6m – edharm_pre6m)
hosptotal_pre6m	Number of psychiatric hospital admissions. Use %GETCIHI and limit to non-elective admissions (ADMCAT U or E) for all hospitalizations at acute care institution (INSTTYPE AT or AP). Select first visit in an episode of care (Sort data by EPI, EPIVISIT, EPIFLAG and pll the record with FIRST.EPI=1). Limit to main diagnosis ICD-9 codes 291.x,292.x,and 294.x-319.x ICD-10 codes F10-

Variable Definitions (add additional rows as needed)	
	F99 (exclude dementia and delirium). For psychiatric hospitalizations in OMHRS, use all codes except 293, 780, 290, 294, and V codes. Use only first diagnosis from Axis 1 or Axis 2, first position at discharge. Exclude discharges with no Axis 1 diagnosis
hospdays_pre6m	Total number of inpatient days for a mental health reason

Psychiatric Outcomes (10 years post admission date)

mhprimcareX_date	Date of Xth primary care visit for a mental health reason, defined as follows (DXCODE found in Appendix B): • (FP/GP [SPEC=00] or Paediatrician [SPEC=26]) and MHA diagnosis code (DXCODE) and outpatient (LOCATION: O, L, H) and non-lab service [substr(FEECODE,1,1) ne 'G'] *OR* • Paediatrician [SPEC=26] and undefined location (LOCATION =U) and MHA diagnosis code [DXCODE] and fee code (FEECODE=K122 or K123 or K704)
primcareX_date	Date of Xth primary care visit for non-mental health reason, defined as all visits to primary care that do not meet the definition of mhprimcareX_date (above)
psychX_date	Date of Xth outpatient visit with a psychiatrist [SPEC=19; LOCATION: O, L, H) for a non-lab service [substr(FEECODE,1,1) ne 'G']
edX_date	Date of Xth ED visit for a mental health reason, defined as follows: • DX10CODE1 = F04-F99 *OR* • DX10CODE2 – DX10CODE10 = X60-X84, Y10-Y19, Y28 **AND** DX10CODE1 not equal to F04-F99 Include suspect diagnoses (%getnacrs where suspect = T) Exclude scheduled ED visits (%getnacrs where INCLSCHEDULED = F) Exclude transfers from another ED (FROM_TYPE ≠ 'E')
hospX_date	Date of Xth psychiatric hospital admission. Use %GETCIHI and limit to non-elective admissions (ADMCAT U or E) for all hospitalizations at acute care institution (INSTTYPE AT or AP). Select first visit in an episode of care (Sort data by EPI, EPIVISIT, EPIFLAG and pll the record with FIRST.EPI=1). Limit to main diagnosis ICD-9 codes 291.x,292.x,and 294.x-319.x ICD-10 codes F10-F99 (exclude dementia and delirium). For psychiatric hospitalizations in OMHRS, use all codes <u>except</u> 293, 780, 290, 294, and V codes. Use only first diagnosis from Axis 1 or Axis 2, first position at discharge. Exclude discharges with no Axis 1 diagnosis
hospX_los	Length of stay (days) for Xth psychiatric hospital admission
involuntaryX_date	Date of Xth involuntary admissions, defined as follows: • OMHRS: PT_STATUS = 1, 4 • DAD: ADMMETH = D, E • OHIP: FEECODE = K623, K624
ltc	Flag if patient has an admission to a long-term care facilited, defined based on presence of IKN in CCRS database
ltc_date	Date of first admission to long-term care facility (ADMDATE in CCRS)
ltc_10y	Flag if patient is a resident of a long-term care facility at the end of the follow-up period

Variable Definitions (add additional rows as needed)	
alcoholX_date	Date of Xth contact with services for alcohol-related disorders over the follow-up period (any diagnosis field in DAD, OMHRS, NACRS, OHIP – codes in Appendix C)
substanceX_date	Date of Xth contact with services for substance-related disorders over the follow-up period (any diagnosis field in DAD, OMHRS, NACRS, OHIP – codes in Appendix D)
substance_opioid	Flag if contact with services for substance-related disorder (above) was related to opioids, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30400, 30401, 30402, 30403, 30470, 30471, 30472, 30473, 30550, 30551, 30552, 30553 • ICD-10: F11 • DSM-IV: 304.00, 305.50
substance_sedative	Flag if contact with services for substance-related disorder (above) was related to sedatives or barbituates, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30410, 30411, 30412, 30413, 30540, 30541, 30542, 30543 • ICD-10: F13 • DSM-IV: 304.10, 305.40
substance_cocaine	Flag if contact with services for substance-related disorder (above) was related to cocaine, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30420, 30421, 30422, 30423, 30560, 30561, 30562, 30563 • ICD-10: F14 • DSM-IV: 304.20, 305.60
substance_cannabis	Flag if contact with services for substance-related disorder (above) was related to cannabis, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30430, 30431, 30432, 30433, 30520, 30521, 30522, 30523 • ICD-10: F12 • DSM-IV: 304.30, 305.20
substance_amphetamine	Flag if contact with services for substance-related disorder (above) was related to amphetamines, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30440, 30441, 30442, 30443, 30570, 30571, 30572, 30573 • ICD-10: F15 • DSM-IV: 304.40, 305.70
substance_hallucinogen	Flag if contact with services for substance-related disorder (above) was related to hallucinogens, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30450, 30451, 30452, 30453, 30530, 30531, 30532, 30533 • ICD-10: F16 • DSM-IV: 304.50, 305.30
substance_poly	Flag if contact with services for substance-related disorder (above) was related to multiple substances, defined as follows (any diagnosis field in DAD, OMHRS, NACRS): • ICD-9: 30470, 30471, 30472, 30480, 30481, 30482, 30483 • ICD-10: F19 • DSM-IV: 304.80
substance_unknown	Flag if contact with services for substance-related disorder (above) was related to unknown substances, defined as follows (any diagnosis field in DAD, OMHRS, NACRS):

Variable Definitions (add additional rows as needed)	
	• ICD-9: 2920, 29211, 29212, 2922, 29281, 29282, 29283, 29284, 29289, 2929, 30460, 30461, 30462, 30463, 30490, 30491, 30492, 30493, 30580, 30581, 30582, 30583, 30590, 30591, 30592, 30593 • ICD-10: F18, F55 • DSM-IV: 292.00, 292.11, 292.12, 292.81, 292.82, 292.83, 292.84, 292.89, 292.90, 304.60, 304.90, 305.10, 305.90 • OHIP: 292, 304
odb_length	Length of time (days) covered by ODB over the study follow-up period
odb_10y	Flag if patient is still covered by ODB at 10-year follow-up
odb_plan	If odb_10y = 1, note the plan code (PLANCODE from ODB database)
death	Whether the patient died from any cause over the follow-up period (DTH from RPDB)
death_date	Date of death (DTHDATE from RPDB)

Physical Co-Morbidities (At any point in patient record)

ami	Flag if patient has a hospitalization for acute myocardial infarction, based on presence of IKN in OMID2016 database NOTE: Only includes patients over the age of 20
ami_date	Date of first admission for acute myocardial infarction (ADMDATE from OMID2016 database)
asthma	Flag if patient has a diagnosis of asthma, based on presence of IKN in ASTHMA2016 database
asthma_date	Date of first diagnosis of asthma (FIRSTOHIP from ASTHMA2016 database)
asthma_10y	Flag if patient is a prevalent case of asthma (PREVyyyy) at the end of the 10-year follow-up period
cancer	Flag if patient has diagnosis of cancer, based on presence of IKN in OCR database
cancer_date	Date of first diagnosis of cancer (DXDATE from OCR database)
cancer_site	Site of cancer, defined by PSITE from OCR database
cancer_stage	Stage of cancer at diagnosis, defined by BEST_STAGE_GRP from OCR database
cancer_10yr	Flag if date of last contact (DOLC) is within five years of the end of the 10-year follow-up period
chf	Flag if patient has diagnosis of congestive heart failure based on presence of IKN in CHF2016 database NOTE: Only includes patients over the age of 40
chf_date	Date of first diagnosis of congestive heart failure (DIAGDATE from CHF database)
chf_10y	Flag if patient is prevalent case (PREVyyyy) at end of 10-year follow-up period
ckd	Flag if patient has diagnosis of chronic kidney disease, defined based on the presence of one of the following codes in DAD, or two in OHIP within a 2-year period (ICD-9: DXCODE1-16; ICD-10: DXCODE1-25): • ICD-9: 40300, 40301, 40310, 40311, 40390, 40391, 40400, 40401, 40402, 40403, 40410, 40411, 40412, 40413, 40490, 40491, 40492, 40493, 585, 586, 5888, 5889, 2504, V451 • ICD-10: E102, E112, E132, E142, I12, I13, N08, N180, N181, N182, N183, N184, N185, N188, N189 N19, T824, Z492, Z992 • OHIP: 403, 585

Variable Definitions (add additional rows as needed)	
ckd_date	Date of first diagnosis of chronic kidney disease, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
ckd_10y	Flag if patient has a hospitalization or visit for chronic kidney disease within 5 years of the maximum follow-up date
copd	Flag if patient has diagnosis of COPD, based on presence of IKN in COPD2016 database NOTE: Only includes patients over the age of 35
copd_date	Date of diagnosis of COPD (DIAGDATE from COPD database)
copd_10y	Flag if patient is prevalent case (PREVyyyy) at end of 10-year follow-up period
cvd	Flag if patient has diagnosis of cardiovascular disease, which includes MI, angina, peripheral vascular disease, and arrhythmia. Definitions found in the file below:  CVD Case Definition.xlsx
cvd_date	Date of first diagnosis of cardiovascular disease, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
cvd_10y	Flag if patient has hospitalization or visit for cardiovascular disease (as defined above) within 5 years of the maximum follow-up date
dementia	Flag if patient has a diagnosis of dementia, based on presence of IKN in DEMENTIA2016 database NOTE: Only includes patients over the age of 40
dementia_date	Date of diagnosis of dementia (DIAGDATE from DEMENTIA2016)
dementia_10y	Flag if patient is a prevalent case of dementia (PREVyyyy) at the end of the 10-year follow-up period
diabetes	Flag if patient has a diagnosis of diabetes, based on presence of IKN in ODD2016 database
diabetes_date	Date of diagnosis of hypertension (DIAGDATE from ODD2016 database)
diabetes_10y	Flag if patient is a prevalent case of diabetes (PREVyyyy) at the end of the 10-year follow-up period
hepatitis	Flag if patient has diagnosis of hepatitis, defined based on the presence of one of the following codes in DAD, or two in OHIP (ICD-9: DXCODE1-16; ICD-10: DXCODE1-25): • ICD-9: 0700, 0701, 0702, 07020, 07021, 0703, 07030, 07031, 0704, 07041, 07042, 07043, 07049, 0705, 07051, 07052, 07053, 07059, 0706, 0709 • ICD-10: B15, B150, B159, B16, B160, B161, B162, B169, B17, B170, B171, B172, B178, B179, B18, B180, B181, B182, B188, B189, B19, B190, B199, B942, O98401, O98402, O98403, O98404, O98409, Z2250, Z2251, Z2258 • OHIP: 070
hepatitis_date	Date of first diagnosis of hepatitis, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits.
hiv	Flag if patient has diagnosis of HIV infection, based on presence of IKN in HIV2016 database NOTE: Only includes patients over the age of 18
hiv_date	Date of diagnosis of HIV infection (DIAGDATE from HIV2016 database)

Variable Definitions (add additional rows as needed)	
hypertension	Flag if patient has a diagnosis of hypertension, based on presence of IKN in HYPER2016 database NOTE: Only includes patients over the age of 20
hypertension_date	Date of diagnosis of hypertension (DIAGDATE from HYPER2016 database)
hypertension_10y	Flag if patient is a prevalent case of hypertension (PREVyyyy) at the end of the 10-year follow-up period
ibd	Flag if patient has a diagnosis of inflammatory bowel disease, based on presence of IKN in OCCC2016 database
ibd_date	Date of diagnosis of inflammatory bowel disease (FIRSTCONTACTDATE from OCCC2016 database)
ibd_10y	Flag if patient is a prevalent case of inflammatory bowel disease (PREVyyyy) at the end of the 10-year follow-up period
lipids	Flag if patient has a diagnosis of a disorder of lipid metabolism, based on DXCODE = 272 in OHIP database
lipids_date	Date of first diagnosis of disorder of lipid metabolism (SERVDATE from OHIP database)
liver	Flag if patient has diagnosis of chronic liver disease, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25) or two OHIP visit diagnoses (DXCODE) or fee codes (FEECODE) within 2 years: • ICD-9: 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 571, 2750, 2751, 7891, 7895 • ICD-10: B16, B17, B18, B19, I85, R17, R18, R160, R160, B942, Z2225, E830, E831, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 • OHIPDX: 571, 573, 070 • OHIPFEE: Z551, Z554
liver_date	Date of first diagnosis of chronic liver disease, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
liver_10y	Flag if patient has hospitalization or visit for chronic liver disease during 10-year follow-up period
mood	Flag if patient has diagnosis of a mood disorder, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25, DSM-IV: AXIS1_DSM4CODE_DISCH1-3) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 296, 2960, 29600, 29601, 29602, 29603, 29604, 29605, 29606, 2961, 29610, 29611, 29612, 29613, 29614, 29615, 29616, 2962, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 2963, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 2964, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 2965, 29650, 29651, 29652, 29653, 29654, 29655, 29656, 2966, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 2967, 29670, 2968, 29680, 29681, 29682, 29689, 2969, 29690, 29699, 3004, 3090, 3091, 311 • ICD-10: F300, F301, F302, F308, F309, F310, F311, F312, F313, F314, F315, F316, F317, F318, F319, F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F338, F339, F341, F348, F349, F380, F381, F388, F39 • DSM-IV: 296.0X, 296.2X, 296.3X, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89, 296.9, 300.4, 301.13, 311.00 • OHIP: 296, 311

Variable Definitions (add additional rows as needed)	
mood_date	Date of first diagnosis of mood disorder, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
mood_10y	Flag if patient has hospitalization or visit for a mood disorder during 10-year follow-up period
anxiety	Flag if patient has diagnosis of an anxiety disorder, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25, DSM-IV: AXIS1_DSM4CODE_DISCH1-3) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 30000, 30001, 30002, 30009, 30010, 30011, 30012, 30013, 30014, 30015, 30016, 30019, 30020, 30021, 30022, 30023, 30029, 3003, 3005, 3006, 3007, 30081, 30089, 3009, 3090, 30900, 30921, 30922, 30923, 30924, 30928, 30929, 3093, 3094, 30981, 30982, 30983, 30989, 3099, 30990 • ICD-10: F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F431, F432, F438 • DSM-IV: 300.XX, 300.00, 300.01, 300.02, 300.21, 300.22, 300.23, 300.29, 300.3, 308.3, 309.21, 309.81 • OHIP: 300, 309
anxiety_date	Date of first diagnosis of anxiety disorder, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
anxiety_10y	Flag if patient has hospitalization or visit for mood disorder during 10-year follow-up period
osteoarthritis	Flag if patient has diagnosis of osteoarthritis, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 71500, 71504, 71509, 71510, 71511, 71512, 71513, 71514, 71515, 71516, 71517, 71518, 71520, 71521, 71522, 71523, 71524, 71525, 71526, 71527, 71528, 71530, 71531, 71532, 71533, 71534, 71535, 71536, 71537, 71538, 71580, 71589, 71590, 71591, 71592, 71593, 71594, 71595, 71596, 71597, 71598 • ICD-10: M150, M151, M152, M153, M154, M158, M159, M160, M161, M162, M163, M164, M165, M166, M167, M169, M170, M171, M172, M173, M174, M175, M179, M180, M181, M182, M183, M184, M185, M189, M190, M191, M192, M198, M199 • OHIP: 715
osteoarthritis_date	Date of first diagnosis of osteoarthritis, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
osteoarthritis_10y	Flag if patient has hospitalization or visit for osteoarthritis during follow-up period
osteoporosis	Flag if patient has diagnosis of osteoporosis, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 73300, 73301, 73302, 73303, 73309, 7331, 73320, 73321, 73322, 73329, 73329, 73340, 73341, 73342, 73343, 73344, 73349, 7335, 7336, 7337, 73381, 73382, 73390, 73391, 73392, 73399 • ICD-10: M810, M811, M812, M813, M814, M815, M816, M818, M819, M820, M821, M828

Variable Definitions (add additional rows as needed)	
	• OHIP: 733
osteoporosis_date	Date of first diagnosis of osteoporosis, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
osteoporosis_10y	Flag if patient has hospitalization or visit for osteoporosis during 10-year follow-up period
deliveryX_date	Date of Xth delivery (B_BDATE), based on presence of IKN in MOMBABY2016 database over follow-up period
deliveryX_stillbirth	Flag if delivery X was a stillbirth based on variable M_STILLBIRTH from MOMBABY2016 record
rheumatoid	Flag if patient has a diagnosis of rheumatoid arthritis, based on presence of IKN in ORAD2016 database
rheumatoid_date	Date of diagnosis of rheumatoid arthritis (DIAGDATE from ORAD2016 database)
rheumatoid_10y	Flag if patient is prevalent case (PREVyyyy) at end of 10-year follow-up period
stroke	Flag if patient has diagnosis of osteoporosis, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 3623, 36230, 36231, 36232, 36233, 36234, 36235, 36236, 36237, 430, 4300, 431, 4310, 4320, 4321, 4329, 4330, 4331, 4332, 4333, 4338, 4339, 4340, 4341, 4349, 4350, 4351, 4352, 4358, 4359, 436, 4360 • ICD-10: H340, H341, G450, G451, G452, G453, G458, G459, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64 • OHIP: 3623, 430, 431, 432, 434, 436
stroke_date	Date of first diagnosis of stroke, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
stroke_10y	Flag if patient has hospitalization or visit for stroke during follow-up period (1)
urinary	Flag if patient has diagnosis of osteoporosis, defined based on the presence of one hospitalization (ICD-9: DXCODE1-16; ICD-10: DX10CODE1-25) or two OHIP visit diagnoses (DXCODE) within 2 years: • ICD-9: 7883 • ICD-10: N393, N394, R32 • OHIP: 788
urinary_date	Date of first diagnosis of chronic urinary problem, as defined above. Use admission date (ADMDATE) when defined by hospitalization, and the date of first OHIP diagnosis (SERVDATE) when defined by outpatient visits
urinary_10y	Flag if patient has hospitalization or visit for a chronic urinary problem within 5 years of the maximum follow-up date

Analysis Plan and Dummy Tables (expand/modify as needed)	
Descriptive Tables (insert or append dummy tables), e.g.:	
Table 1. Baseline characteristics according to primary/secondary exposure	
Table 2. Outcomes according to primary/secondary exposure	
Table 3. Covariates (baseline characteristics) according to outcomes	
Statistical Model(s)	
Type of model	
Primary independent variable	
Dependent variable	
Covariates	
Sensitivity Analyses	
Type of model	
Primary independent variable	
Dependent variable	
Covariates	

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:		

APPENDIX A – List of Diagnostic Codes to Exclude from Comparison Group

OMHRS:

29510 = SCHIZOPHRENIA, DISORGANIZED TYPE
29520 = SCHIZOPHRENIA, CATATONIC TYPE
29530 = SCHIZOPHRENIA, PARANOID TYPE
29540 = SCHIZOPHRENIFORM DISORDER
29560 = SCHIZOPHRENIA, RESIDUAL TYPE
29570 = SCHIZOAFFECTIVE DISORDER
29590 = SCHIZOPHRENIA, UNDIFFERENTIATED TYPE
29710 = DELUSIONAL DISORDER
29730 = SHARED PSYCHOTIC DISORDER
29880 = BRIEF PSYCHOTIC DISORDER
29890 = PSYCHOTIC DISORDER NOS

DAD (ICD-10):

F20 = SCHIZOPHRENIA
F200 = PARANOID SCHIZOPHRENIA
F201 = HEBEPHRENIC SCHIZOPHRENIA
F202 = CATATONIC SCHIZOPHRENIA
F203 = UNDIFFERENTIATED SCHIZOPHRENIA
F204 = POST-SCHIZOPHRENIC DEPRESSION
F205 = RESIDUAL SCHIZOPHRENIA
F206 = SIMPLE SCHIZOPHRENIA
F208 = OTHER SCHIZOPHRENIA
F209 = SCHIZOPHRENIA, UNSPECIFIED
F22 = PERSISTENT DELUSIONAL DISORDERS
F220 = DELUSIONAL DISORDER
F228 = OTHER PERSISTENT DELUSIONAL DISORDERS
F229 = PERSISTENT DELUSIONAL DISORDER, UNSPECIFIED
F23 = ACUTE AND TRANSIENT PSYCHOTIC DISORDERS
F230 = ACUTE POLYMORPHIC PSYCHOTIC DISORDER WITHOUT SYMPTOMS OF SCHIZOPHRENIA
F231 = ACUTE POLYMORPHIC PSYCHOTIC DISORDER WITH SYMPTOMS OF SCHIZOPHRENIA
F232 = ACUTE SCHIZOPHRENIA-LIKE PSYCHOTIC DISORDER
F233 = OTHER ACUTE PREDOMINANTLY DELUSIONAL PSYCHOTIC DISORDERS
F238 = OTHER ACUTE AND TRANSIENT PSYCHOTIC DISORDERS
F239 = ACUTE AND TRANSIENT PSYCHOTIC DISORDER, UNSPECIFIED
F24 = INDUCED DELUSIONAL DISORDER

F25 = SCHIZOAFFECTIVE DISORDERS
F250 = SCHIZOAFFECTIVE DISORDER, MANIC TYPE
F251 = SCHIZOAFFECTIVE DISORDER, DEPRESSIVE TYPE
F252 = SCHIZOAFFECTIVE DISORDER, MIXED TYPE
F258 = OTHER SCHIZOAFFECTIVE DISORDERS
F259 = SCHIZOAFFECTIVE DISORDER, UNSPECIFIED

F28 = OTHER NONORGANIC PSYCHOTIC DISORDERS
F29 = UNSPECIFIED NONORGANIC PSYCHOSIS

DAD (ICD-9):
295 = SCHIZOPHRENIAS
29500 = SIMPL SCHIZOPHREN-UNSPEC
29501 = SIMPL SCHIZOPHREN-SUBCHR
29502 = SIMPLE SCHIZOPHREN-CHR
29503 = SIMP SCHIZ-SUBCHR/EXACER
29504 = SIMPL SCHIZO-CHR/EXACERB
29505 = SIMPL SCHIZOPHREN-REMISS
2951 = HEBEPHRENIA-UNSPEC
29510 = HEBEPHRENIA-UNSPEC
29511 = HEBEPHRENIA-SUBCHRONIC
29512 = HEBEPHRENIA-CHRONIC
29513 = HEBEPHREN-SUBCHR/EXACERB
29514 = HEBEPHRENIA-CHR/EXACERB
29515 = HEBEPHRENIA-REMISSION
2952 = CATATONIA-UNSPEC
29520 = CATATONIA-UNSPEC
29521 = CATATONIA-SUBCHRONIC
29522 = CATATONIA-CHRONIC
29523 = CATATONIA-SUBCHR/EXACERB
29524 = CATATONIA-CHR/EXACERB
29525 = CATATONIA-REMISSION
2953 = PARANOID SCHIZO-UNSPEC
29530 = PARANOID SCHIZO-UNSPEC
29531 = PARANOID SCHIZO-SUBCHR
29532 = PARANOID SCHIZO-CHRONIC
29533 = PARAN SCHIZO-SUBCHR/EXAC
29534 = PARAN SCHIZO-CHR/EXACERB
29535 = PARANOID SCHIZO-REMISS
2954 = AC SCHIZOPHRENIA-UNSPEC
29540 = AC SCHIZOPHRENIA-UNSPEC
29541 = AC SCHIZOPHRENIA-SUBCHR
29542 = AC SCHIZOPHRENIA-CHR
29543 = AC SCHIZO-SUBCHR/EXACERB
29544 = AC SCHIZOPHR-CHR/EXACERB
29545 = AC SCHIZOPHRENIA-REMISS
2955 = LATENT SCHIZOPHREN-UNSP
29550 = LATENT SCHIZOPHREN-UNSP
29551 = LAT SCHIZOPHREN-SUBCHR
29552 = LATENT SCHIZOPHREN-CHR
29553 = LAT SCHIZO-SUBCHR/EXACER
29554 = LATENT SCHIZO-CHR/EXACER
29555 = LAT SCHIZOPHREN-REMISS

2956 = RESID SCHIZOPHREN-UNSP
29560 = RESID SCHIZOPHREN-UNSP
29561 = RESID SCHIZOPHREN-SUBCHR
29562 = RESIDUAL SCHIZOPHREN-CHR
29563 = RESID SCHIZO-SUBCHR/EXAC
29564 = RESID SCHIZO-CHR/EXACERB
29565 = RESID SCHIZOPHREN-REMISS
2957 = SCHIZOAFFECTIVE-UNSPEC
29570 = SCHIZOAFFECTIVE-UNSPEC
29571 = SCHIZOAFFECTIVE-SUBCHR
29572 = SCHIZOAFFECTIVE-CHRONIC
29573 = SCHIZOAFF-SUBCHR/EXACER
29574 = SCHIZOAFFECT-CHR/EXACER
29575 = SCHIZOAFFECTIVE-REMISS
2958 = SCHIZOPHRENIA NEC-UNSPEC
29580 = SCHIZOPHRENIA NEC-UNSPEC
29581 = SCHIZOPHRENIA NEC-SUBCHR
29582 = SCHIZOPHRENIA NEC-CHR
29583 = SCHIZO NEC-SUBCHR/EXACER
29584 = SCHIZO NEC-CHR/EXACERB
29585 = SCHIZOPHRENIA NEC-REMISS
2959 = SCHIZOPHRENIA NOS-UNSPEC
29590 = SCHIZOPHRENIA NOS-UNSPEC
29591 = SCHIZOPHRENIA NOS-SUBCHR
29592 = SCHIZOPHRENIA NOS-CHR
29593 = SCHIZO NOS-SUBCHR/EXACER
29594 = SCHIZO NOS-CHR/EXACERB
29595 = SCHIZOPHRENIA NOS-REMISS
297 = DELUSIONAL DISORDERS
2970 = PARANOID STATE, SIMPLE
2971 = PARANOIA
2972 = PARAPHRENIA
2973 = SHARED PARANOID DISORDER
2978 = PARANOID STATES NEC
2979 = PARANOID STATE NOS
298 = OTHER PSYCHOSES
2980 = REACT DEPRESS PSYCHOSIS
2981 = EXCITATIV TYPE PSYCHOSIS
2982 = REACTIVE CONFUSION
2983 = ACUTE PARANOID REACTION
2984 = PSYCHOGEN PARANOID PSYCH
2988 = REACT PSYCHOSIS NEC/NOS
2989 = PSYCHOSIS NOS

OHIP
295 = SCHIZOPHRENIA

297 = PARANOID STATES
298 = OTHER PSYCHOSES

APPENDIX B – OHIP fee codes for identifying primary care visits for mental health reasons

Psychotic Disorders
295 Schizophrenia
296 Manic-depressive psychoses, involutional melancholia
297 Other paranoid states
298 Other psychoses

Non-Psychotic Disorders
300 Anxiety neurosis, hysteria, neurasthenia, obsessive-compulsive neurosis, reactive depression
301 Personality disorders
302 Sexual deviations
306 Psychosomatic illness
309 Adjustment reaction
311 Depressive disorder

Substance Use Disorders
303 Alcoholism
304 Drug dependence

Social Problems
897 Economic problems
898 Marital difficulties
899 Parent-child problems
900 Problems with aged parents or in-laws
901 Family disruption/divorce
902 Education problems
904 Social maladjustment
905 Occupational problems
906 Legal problems
909 Other problems of social adjustment

Other
291 Alcoholic psychosis, delirium tremens, Korsakov's psychosis
292 Drug psychosis
299 Childhood psychoses (e.g., autism)
307 Habit spasms, tics, stuttering, tension headaches, anorexia nervosa, sleep disorders, enuresis
313 Behaviour disorders of childhood and adolescence
314 Hyperkinetic syndrome of childhood
315 Specified delays in development (e.g., dyslexia, dyslalia, motor retardation)

APPENDIX C – Alcohol Related Diagnostic Codes

OMHRS (DSM-IV)
291.00 = ALCOHOL – INTOXICATION OR WITHDRAWAL DELIRIUM
291.10 = ALCOHOL – INDUCED PERSISTING AMNESTIC DISORDER
292.20 = ALCOHOL – INDUCED PERSISTING DEMENTIA
291.30 = ALCOHOL – INDUCED PSYCHOTIC DISORDER, WITH HALLUCINATIONS
291.50 = ALCOHOL – INDUCED PSYCHOTIC DISORDER, WITH DELUSIONS
291.81 = ALCOHOL – WITHDRAWAL
291.89 = ALCOHOL – INDUCED ANXIETY/MOOD DISORDER OR SEXUAL DYSFUNCTION
291.90 = ALCOHOL – RELATED DISORDER NOT OTHERWISE SPECI ED (NOS)
303.00 = ALCOHOL INTOXICATION
303.90 = ALCOHOL DEPENDENCE
305.00 = ALCOHOL ABUSE

DAD/NACRS (ICD-10)
F10 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF ALCOHOL

DAD (ICD-9)
2910 = DELIRIUM TREMENS
2911 = ALCOHOL AMNESTIC SYND
2912 = ALCOHOLIC DEMENTIA NEC
2913 = ALCOHOL HALLUCINOSIS
2914 = PATHOLOGIC ALCOHOL INTOX
2915 = ALCOHOLIC JEALOUSY
2918 = ALCOHOLIC PSYCHOSIS NEC
2919 = ALCOHOLIC PSYCHOSIS NOS
30300 = AC ALCOHOL INTOX-UNSPEC
30301 = AC ALCOHOL INTOX-CONTIN
30302 = AC ALCOHOL INTOX-EPISOD
30303 = AC ALCOHOL INTOX-REMISS
30390 = ALCOH DEP NEC/NOS-UNSPEC
30391 = ALCOH DEP NEC/NOS-CONTIN
30392 = ALCOH DEP NEC/NOS-EPISOD
30393 = ALCOH DEP NEC/NOS-REMISS
30500 = ALCOHOL ABUSE-UNSPEC
30501 = ALCOHOL ABUSE-CONTINUOUS
30502 = ALCOHOL ABUSE-EPISODIC
30503 = ALCOHOL ABUSE-IN REMISS

OHIP
291 = ALCOHOLIC PSYCHOSIS
303 = ALCOHOLISM

APPENDIX D – Substance Related Diagnostic Codes

OMHRS (DSM-IV)

292.00 = SUBSTANCE – WITHDRAWAL
292.11 = SUBSTANCE – INDUCED PSYCHOTIC DISORDER, WITH DELUSIONS
292.12 = SUBSTANCE – INDUCED PSYCHOTIC DISORDER, WITH HALLUCINATIONS
292.81 = SUBSTANCE – INTOXICATION OR WITHDRAWAL DELIRIUM
292.82 = SUBSTANCE – INDUCED PERSISTING DEMENTIA
292.83 = SUBSTANCE – INDUCED PERSISTING AMNESTIC DISORDER
292.84 = SUBSTANCE – INDUCED MOOD DISORDER
292.89 = SUBSTANCE – INTOXICATION OR INDUCED ANXIETY DISORDER/SEXUAL DYSFUNCTION
292.90 = SUBSTANCE – RELATED NOS
304.00 = OPIOID DEPENDENCE
304.10 = SEDATIVE, HYPNOTIC OR ANXIOLYTIC DEPENDENCE
304.20 = COCAINE DEPENDENCE
304.30 = CANNABIS DEPENDENCE
304.40 = AMPHETAMINE DEPENDENCE
304.50 = HALLUCINOGEN DEPENDENCE
304.60 = INHALANT OR PHENCYCLIDINE DEPENDENCE
304.80 = POLYSUBSTANCE DEPENDENCE
304.90 = OTHER (OR UNKNOWN) SUBSTANCE DEPENDENCE
305.10 = NICOTINE DEPENDENCE
305.20 = CANNABIS ABUSE
305.30 = HALLUCINOGEN ABUSE
305.40 = SEDATIVE, HYPNOTIC OR ANXIOLYTIC ABUSE
305.50 = OPIOID ABUSE
305.60 = COCAINE ABUSE
305.70 = AMPHETAMINE ABUSE
305.90 = OTHER (OR UNKNOWN) SUBSTANCE ABUSE

DAD/NACRS (ICD-10)

F11 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF OPIOIDS
F12 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF CANNABINOIDS
F13 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF SEDATIVES OR HYPNOTICS
F14 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF COCAINE
F15 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF OTHER STIMULANTS, INCLUDING CA EINE
F16 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF HALLUCINOGENS
F18 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO USE OF VOLATILE SOLVENTS
F19 = MENTAL AND BEHAVIOURAL DISORDERS DUE TO MULTIPLE DRUG USE AND USE OF OTHER PSYCHOACTIVE SUBSTANCES
F55 = ABUSE OF NON-DEPENDENCE-PRODUCING SUBSTANCES

DAD (ICD-9)

2920 = DRUG WITHDRAWAL SYNDROME
29211 = DRUG PARANOID STATE
29212 = DRUG HALLUCINOSIS
2922 = PATHOLOGIC DRUG INTOX
29281 = DRUG-INDUCED DELIRIUM
29282 = DRUG-INDUCED DEMENTIA
29283 = DRUG AMNESTIC SYNDROME
29284 = DRUG DEPRESSIVE SYNDROME

29289 = DRUG MENTAL DISORDER NEC
2929 = DRUG MENTAL DISORDER NOS
30400 = OPIOID DEPENDENCE-UNSPEC
30401 = OPIOID DEPENDENCE-CONTIN
30402 = OPIOID DEPENDENCE-EPISOD
30403 = OPIOID DEPENDENCE-REMISS
30410 = BARBITURAT DEPEND-UNSPEC
30411 = BARBITURAT DEPEND-CONTIN
30412 = BARBITURAT DEPEND-EPISOD
30413 = BARBITURAT DEPEND-REMISS
30420 = COCAINE DEPEND-UNSPEC
30421 = COCAINE DEPEND-CONTIN
30422 = COCAINE DEPEND-EPISODIC
30423 = COCAINE DEPEND-REMISS
30430 = CANNABIS DEPEND-UNSPEC
30431 = CANNABIS DEPEND-CONTIN
30432 = CANNABIS DEPEND-EPISODIC
30433 = CANNABIS DEPEND-REMISS
30440 = AMPHETAMIN DEPEND-UNSPEC
30441 = AMPHETAMIN DEPEND-CONTIN
30442 = AMPHETAMIN DEPEND-EPISOD
30443 = AMPHETAMIN DEPEND-REMISS
30450 = HALLUCINOGEN DEP-UNSPEC
30451 = HALLUCINOGEN DEP-CONTIN
30452 = HALLUCINOGEN DEP-EPISOD
30453 = HALLUCINOGEN DEP-REMISS
30460 = DRUG DEPEND NEC-UNSPEC
30461 = DRUG DEPEND NEC-CONTIN
30462 = DRUG DEPEND NEC-EPISODIC
30463 = DRUG DEPEND NEC-IN REM
30470 = OPIOID/OTHER DEP-UNSPEC
30471 = OPIOID/OTHER DEP-CONTIN
30472 = OPIOID/OTHER DEP-EPISOD
30473 = OPIOID/OTHER DEP-REMISS
30480 = COMB DRUG DEP NEC-UNSPEC
30481 = COMB DRUG DEP NEC-CONTIN
30482 = COMB DRUG DEP NEC-EPISOD
30483 = COMB DRUG DEP NEC-REMISS
30490 = DRUG DEPEND NOS-UNSPEC
30491 = DRUG DEPEND NOS-CONTIN
30492 = DRUG DEPEND NOS-EPISODIC
30493 = DRUG DEPEND NOS-REMISS
30520 = CANNABIS ABUSE-UNSPEC
30521 = CANNABIS ABUSE-CONTIN
30522 = CANNABIS ABUSE-EPISODIC
30523 = CANNABIS ABUSE-IN REMISS
30530 = HALLUCINOG ABUSE-UNSPEC
30531 = HALLUCINOG ABUSE-CONTIN
30532 = HALLUCINOG ABUSE-EPISOD
30533 = HALLUCINOG ABUSE-REMISS
30540 = BARBITURATE ABUSE-UNSPEC
30541 = BARBITURATE ABUSE-CONTIN

30542 = BARBITURATE ABUSE-EPISOD
30543 = BARBITURATE ABUSE-REMISS
30550 = OPIOID ABUSE-UNSPEC
30551 = OPIOID ABUSE-CONTINUOUS
30552 = OPIOID ABUSE-EPISODIC
30553 = OPIOID ABUSE-IN REMISS
30560 = COCAINE ABUSE-UNSPEC
30561 = COCAINE ABUSE-CONTINUOUS
30562 = COCAINE ABUSE-EPISODIC
30563 = COCAINE ABUSE-IN REMISS
30570 = AMPHETAMINE ABUSE-UNSPEC
30571 = AMPHETAMINE ABUSE-CONTIN
30572 = AMPHETAMINE ABUSE-EPISOD
30573 = AMPHETAMINE ABUSE-REMISS
30580 = ANTIDEPRESS ABUSE-UNSPEC
30581 = ANTIDEPRESS ABUSE-CONTIN
30582 = ANTIDEPRESS ABUSE-EPISOD
30583 = ANTIDEPRESS ABUSE-REMISS
30590 = DRUG ABUSE NEC-UNSPEC
30591 = DRUG ABUSE NEC-CONTIN
30592 = DRUG ABUSE NEC-EPISODIC
30593 = DRUG ABUSE NEC-IN REMISS

OHIP
292 = DRUG INDUCED PSYCHOSIS
304 = DRUG DEPENDENCE, DRUG ADDICTION

Curriculum Vitae

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Oral Presentations:

Rodrigues M, Stranges S, Ryan BL & Anderson KK. Growing Burden of Disease: The prevalence of multimorbidity after a first episode of psychosis. International Multimorbidity Symposium. November 2019. London, Ontario.

Rodrigues M, Stranges S, Ryan BL & Anderson KK. Growing Burden of Disease: The prevalence of multimorbidity after a first episode of psychosis. Mental Health Research and Innovation Day. October 2019. London, Ontario.

Poster Presentations:

Rodrigues M, Wiener JC, Stranges S, Ryan BL & Anderson KK. The risk of physical multimorbidity after a first episode of psychosis: A systematic review and meta-analysis. Mental Health Research and Innovation Day. October 2019. London, Ontario.

Rodrigues M, Stranges S, Ryan BL & Anderson KK. Growing Burden of Disease: The prevalence of multimorbidity after a first episode of psychosis. Canadian Academy of Psychiatric Epidemiology (CAPE) Annual Scientific Symposium. September 2019. Quebec City, Quebec.

Rodrigues M, Wiener JC, Stranges S, Ryan BL & Anderson KK. The risk of physical multimorbidity after a first episode of psychosis: A systematic review and meta-analysis. CAPE Annual Scientific Symposium. September 2019. Quebec City, Quebec.

Rodrigues M, Wiener JC, Stranges S, Ryan BL & Anderson KK. The risk of physical multimorbidity after a first episode of psychosis: Emerging findings from a systematic review and meta-analysis. Department of Psychiatry Academic Research Day. June 2019. London, Ontario.

Rodrigues M, Wiener JC, Stranges S, Ryan BL & Anderson KK. The risk of physical multimorbidity after a first episode of psychosis: Emerging findings from a systematic review and meta-analysis. London Health Research Day. April 2019. London, Ontario.