7-27-2021 9:00 AM

Incidence of cancer and stage at diagnosis among people with recent-onset psychotic disorders

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

Abstract

Evidence on cancer incidence in people with psychotic disorders, compared to the general population, is equivocal, although those with psychotic disorders so have more advanced stage of cancer at the time of diagnosis. The objective of this thesis was to compare cancer incidence and stage at diagnosis for people with psychotic disorders, relative to the general population. Our systematic review did not observe a significant difference in overall cancer incidence among people diagnosed with psychotic disorders (RR = 1.08, 95% CI: 1.00 to 1.16), however people with psychotic disorders were more likely to be present with advanced stage cancer at diagnosis (OR = 1.22, 95% CI: 1.02 to 1.46). Our cohort study found an elevated incidence of cancer in people with non-affective psychotic disorder, relative to the general population (IRR = 1.09, 95%CI: 1.05 to 1.12). Significant heterogeneity was found by cancer site. We found significant effect modification by sex, which was removed when we excluded prostate cancer. Additionally, we identified higher odds of more advanced stage at diagnosis in people with psychotic disorders (OR = 1.23, 95% CI: 1.13, 1.34). These findings are indicative of a significant diagnostic delay and a need to increase education and targeted access to care. Future research should examine the confounding effects of lifestyle factors and anti-psychotic medication, as well as potentially intermediary effects of cardiometabolic disorders.

Keywords: cancer, psychosis, schizophrenia, psychotic disorders, stage at diagnosis

Summary for lay audience

It is unclear whether there is a higher incidence of cancer among people with psychotic disorders, as many studies have been published which have found the incidence to be higher or lower than the general population. There is evidence that people with psychotic disorders are more likely to have more advanced stage cancer at diagnosis; however, this evidence is limited by shortcomings and inconsistencies in the methodology of studies conducted on this topic. Although there have been studies on stage at diagnosis and mortality from cancer in Canada, there have been no Canadian studies to date which examine the incidence of cancer among people with psychotic disorders. The provincial health administrative data under Canada's universal healthcare system provided an opportunity to answer these questions using large, population-based data. Our objectives were to 1) examine the incidence of cancer in people with psychotic disorders and 2) compare the stage of cancer at diagnosis in people with psychotic disorders to that of the general population. Our systematic review did not find a difference in cancer incidence for people diagnosed with psychotic disorders, however people with psychotic disorders were more likely to have a more advanced stage cancer at the time they were diagnosed. Our cohort study found that people with non-affective psychotic disorders had a higher incidence of cancer compared to the general population. We also found that the incidence of certain cancers was higher and lower in people with non-affective psychotic disorders. There was a difference in the incidence of cancer among males with psychotic disorders relative to females with psychotic disorders. This difference was removed when we exclude prostate cancer from our analyses, suggesting that prostate cancer accounts for this difference that had been noted in previous studies. The differences found by cancer site are likely the product of different levels of exposure to risk factors for developing cancer among people with non-affective psychotic disorders, including smoking, cardiometabolic

disorders, antipsychotic medication, and screening behaviour. Additionally, we found that people with non-affective psychotic disorders were more likely to have a higher stage at the time they were diagnosed with cancer. This indicates a delay in the diagnosis of cancer in people with non-affective psychotic disorders. Furthermore, we found that people with non-affective psychotic disorders were more likely to have missing data on stage at diagnosis. We recommend that future studies examine the role of risk factors such as smoking, cardiometabolic disorders, and antipsychotic medication in the risk of cancer among people with psychotic disorders. It is also recommended that we implement programs which target cancer education, screening, and early diagnosis among people with psychotic disorders, which may translate into more favorable health outcomes.

Acknowledgements

I would like to thank the people that have provided me guidance and support throughout my masters:

- I would like to thank my supervisor, Dr. Kelly Anderson, for her continued support in my graduate career. You are an inspiration and I look forward to continuing to work with you during my PhD studies.
- To Drs. Phil Blanchette and Yayuan Zhu, thank you for your input and feedback on this project.
- I would also like to thank my friend Josh, who has been a very valuable mentor throughout my masters. Thanks for helping me out and being there when things got tricky in and out of school.
- I'd like to thank my family for their support and fun times when I see them
- To my friends in London, thank you for the great times and laughs over the last couple of years.
- To Hana, thank you for being you and showing me how to live life to its fullest. You motivate me to work hard and be the best I can. You make the hardest of times manageable and give me a greater reason to push through them. Thank you for listening to me ramble on about whatever project I was currently working on.

Co-Authorship statement

This integrated-manuscript thesis contains extended versions of two manuscripts which will be submitted for publication by peer-reviewed journals.

Chapter 2: Wootten J, Wiener JC, Blanchette P, Anderson KK. Cancer Incidence and Stage at Diagnosis among People with Psychotic Disorders: Systematic Review and Meta-Analysis. Being prepared for journal submission.

Jared Wootten was involved in the conception and design of the study, as well as study screening, data extraction, analysis and interpretation of data, risk of bias assessment, and writing the manuscript. Joshua C. Wiener was involved in study screening, data extraction, risk of bias assessment, and revision of the manuscript. Dr. Phil Blanchette was involved in the interpretation of data, provision of content expertise, and revision of the manuscript. Dr. Kelly K. Anderson was involved in the conception and design of the study, interpretation of data, provision of content expertise, and revision of the manuscript.

Chapter 3: Wootten J, Richard L, Blanchette P, Zhu Y, Anderson KK. Cancer incidence and stage at diagnosis among people with recent-onset psychotic disorders: A retrospective cohort study using Ontario health administrative data. Being prepared for journal submission.

Jared Wootten was involved in the conception and design of the study, analysis and interpretation of data, as well as writing the manuscript. Lucie Richard was involved in the coding, cleaning, and preparation of the dataset prior to analysis. Drs. Phil Blanchette and Yayuan Zhu were involved in

the interpretation of data, provision of content expertise, and revision of the manuscript. Dr. Kelly K. Anderson was involved in the conception and design of the study, interpretation of data, provision of content expertise, and revision of the manuscript.

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1 Introduction

1.1 Thesis overview and description

1.1.1 Thesis overview

The risk of cancer among people with psychotic disorders remains a contentious issue. Prior meta-analyses have produced equivocal results regarding whether the incidence of cancer is elevated or decreased among people diagnosed with psychotic disorders, relative to the general population.[1,2] Furthermore, there is evidence to suggest that people with psychotic disorders are more likely to be diagnosed with later stage cancer.[3]

Many theories have been proposed to explain differences in the incidence of cancer at various sites throughout the body in people with psychotic disorders. These theories have examined a number of biological, behavioural, and environmental factors influencing cancer risk.[1] For example, people with psychotic disorders are more likely to smoke, consume alcohol at higher rates, and less likely to attend regular cancer screening.[4–6] Additionally, it is hypothesized that people with psychotic disorders have a genetic factor which reduces the risk of developing cancer.[7–9]

The overall aim of this thesis was to examine the incidence of cancer and stage at diagnosis in people with psychotic disorders, compared to the general population. This chapter will present background information on psychotic disorders and the physical health of people with psychotic disorders, as well as information on factors affecting physical health among people with psychotic disorders. Chapter 2 presents the findings from a systematic review and meta-analysis of prior

evidence on the incidence of both cancer overall, as well as site-specific cancers, and compared the stage at diagnosis between people with any psychotic disorders and the general population. Chapter 3 presents the findings from a population-based retrospective cohort study comparing the incidence and stage at diagnosis of all cancers between people with non-affective psychotic disorders (NAPD) and the general population in Ontario. Finally, chapter 4 includes an integrated discussion of the findings of the two studies and future research directions.

1.2 Psychosis

1.2.1 Psychosis & psychotic disorders

Psychosis refers to a cluster of symptoms which includes delusions, hallucinations, disorganized thought or speech patterns, and erratic or unusual behaviour.[10] Those experiencing an episode of psychosis have difficulty discerning between what is reality and what is not. The cluster of disorders which feature psychotic symptoms are termed psychotic disorders,[11] although psychosis may also occur as the result of drug use, metabolic disorders, strokes, or neurodegenerative diseases, termed organic psychoses.[11] The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) characterizes schizophrenia spectrum disorder and other psychotic disorders as including positive symptoms – delusions, hallucinations, and disorganized thinking, speech and motor behaviour – as well as negative symptoms, which include flat affect and withdrawal from social relationships.[12]

Delusions refer to beliefs held by someone which are fixed despite evidence to the contrary. Delusions are seen as being either bizarre or ordinary.[12] Bizarre delusions are those which are implausible, unable to be understood by members of that person's culture, and not derived from ordinary life experiences.[12] Conversely, ordinary delusions are those which are derived from

everyday experiences and can be understood by other members of the person's culture, but are not accepted by other members of the persons culture.[12] Delusions are further categorized into persecutory, referential, grandiose, erotomania, and nihilistic delusions, referring to their content and theme.

Hallucinations are false perceptions occurring in the absence of external stimuli.[12] Hallucinations can occur in any sensory domain, whether it be visual, auditory, tactile, olfactory and others.[12] In the case of psychotic disorders, sensory hallucinations are the most common, often presenting as voices which appear as distinct from the person's own thoughts.[12]

Disorganized thoughts, speech, and behaviour are often displayed as rapidly shifting topics, difficulty concentrating, inability to follow a conversation, and difficulty performing everyday tasks, such as maintaining personal hygiene.[13]

Broadly speaking, psychotic disorders are divided into affective and non-affective psychotic disorders. Affective psychoses can be described as primarily mood disorders which also include psychotic features, occurring primarily during episodes of mania and depression in people with bipolar disorder and major depressive disorder.[14] Non-affective psychotic disorders are those which do not feature affective symptoms and include delusional disorder, schizophrenia spectrum disorder, and unspecified non-organic psychosis.

Previous iterations of the DSM viewed schizophrenia as the most characteristic psychotic disorder, with a series of sub-types. The inclusion of spectrum in 'schizophrenia spectrum disorder' in the DSM-5 characterizes schizophrenia as a disorder existing along a spectrum with other psychotic disorders.[14] Abandonment of sub-categorization of schizophrenia is justified with findings that sub-types were temporally unstable, in addition to being irrelevant to informing treatment.[15–17]

1.2.2 Physical health among people with psychotic disorders

People with psychotic disorders have higher mortality rates relative to the general population.[18–20] A meta-analysis of 34 studies found that those with psychotic disorders had a standardized mortality rate of 3.09 (95% CI: 1.9 to 5.0) compared to those without,[21] translating to a 15-year reduction in life expectancy.[22] Approximately 60% of this excess mortality is attributable to somatic comorbidities, which poses a complicating challenge in the treatment of these disorders.[23]

People with psychotic disorders are at an increased risk of developing a number of illnesses, including diabetes, gastrointestinal illnesses, cardiovascular illnesses, respiratory illnesses, and HIV. A systematic review conducted by Rodrigues *et al.* found that those diagnosed with psychotic disorders had a 69% increased risk of having two or more comorbidities and over three times the risk of having three or more comorbidities, compared to those without psychotic disorders.[24]

In particular, people with psychotic disorders are at a higher risk of cardiometabolic disorders, with 66% of people with schizophrenia or bipolar disorder suffering from at least one cardiometabolic disorder, and 39% suffering from at least two.[25] These cardiometabolic comorbidities often progress, resulting in cardiovascular disease and high risk of stroke.[26] People with schizophrenia are at a 53% higher risk of cardiovascular disease, 71% higher risk of stroke, 20% higher risk of coronary heart disease, and 81% higher risk of congestive heart failure, relative to the general population.[26] Accordingly, these conditions account for a larger proportion of mortality among people with psychotic disorders. An estimated two-thirds of people with psychotic disorders die from coronary heart disease, compared to half in the general population.[27]

Furthermore, antipsychotic have been shown to increase the risk of cardiometabolic disorders among people with psychotic disorders.[28,29]

1.2.3 Risk factors among people with psychotic disorders

The higher risk of medical comorbidities, and cardiometabolic comorbidities in particular, are a product of lifestyle, psychosocial, and environmental risk factors, in conjunction with long-term use of antipsychotic medication.

Firstly, it has been consistently documented that people with PD are more likely to be of lower socioeconomic status (SES).[30–32] Low SES is associated with increased risk of a number of conditions including cardiovascular disease, metabolic disorder, and obesity.[33–36] Furthermore, low SES itself is an important prognostic factor and is associated with higher mortality risks for cardiovascular disease and a number of cancers.[37–41]

Despite advancements in treatments, diagnostic practices, and a stability of deaths due to suicide and accidents, the longevity gap for those with schizophrenia has been widening over the past 50 years.[42] It is hypothesized that increased rates of homelessness and poverty among people with psychotic disorders is responsible for this trend.[42] De-institutionalization in the 1970s was defined by a shift in the management of psychiatric disorders from an inpatient institutional setting to a community-based care approach.[43] Although beneficial in some respects, the implementation of de-institutionalization has shifted mental health supports to inadequate and defunded social safety nets, resulting in higher rates of incarceration and homelessness.[43]

Secondly, people with psychotic disorders are more likely to be exposed to harmful lifestyle factors. People with psychotic disorders are more likely to have a sedentary lifestyle and poor eating habits.[24,44–48] Men and women with schizophrenia are more likely to consume diets

rich in saturated fats, total fats, and sodium, with higher overall caloric intake.[49,50] In combination with the low activity levels observed in people with schizophrenia, these factors contribute to higher prevalence of obesity, hypertension, and insulin resistance.[51–53] Furthermore, the risk of developing these conditions is worsened by antipsychotic medication[54] – prior research suggests that antipsychotic-naïve people with psychotic disorders already have a higher risk of diabetes and obesity, however this risk is further increased once they begin treatment with antipsychotic medication.[28] A meta-analysis found that relative to drug-naïve patients, medicated, multi-episode patients with schizophrenia had a significantly higher prevalence of hypertriglyceridemia, low HDL cholesterol, and metabolic syndrome, a pre-cursor to diabetes.[55] Antipsychotic medication increases the risk of cardiometabolic disorders, obesity, and diabetes in particular, through a number of pathways.[56,57] Antipsychotics have been shown to overstimulate appetite through antagonism of the dopaminergic, histaminergic, and serotonergic systems.[58,59] Antipsychotics also induce atherogenic dyslipidemia with increased fasting triglycerides and low serum HDL cholesterol, increasing the risk of insulin resistance.[56]

Additionally, people with psychotic disorders are more likely to suffer from comorbid alcohol and substance use disorders.[60] It is estimated that 10.4% of people who have schizophrenia spectrum disorder abuse alcohol, and 11.5% abuse other substances.[61] Alcohol has been causally implicated in many major diseases, including various cancers, diabetes mellitus, epilepsy, hypertensive heart disease, ischaemic heart disease (IHD), ischaemic and haemorrhagic stroke, conduction disorders and other dysrhythmias, lower respiratory infections, and cirrhosis of the liver.[62] Additionally, alcohol abuse is associated with a number of adverse cardiovascular outcomes, including: atrial fibrillation, myocardial infarction, and congestive heart failure.[63]

People with schizophrenia and other psychoses have long been known to smoke at much higher rates than the general population with demonstrated effects on health.[64,65] Smoking is associated with a doubling of stroke risk, and a higher risk of coronary heart disease, peripheral vascular disease, chronic lung disease, lung cancer, and bladder cancer.[66–68]

1.3 Cancer

1.3.1 Cancer and cancer staging

Cancer, also referred to as malignant tumours or neoplasms, refers to a group of diseases characterized by uncontrolled replication and proliferation of abnormal cells, caused by DNA mutations, which may spread to other tissues and harm normal tissue.[69] Metastases refers to the spread of cancerous cells through the circulatory or lymphatic system to distant tissues throughout the body.[69]

Accurate staging of cancer allows physicians to describe the extent of disease in order to inform appropriate treatment and allow comparison across cases worldwide.[70] Cancer is most commonly staged according to the TNM system developed by the American Joint Committee on Cancer (AJCC) and International Union for Cancer Control (UICC). TNM is an abbreviation of Tumour, Stage, and Metastases, representing each of the three criteria dictating the stage of a particular cancer.[70] The T category describes the tumour size and the extent to which it has spread into nearby tissues, using T1 through T4, with increasing values indicating larger size and greater spread.[70,71] The N category is used to describe the number, size, or location of nearby lymph nodes affected by the spread, using N1 through N3.[70,71] The M category indicates whether the cancer has metastasized to distant sites (M1), or not (M0).[70,71]

TNM staging can be condensed into the five-stage roman numeral staging.[71] Stage 0 indicates carcinoma in situ, i.e. abnormal cells which have not yet spread to nearby tissue.[71] Stages

I – III indicate the presence of cancer, with increasing stage corresponding to tumour size and regional spread.[71] Stage IV indicates metastases of the cancer to distant sites.[71] Tumour grading refers to the pathological determination of differentiation of tumour cells.[72] Well-differentiated tumour cells have structure and resemblance similar to normal tissue and progress more slowly, whereas undifferentiated or poorly-differentiated cells lack typical tissue structure and progress more aggressively.[72]

Cancer may be staged at different points throughout the diagnosis to treatment continuum.[73] Most commonly, clinical staging involves the staging of cancer prior to treatment, during a physical exam, imaging, or biopsy.[73] Pathological staging may be performed on the tumour excised during a surgical procedure.[73] Post-neoadjuvant therapy staging is performed prior to non-surgical treatments to assess the effectiveness of said treatment on reducing tumour size.[73] Retreatment staging is performed in the event that a cancer recurs or progresses.[73]

1.3.2 Cancer screening

Over recent decades, substantial efforts have been made in high income countries to implement screening programs for early identification of cancer and pre-cancerous lesions. Overall, these efforts have resulted in significant reductions in patient mortality, as well as improved treatment and management of cancers. However, increased screening has not provided consistent benefit for all cancer types.

As part of the Colon Cancer Check program in Ontario, participation in fecal occult blood tests increased from 7.6% to 14.8% and large bowel endoscopy increased from 3.4% to 5.7%.[74] Increased rates of colonoscopy and colorectal cancer screening were associated with reductions in colorectal cancer mortality.[75] A useful feature of colonoscopies is the ability to remove pre-cancerous adenomatous polyps during the procedure, aiding substantially in reducing colorectal

cancer mortality.[76] Dramatic increases in screening from 2000 to 2008 resulted in increases in the incidence of colorectal cancer cases, largely from increased detection of early-stage cancers.[77] More targeted efforts in cancer screening reduced colorectal cancer incidence to rates below those from the period prior to 2000.[77]

Introduction of the pap smear has allowed for screening of pre-cancerous lesions and early-stage cervical cancer.[78] Widespread pap smear use has resulted in a significant decrease in early- and late-stage cervical cancer incidence among women in Canada.[79] These changes also coincide with vaccination for HPV; however, it is estimated that somewhere between 105,000 and 492,000 cases of cervical cancer have been prevented as a result of screening.[80,81] More recently, HPV DNA testing has allowed for greater and more advanced detection of cervical cancer.[82]

From the early 1980's to the early 1990's, there was a dramatic increase in prostate cancer screening, mainly through prostate-specific antigen (PSA) testing, resulting in a 6.4% increase in incidence every year, mainly from detection of early stage prostate cancer.[83] However, this increase in screening did not result in reductions in prostate cancer mortality.[83] In Canada, the introduction of prostate specific antigen (PSA) testing resulted in dramatic increases in prostate cancer incidence from 1990 to 1993.[84] It has been found that the use of PSA, a highly sensitive test, is responsible for significant overdiagnosis of prostate cancer cases which would have never been diagnosed in the absence of the screening program, and consequently unnecessary treatment.[84,85] Similarly, these trends were accompanied by increases in radical prostatectomies.[83]

A similar situation has been found for breast cancer. Revised examinations of the results of the Canadian National Breast Cancer Screening Study found that 55% of breast cancer among women aged 40 to 49 and 16% for women aged 50 to 59.[86]

1.3.3 Cancer etiology

The development of cancer is the result of an accumulation in mutations of genes which serve to regulate cell growth and proliferation and maintain the integrity of genetic material.[87] These mutations can be inherited, happen at random, or be acquired somatically through exposure to carcinogens.[88] A number of specific genes associated with the development of many cancers, such as the BRCA genes, have been identified.[89] As an example, it is estimated that the presence of mutations at the BRCA 1/2 genes increases the lifetime risk of breast cancer in women from 12% to somewhere between 40% and 85%.[90]

The remainder of oncogenesis is caused by physical, chemical, and biologic carcinogens.[88] Physical carcinogens are defined as agents which produce cancer through physical properties and physical effects, which include radiation, temperature, mechanical trauma, and solid materials.[91] Asbestos exposure is an identified physical carcinogen which resulted in inflammation, fibrosis, and irritation of the lung tissue, ultimately causing lung cancer.[92] Because asbestos was a commonly used building material, its widespread exposure accounts for 5 to 7% of all lung cancer worldwide and 1% of mortality in developed countries.[93] Another example is the role of ultraviolet (UV) radiation in producing melanoma.[94]

Chemical carcinogens differ in that they produce cancer as a result of chemical properties and effects.[95] Most chemical carcinogens are metabolized into mutagenic electrophiles, which are in turn attracted to nucleophilic species such as DNA and protein, thereby causing damage.[95] Smoking is an identified chemical carcinogen responsible for lung, bladder, and head/neck cancers.[66,67,96,97]

A biological carcinogen is any biological substance involved in cancer development, including plants, animals, bacteria, fungi, or viruses.[98] Biological carcinogens can act directly to

induce carcinogenesis by incorporation of genome, or inducing expression of oncogenes.[98] The human papilloma virus (HPV) is a sexually transmitted infection which disrupts cytokine expression and interferes with the interferon pathway through incorporation of its genome into the host's cells, resulting in uninhibited cell growth and proliferation.[99] Biological carcinogens may also act indirectly by altering metabolizing enzymes, producing inflammation or other carcinogenic toxins.[98] Infection with H. pylori, hepatitis B virus (HBV), and hepatitis C virus stimulate the production of pro-inflammatory cytokines, thereby producing chronic inflammation and DNA damage through reactive oxygen species (ROS).[100]

1.3.4 Cancer risk factors

Exposure to carcinogenic compounds is determined by a combination of environmental exposures and lifestyle factors. Because there are innumerable lifestyle and environmental exposures that are associated with carcinogenesis, this background will not provide an exhaustive overview of these factors. Rather, we will provide some detail on a number of factors relevant to this thesis. As previously mentioned, tobacco smoke represents a significant chemical carcinogen, exposure to which may be considered either a lifestyle factor by smoking directly, or indirectly through environmental exposure.

It is estimated that diet represents 30-35% of the risk contribution to cancer.[101] Carbohydrate intake, higher glycemic index diet, insulinemia, and type II diabetes are associated with a higher risk of breast cancer.[102–105] Additionally, diets high in processed and red meat are associated with increased risk of colorectal, bladder, kidney, esophageal, and endometrial cancer.[105–108] A meta-analysis of prospective cohort studies found that for every 100g/day increase in red meat consumption, there was an associated 17% increased risk (95% CI: 1.05 to 1.31) of

colorectal cancer.[108] Dietary fibre intake has demonstrated an inverse-dose response relationship with breast and colorectal cancer risk.[109,110]

Alcohol is another chemical carcinogen associated with the development of a wide variety of cancers. An Australian cohort study of participants over 45 years old, found that increasing alcohol consumptions was associated with a significant increase in the risk of upper aerodigestive, oral, pharyngeal, esophageal, colorectal, liver, and breast cancer.[111]

Carcinogenesis occurring through environmental or occupational exposure typically occurs via indoor and outdoor air pollutants, as well as pollutants in soil and water.[112] These exposures vary significantly by socioeconomic status (SES), ethnicity, and other sociodemographic characteristics, such that cancer incidence does as well. Ecological studies of air pollution have found that lung cancer risk is elevated among those living in urban areas with exposure to higher levels of pollution, relative to people living in rural areas.[112] The European Study of Cohorts for Air Pollution Effects (ESCAPE), examining pollution levels in 17 European countries, found that particulate matter air pollution is significantly associated with lung cancer incidence.[113] Regarding SES, lower income, and racialized communities are more likely to reside near industrial facilities, exposing them to toxic and carcinogenic byproducts.[114–116] These trends are consistently demonstrated globally, with the exception of some European countries.[116] Additionally, children of parents living in more deprived areas with less education have a higher risk of environmental exposure to tobacco smoke.[117] The co-occurrence of ambient air pollution and tobacco smoke have an additive synergistic effect on lung cancer risk.[118] As such, those with lower SES and less education have a higher odds of developing lung cancer, cervical cancer, head and neck cancers, and cancers of the gastrointestinal tract.[119,120] This association between lower SES and higher

incidence of cancers persists in Canada which has a universal healthcare system, suggesting that these differences are much more deeply rooted than barriers as a result of cost.[120]

1.4 Cancer among people with psychotic disorders

Compared to other physical health issues, our understanding of the risk of cancer among people with psychotic disorders is much more unclear. In 1909, the *Report of the Commissioners in Lunacy* hypothesized that people with psychotic disorders experienced lower rates of cancer, relative to the general population.[121] Since that time, a large number of cohort studies have been conducted, producing conflicting results.[7,8,122–124] A number of meta-analyses examining cancer incidence in people with schizophrenia have examined varying subsets of the literature, differentiated by methodology and cancer sites.[1,2,125–127] These meta-analyses have produced similarly conflicting findings. There is also evidence to suggest that people with psychotic disorders are more likely to present with more advanced stage cancer at diagnosis, indicative of a diagnostic delay.[6] Prior meta-analyses have only synthesized estimates of site-specific cancer incidence for a handful of sites, failing to explore the full scope of site-specific incidence in people with psychotic disorders, relative to the general population.

1.5 Rationale and objectives

There still remains significant debate regarding whether people with psychotic disorders experience an elevated incidence of cancer compared to the general population. Furthermore, the current literature on stage-at-diagnosis of cancer among people with psychotic disorders is limited by a variety of methodological shortcomings and inconsistencies. This thesis will examine the incidence of cancer and stage and stage at diagnosis in people with psychotic disorders, relative to the general population, with two overarching objectives:

1. To review the literature regarding cancer incidence and stage at diagnosis among people with psychotic disorders (Chapter 2).
2. To examine cancer incidence and stage at diagnosis in people with psychotic disorders in Ontario using a retrospective cohort design based on health administrative data (Chapter 3).

Chapter 2

2 Cancer Incidence and Stage at Diagnosis among People with Psychotic Disorders: Systematic Review and Meta-Analysis.

2.1 Abstract

Background: A number of studies suggest a lower incidence of cancer in those with psychotic disorders compared to the general population, whereas others have found the opposite. Additionally, other research has found that people with psychotic disorders have more advanced stage cancer at diagnosis and higher cancer-specific mortality rates, suggesting disparities in access to treatment. This systematic review examined the incidence and stage at diagnosis of cancer among people with psychotic disorders, relative to the general population.

Methods: We performed an electronic search of the MEDLINE, PsycINFO, EMBASE, and CINAHL databases. Articles were included if they examined cancer incidence in people with psychotic disorders and used a non-psychotic or general population comparison group. Random-effects meta-analyses were used to examine cancer risk and stage at diagnosis in people with psychosis, relative to the general population.

Results: Thirty-nine articles were included in the review. The pooled age-adjusted risk ratio for all cancers in people with psychotic disorders was 1.08 (95% CI: 1.00 to 1.16), relative to the general population. People with psychotic disorders had 22% higher (95% CI: 2% to 46%) odds of metastases at diagnosis, compared to people without psychotic disorders.

Conclusions: Our systematic review did not observe a significant difference in overall cancer incidence among people diagnosed with psychotic disorders, however people with psychotic disorders were more likely to be present with advanced stage cancer at diagnosis. This may reflect a need for improved education and access to cancer screening and diagnosis for patients diagnosed with psychotic disorders. Future studies are encouraged to account for a wider range of confounding factors when examining cancer incidence in people with psychotic disorders.

Keywords: cancer, psychosis, schizophrenia, psychotic disorders, stage at diagnosis

2.2 Background

People who suffer from psychotic disorders, including schizophrenia spectrum disorder, have elevated rates of mortality compared to the general population,[18,19] and it is estimated that 59% of this excess mortality is attributable to concurrent medical illnesses.[128] The cause of these disparities is thought to be the product of biological mechanisms and a number of lifestyle factors – such as poor diet, smoking, drug use, and lack of exercise – as well as due to ongoing use of medications, healthcare seeking behaviour, and differential treatment within the healthcare system.[18,24] Extensive research has been done examining concurrent medical illnesses in those with psychotic disorders, definitively identifying elevated incidence of liver disease, renal disease, diabetes, congestive heart failure, and myocardial infarction.[19]

However, the incidence of cancer in people with psychotic disorders, relative to the general population, has remained an area of contention since the Report of the Commissioners of Lunacy in 1909,[121,129,130] which first reported lower rates of cancer in patients with schizophrenia. Subsequent studies examining the incidence of cancer in those with psychotic disorders have produced contrasting results. Some have suggested a lower incidence of cancer, relative to the general population,[8,122,123] whereas others have found the opposite.[7,124] Six prior meta-analyses have examined cancer incidence across various sites in people with schizophrenia.[1,2,125–127,131] A meta-analysis of multiple cancer sites, performed by Catts et

al., found no difference between the overall cancer incidence in people with schizophrenia and the general population; however, an elevated incidence of lung and breast cancer was found.[1] The elevated incidence of lung cancer was reduced after controlling for smoking prevalence. These results conflict with a similar meta-analysis, which found an slightly decreased risk of cancer overall among people with schizophrenia, as well as decreased risk of colorectal cancer, prostate cancer, and lung cancer among women with schizophrenia.[2] Other meta-analyses examining cancer incidence at specific sites have identified an increased risk of breast cancer,[1,126,131] a decreased incidence of liver cancer,[125] and no difference in lung cancer incidence for people with schizophrenia, relative to the general population.[127]

There is also evidence that people with psychotic disorders may be more likely to present with a more advanced stage of cancer at diagnoses. presence of distant metastases. A meta-analysis of stage at diagnosis and cancer-specific mortality found that those with pre-existing mental illnesses, including psychotic disorders, had a 19% higher odds (OR: 1.19, 95%CI: 1.06, 1.33) of advanced stage cancer at diagnosis, whereas people with psychotic disorders had 30% higher odds (OR: 1.30, 95%CI: 1.01, 1.68), relative to those without pre-existing mental illnesses.[6] This meta-analysis examined all mental illnesses, with psychotic disorders representing one category of disorders.

All of the previous meta-analyses of cancer incidence have exclusively focused on people with schizophrenia, and restricting inclusion criteria to specific measures of incidence, significantly reducing the scope to a subset of the available literature, regarding cancer incidence among people with psychotic disorders, largely excluding affective psychoses, such as bipolar disorder. Furthermore, prior meta-analyses have only synthesized estimates of site-specific cancer incidence for a handful of sites, failing to explore the full scope of site-specific incidence in people with psychotic disorders, relative to the general population.

The objective of this study was to perform a systematic review and meta-analysis of literature comparing the incidence of any type of cancer and stage at diagnosis among people with psychotic disorders, relative to the general population.

2.3 Methods

This systematic review was pre-registered with PROSPERO (Protocol # CRD42020179833). We followed the PRISMA reporting guidelines for systematic reviews and meta analyses, and the checklist can be found in Appendix X.[132]

2.3.1 Search Strategy and Study Selection

We conducted electronic literature searches of the MEDLINE (1966-2020), PsycINFO (1880 - 2020), and EMBASE (1947-2020) databases via Ovid, as well as the CINAHL (1937-2020) database via EBSCOhost, in May 2020. A research librarian at the University of Western Ontario was consulted regarding the search terms and selection of databases. The search terms were developed following examination of subject headings and related terms pertaining to cancer incidence, stage of cancer, and psychotic disorders in each database. The final search strategy for each database and their respective number of results can be found Appendix A2. No restrictions were placed on date of publication. Additional articles were identified via forwards and backwards citation tracing.

The articles underwent title and abstract screening by a single reviewer (JW). At this stage, articles were excluded if they were not related to physical illness among people with mental illnesses, or if there was explicit mention of study design other than case-control, cohort, or cross-sectional design. Full-text screening was done in duplicate by two reviewers (JW, JCW). Conflicts between reviewers were resolved by consensus. If consensus could not be reached, a third reviewer (KKA) was introduced as a tiebreaker.

Studies were included if they examined cancer incidence or stage at diagnosis in a sample of people with a diagnosis of any psychotic disorder (schizophrenia, schizoaffective disorder, delusional disorder, affective psychoses, psychosis NOS) using standardized diagnostic criteria, such as DSM or ICD, as well as a non-psychotic or general population comparison group. Furthermore, studies which used a cohort, case-control, or cross-sectional study design were included; those which used other study designs, including randomized control trials and descriptive studies, were excluded. Studies that included both clinical diagnoses and standardized interviews were eligible for inclusion. No restrictions were placed on the age of the sample. Studies which included people with other non-psychotic mental disorders, without providing stratum specific estimates for psychotic disorders, were excluded. Non-peer reviewed studies were excluded. No restrictions were placed on the date of publication.

2.3.2 Data Extraction

Data were extracted independently, in duplicate, by two reviewers (JW, JCW) using a pilot tested data extraction tool. Descriptive data pertaining to the following items were collected: year of publication, country, study objectives, study design, participant source, inclusion/exclusion criteria, psychiatric diagnoses of participants, age of participants, sample size, and sex breakdown. We extracted crude and adjusted estimates of the cumulative incidence of overall and site-specific cancers, as well as estimates stratified by psychiatric diagnosis. In addition, the number of people with each stage at diagnosis were extracted, where available, for people with psychotic disorders and those without.

The risk of bias for each study was assessed independently by two reviewers, using the Tool to Assess Risk of Bias in Cohort and Case-Control Studies by CLARITY.[133]

2.3.3 Data Synthesis

Data collected from included articles were summarized both qualitatively and quantitatively. Study characteristics and a summary of findings were displayed in tables. Articles which contained suitable data for quantitative synthesis were included in a random effects meta-analysis, using the Dersimonian-Laird estimator of residual heterogeneity, to produce pooled estimates of the incidence of cancer relative to the general population, as well as odds ratios for stage at diagnosis.[134] If studies did not report an age-adjusted effect measure of incidence and associated confidence intervals, or count data for stage at diagnoses, they were excluded from the quantitative synthesis.

Two meta-analyses of cancer incidence were performed on the age-adjusted effect measures, all of which were assumed to approximate an age-adjusted risk ratio.[131] To explore whether the use of varying effect measures influenced the pooled effect estimate, sensitivity analyses were performed using subgroup analyses with consistent measures. Sensitivity analyses of outlier influence on pooled estimates were conducted by identifying outliers using the *'find.outliers'* function in the *dmetar* package in RStudio, and excluding those studies from the meta-analysis. The first meta-analysis examined the relative risk of cancer at all sites in people with psychotic disorders, relative to the general population. Estimates of the incidence of site-specific cancers were excluded from this analysis. The second meta-analysis examined the incidence of site-specific cancers among people with psychotic disorders, relative to the general population.

Regarding the meta-analysis of stage at diagnosis, two-by-two tables were constructed of the number of people with stage IV or metastases at diagnosis among those with psychotic disorders and those without. These tables were used to produce odds ratios of metastases at diagnosis among those with psychotic disorders relative to those without.

Results of these meta-analyses were displayed in a forest plot stratified by psychotic disorder diagnosis, as previous studies have identified differences in incidence by psychiatric diagnosis.[135,136] Sub-group differences by psychotic disorder diagnosis were examined using a Q-test. Heterogeneity in each meta-analysis was assessed using an I^2 statistic. An I^2 statistic of 25%, 50%, or 75% indicates low, moderate, and high levels of heterogeneity, respectively.[137] Publication bias was assessed by visual assessment of funnel plots, in addition to an Egger's test of asymmetry.[138]

All meta-analyses were conducted in Rstudio v1.2.5033,[139] using the *metafor* package,[134] and findings are presented as risk ratios (RR) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

2.4 Results

2.4.1 Search results

An outline of exclusions at each step of the screening process can be found in Figure 1. The electronic literature search initially returned 848 unique citations, and an additional five articles were identified from forwards and backwards reference searching. Of these, 729 were deemed ineligible upon review of title and abstract.

We screened the full-text of 120 articles, and 81 were excluded for the following reasons: did not report data on incidence or stage at diagnosis (n=44); not a case-control, cross-sectional study, or cohort study (n=14); sample did not include people with psychotic disorders, or did not differentiate people with psychotic disorders from other mental illnesses (n=16); did not have a comparison group or the comparison group included people with other mental illnesses (n=2); or no full-text version was published or available (n=3). Forty articles were deemed eligible for inclusion in the review.

There were a number of studies which met a majority of the inclusion criteria, but were excluded due to the absense of a single criterion. A Danish cohort study examining colon cancer in patients with serious mental illnesses was excluded because the authors did not distinguish between those with psychotic disorders and those with other psychiatric illnesses.[140] Similarly, a study examining antipsychotic use on gastric cancer risk was excluded on the basis that the provided odds ratios of developing cancer were not, in fact, measures of cancer incidence as stated in the inclusion criteria.[141]

2.4.2 Study Characteristics

The characteristics of included studies can be found in Table 2.1, and a comprehensive summary of findings table can be found in Appendix B1. Thirty studies examined incidence of cancer, eight examined stage at diagnosis, and one study included information on both incidence and stage at diagnosis. Thirty-eight of the included studies were retrospective cohort studies of health administrative data, and one was a case-control study using a clinical sample. As such, the majority of studies ascertained the outcome of cancer via linkage to a cancer registry, with a median follow-up period of 15.5 years (IQR: 10.0 to 26.3).

Thirty-five studies included people with schizophrenia in their sample, twelve included people with schizoaffective disorders, thirteen included people with affective psychoses, and four included people with psychosis NOS. Two studies did not specify which psychotic disorders were included.

In terms of the comparison group, twenty-four studies used a general population comparison group, whereas fifteen studies used a sample of people without psychotic disorders selected from a list of patients or people eligible for a benefits program, three of which were matched on age, sex, and other covariates.

All studies that reported measures of incidence adjusted for confounding factors in their estimates of incidence, with six additionally reporting crude measures. The confounding factors that were adjusted for in each estimate can be found in the extended summary of findings table in Appendix A3.

2.4.3 Risk of Bias

The complete findings of the risk of bias assessment can be found in appendix A3, and a summary of those findings is displayed in Figure 2.2. The most common issues identified across included studies were the inability to ensure that the outcome of interest was not present at the beginning of each study, assessment of exposure, inclusion of important confounding factors, and missing data. Seventy-four per cent of studies presented an intermediate risk of bias for assessment of exposure, with a significant portion of remaining studies missing information on this item (12.8%). Regarding the inclusion of important confounding factors, 66.7% of studies presented intermediate risk of bias and 28% presented a high risk of bias. Only 51% of studies had a low risk of bias for ensuring that cancer was absent at the start of the study. A large portion of studies (49%) did not report the extent of missing data. As most studies used health administrative data, the assessment of outcome and measurement of confounding factors were found to have a low risk of bias in the majority of studies.

2.4.4 Meta-Analyses

A total of eight studies were excluded from the quantitative synthesis for the following reasons: articles did not report data for a meta-analysis (n = 5) or reported sources of data that were duplicate of another study included in the review (n = 3). Thirty-one studies remained with suitable data for meta-analysis, with twenty-four studies reporting incidence estimates, six reporting stage at diagnosis, and one reporting both. Sixteen studies reported standardized incidence ratios (SIR), five reported incidence rate ratios (IRR), three reported hazards ratios (HR), and three reported standardized risk ratios (RR). For studies included in the meta-analysis that reported data on stage at diagnosis (n = 7), five included those diagnosed at stages I through IV, while the remainder only reported the proportion of patients with local

vs. metastasized cancers. Two studies produced adjusted odds ratios using logistic regression: one adjusting for age, gender, comorbidities, income, and type of cancer, while the other adjusted for age and gender.

2.4.4.1 *Overall Cancer Incidence*

The results of the meta-analysis of cancer risk are displayed in Figure 2.5. The overall pooled estimate of age-adjusted risk ratio of cancer in people diagnosed with psychotic disorders, relative to the general population, was 1.08 (95% CI: 1.00, 1.16). This suggests that the age-adjusted incidence of cancer among people with psychotic disorders was slightly elevated, relative to the general population, although the 95% CI includes the possibility of a null effect. A very high level of heterogeneity was found across age-adjusted measures of cancer risk (I^2 = 95.7%, tau^2 = 0.05). Seven estimates were considered outliers, and removal of these produced a pooled estimate of 1.05 (95% CI: 1.02 to 1.10), as well as substantially reduced statistical heterogeneity (I^2 = 70.1%; tau^2 = 0.006).

Evaluation of the funnel plot displayed in Appendix 2F did not suggest publication bias, and Egger's test of asymmetry indicated that there was insufficient evidence to suggest asymmetry in the funnel plot (z = 0.4169, p = 0.6768)

Based on the available information provided by the studies, sub-group analyses were conducted according to affective psychotic disorders, non-affective psychotic disorders, and samples which included a mix of affective and non-affective psychotic disorders. A Q-test revealed no statistically significant difference in cancer incidence between psychotic disorders (Q_M = 9.23, df = 4, p = 0.06).

2.4.4.2 *Site-Specific Cancer Incidence*

We were able to produce site-specific estimates of cancer risk for twenty-six cancer types (Figure 2.6). Elevated risk ratios were found for cancer of the brain (RR: 1.41, 95%CI: 1.07, 1.75), breast (RR: 1.22, 95%CI: 1.02, 1.43), nasopharynx (RR: 1.18, 95%CI: 1.02, 1.34), cervix uteri (RR:1.33, 95%CI: 1.15, 1.51), and corpus uteri (RR:1.71, 95%CI: 1.17, 2.25). Lower risk ratios were found for cancers of the colon and rectum (RR: 0.87, 95%CI: 0.80, 0.95), prostate (RR:0.54, 95%CI: 0.47, 0.62), and skin (RR: 0.72, 95%CI: 0.63, 0.81).

2.4.4.3 Stage at Diagnosis

The results of the meta-analysis of stage at diagnosis are displayed in Figure 2.7. The pooled estimate of the odds ratio of metastases at diagnosis for people with psychotic disorders, relative to the general population, was 1.22 (95% CI: 1.02 to 1.46). A very high level of heterogeneity was found (I^2 = 96%, tau^2 = 0.05). Three estimates were considered outliers, and removal of these produced a pooled OR of 1.12 (95% CI: 1.00 to 1.25), as well as reduced statistical heterogeneity (I^2 = 85.20%; tau^2 = 0.009). However, these pooled analyses include a small number of heterogenous studies.

Evaluation of the funnel plot displayed in Appendix 2G did not reveal any evidence of publication bias. Egger's test of asymmetry indicated that there was insufficient evidence to suggest asymmetry in the funnel plot (z = 1.4635, p = 0.1433). However, the power of the egger's test to detect publication bias may have been limited by the number of studies.[138]

2.5 Discussion

This meta-analysis did not find a significant difference in overall cancer risk for those with psychotic disorders, relative to the general population. Prior meta-analyses of overall cancer incidence in

people with psychotic disorders have focused on people with schizophrenia. One such meta-analysis found an decreased risk of cancer (SIR = 0.90, 95% CI: 0.81 to 0.99),[2] whereas another found no difference (SIR = 1.05, CI 0.95 to 1.15).[1] The current systematic review and meta-analysis builds on this prior evidence by examining cancer incidence as well as stage at diagnosis in people with other psychotic disorders, in addition to schizophrenia, by including a broader range of estimates of incidence as well as data on stage at diagnosis.

It was first hypothesized that people with psychotic disorders had a lower incidence of cancer, relative to those without psychotic disorder,[121] and since that time a wide range of theories to explain this phenomenon have been proposed. Three studies compared cancer incidence among people with schizophrenia to both relatives without schizophrenia and to the general population.[7–9] Relatives of people with schizophrenia were found to have a lower incidence of cancer, relative to the general population. The authors of these studies hypothesized that there may be shared genetic factors that are associated with schizophrenia and a lower risk for developing cancer.

Other studies have examined dopamine, and its role in the regulation of cell proliferation, as an important factor affecting cancer risk in people with psychotic disorders.[142,143] Indeed, the effects of dopamine antagonists, including antipsychotics and anti-emetics, have been explored through a number of models, with effects on cancer risk largely heterogeneous by cancer site. Both in vitro and rodent models have demonstrated largely anti-cancer effects via a number of pathways, with the exception of breast and liver cancer in females, where dopamine antagonists were found to increase risk.[144] However, the evidence for a causal relationship between antipsychotic exposure and cancer is not proven.[145]

The effect of dopamine antagonists on breast cancer has been examined in epidemiological studies, wherein exposure to dopamine antagonists is significantly associated with an increased risk of breast and endometrial cancer.[146–148] Although the mechanism of action is unclear, it is also thought that

antipsychotic medication may increase levels of prolactin, which is associated with breast carcinogenesis.[145,149] A number of included studies identified an elevated risk of sex-specific cancers among females with schizophrenia, namely cancer of the breast, uterus, and cervix.[8,136,150–154] One such study found the risk of all cancers to be higher among females with schizophrenia, relative to the general population, but not among males with schizophrenia.[155] This difference was eliminated when female-specific cancers were excluded from the analysis.[155] Our meta-analysis found the risk of breast, cervical, and uterine cancer to be significantly elevated among females with psychotic disorders, which is consistent with the findings of prior meta-analyses of breast cancer in people with schizophrenia.[1,126,131] To our knowledge, there are no prior meta-analyses of the risk of cervical and uterine cancer among women with psychotic disorders.

Antipsychotic medication has also been associated with a reduced risk of prostate and colorectal cancer.[156] A cohort study published in 1992 identified a significantly lower incidence of prostate cancer among males with schizophrenia who were prescribed large doses of phenothiazines.[157] It is hypothesized that elevated prolactin levels suppress testosterone levels, an important factor in prostatic tumour growth.[158] Regarding colorectal cancer, antipsychotic medication has been found to exert anti-oncogenic effects in vitro via downregulation of fibroblast growth factor receptors in colorectal cancer cells.[159] In the current review, people with psychotic disorders were found to have a significantly reduced risk of both prostate and colorectal cancers.

Other health and behavioral factors, such as cardiometabolic disorders and smoking, might have a bigger influence on cancer risk.[145] People with psychotic disorders have a higher risk of developing cardiometabolic disorders such as cardiovascular disease, diabetes, and obesity. This is largely a result of sedentary lifestyle and poor eating habits, the effects of which are exacerbated by exposure to anti-psychotic medication.[24,44–48]

Diabetes and obesity are established risk factors for a variety of cancers, including breast and colorectal cancer.[104,105] However, diabetes is negatively associated with prostate cancer risk and PSA score as a result of reduced insulin response and lower levels of testosterone.[160–162]

Additionally, people with schizophrenia have been found to smoke at much higher rates compared to the general population.[163] Although the association between smoking and both lung and bladder cancer is well established and thoroughly documented,[66,67] this meta-analysis did not find a significantly elevated risk of lung or bladder cancer among people with psychotic disorders, which is similar to previous meta-analyses.[1,2,127] However, one prior meta-analysis found an elevated risk of lung cancer among people with schizophrenia, which was attenuated when estimates were adjusted for smoking behaviour.[1]

Screening uptake represents another factor which may influence both observed cancer incidence as well as stage at diagnosis among people with psychotic disorders. Women with psychotic disorders have significantly lower odds of receiving cervical and breast cancer screening, compared to women without psychotic disorders.[164–167] However, prior meta-analyses have challenged the hypothesis that the lower incidence of particular cancers in people with psychotic disorders are the result of delayed detection, citing post-mortem data which found that undiagnosed cancer was a rare event.[1] This review further suggested that the aggressive nature of lung and bladder cancer, along with the rapid course of these cancers, makes it very unlikely that there would be diagnostic delay for people with psychotic disorders.[1] While it is accurate that cancer is unlikely to go entirely undetected, this does not preclude the existence of a diagnostic delay. Furthermore, the more advanced stage at diagnosis in this population is in and of itself indicative of this delay. Furthermore, this diagnostic delay has been shown to account for a portion of the difference in cancer mortality between people with psychotic disorders and those without.[168] Our review identified a significantly elevated odds of metastases at diagnosis for people with psychotic

disorders. Although we do not have data on stage at diagnosis for site-specific cancers, this does suggest a more advanced cancer at diagnosis, possibly indicative of delays in detection and diagnosis.

Interestingly, two studies examined the effect of age on the relationship between psychotic disorders and cancer incidence. Both studies found a higher risk of cancer among people with psychotic disorders that was more pronounced in the younger age categories (20-39 and 20-29).[155,169]

Finally, numerous studies have identified elevated mortality rates in people with psychotic disorders following cancer diagnoses, relative to people without psychotic disorders.[170–176] A degree of this elevated mortality is likely attributable to differences in treatment access and quality of care, and exacerbated by other medical comorbidities.[174,175,177] However, no studies to date have examined cancer incidence, stage at diagnosis, and mortality within the same cohort.

2.5.1 Limitations of Included Studies

The risk of bias assessment identified several limitations to the studies included in this review, such as issues regarding ensuring that cancer was not present at the start of each study, selection bias, and inclusion of important confounding factors. For several included studies, there was no clear lookback window or similar methods to exclude prevalent cases of cancer prior to the start of the study. Therefore, it could not be ensured that studies were including incident cases of cancer, rather than prevalent or recurrent cancer cases.

Most included studies used population-based health administrative data, however a number of databases only included individuals eligible for a specific health insurance program and often only represented a particular subset of the population, such as those with disability benefits or lower income – as such, they are likely of lower socioeconomic status. Conversely, a number of studies included data from private health insurance programs, which would include people who are likely employed and of higher

socioeconomic status in countries. Therefore, the sampled populations are substantially heterogenous across the included studies. Furthermore, included studies variably reported case definitions, limiting the ability to assess the validity of these case definitions.

A majority of studies included in this review did not adequately control for important confounding factors, either through matching or multivariable regression models, and many studies relied on indirect standardization to control for age and sex. The etiology of cancer is complex, and consideration of a wide range of environmental, lifestyle, and biological factors is important when evaluating cancer risk in any population.

Additionally, a large proportion of studies did not report the extent of missing data within their samples. Therefore, we are unable to account for how this may have influenced the results of individual studies regarding incidence or stage at diagnosis.

Finally, our meta-analysis found evidence of a lower risk of skin cancer among people with psychotic disorders. However, it should be noted that included studies had varying definitions of skin cancer, with one study excluding non-melanoma skin cancer.[178] Therefore, pooled estimates of skin cancer risk may be unreliable. Additionally, some studies reported estimates of site-specific cancers with a small number of outcome events, thereby creating extremely wide confidence intervals, often extending down to zero.

2.5.2 Limitations of the Review

The findings of this review must be considered in light of its limitations. Firstly, the literature search did not include grey literature or other unpublished studies, thereby excluding a body of potentially relevant research and potentially introducing publication bias. Secondly, a high degree of statistical heterogeneity was found in each of our meta-analyses. This is likely the result of the wide range of studies

included in the meta-analysis. All effect measures of cancer risk which adjusted for age, at a minimum, were assumed to approximate an age-adjusted risk ratio. Although this decision was made in order to analyze a broader range of studies with varying methodology, this likely contributed to the observed heterogeneity. A majority of the studies adjusted for age and sex, however a smaller number of studies accounted for other confounding variables, so the estimates included in the meta-analysis have varying amounts of residual confounding. Lastly, the power of the Egger's test to detect publication bias across studies reporting stage at diagnosis was limited by the smaller number of studies available for meta-analysis.[138] Therefore, it is unclear whether publication bias was present in our examination of stage at diagnosis.

2.6 Conclusions

This systematic review and meta-analysis identified no significant difference in overall cancer risk among people with psychotic disorders; however, differences were found for specific cancer sites. These differences are likely the products of antipsychotic medication exposure, environmental factors, and biological factors—the effects of which need to be further investigated. People with psychotic disorders have higher odds of metastases at diagnosis compared to people without psychotic disorders, suggesting delayed detection and diagnosis. These disparities in access of treatment may be contributing to higher mortality among patients with psychotic disorders.[164,167,179–181] Programs which target cancer education, screening, and early diagnosis among individuals with psychotic disorders may translate into better health outcomes.

As informed by the findings of this review, there are a number of suggestions for future research conducted in this area. Firstly, it is suggested that future research consider additional confounders, such as obesity and related cardiometabolic comorbidities, in the relationship between psychotic disorder

diagnoses and cancer risk. Secondly, we suggest that future research explore age and gender-related differences in cancer incidence among people with psychotic disorders in order to understand how these variables may modify this relationship. Lastly, it is suggested that future research aim to better elucidate the interrelationships between incidence, stage at diagnosis, and treatment with mortality among people with psychotic disorders.

2.7 Acknowledgements

This work is supported by a grant from the Canadian Institutes of Health Research (PJT 153022) and by an Early Researcher Award from the Ontario Ministry of Research, Innovation, and Science.

2.8 Competing Interests

The authors have no competing interests to declare.

2.9 Supplementary material

Additional information and data can be found in the appendices.

2.10 Tables and Figures

Table 2.1: Comparison of current meta-analysis with similar meta-analyses

	Current meta-analysis	Catts et al., 2008	Li et al., 2018
Exposure of interest	Diagnosis with psychotic disorders (affective and non-affective)	Diagnosis with schizophrenia, and relatives of people diagnosed with schizophrenia	Diagnosis with schizophrenia
Outcome of interest	• Overall cancer incidence (age-adjusted) • Site-specific cancer incidence (age-adjusted) • Stage at diagnosis	• Overall cancer incidence • Site-specific cancer incidence for 6 common sites	• Overall cancer incidence • Site-specific cancer incidence for 6 common sites
Measures analyzed	Multiple measures of incidence	Standardized incidence ratio (SIR)	Multiple measures of incidence

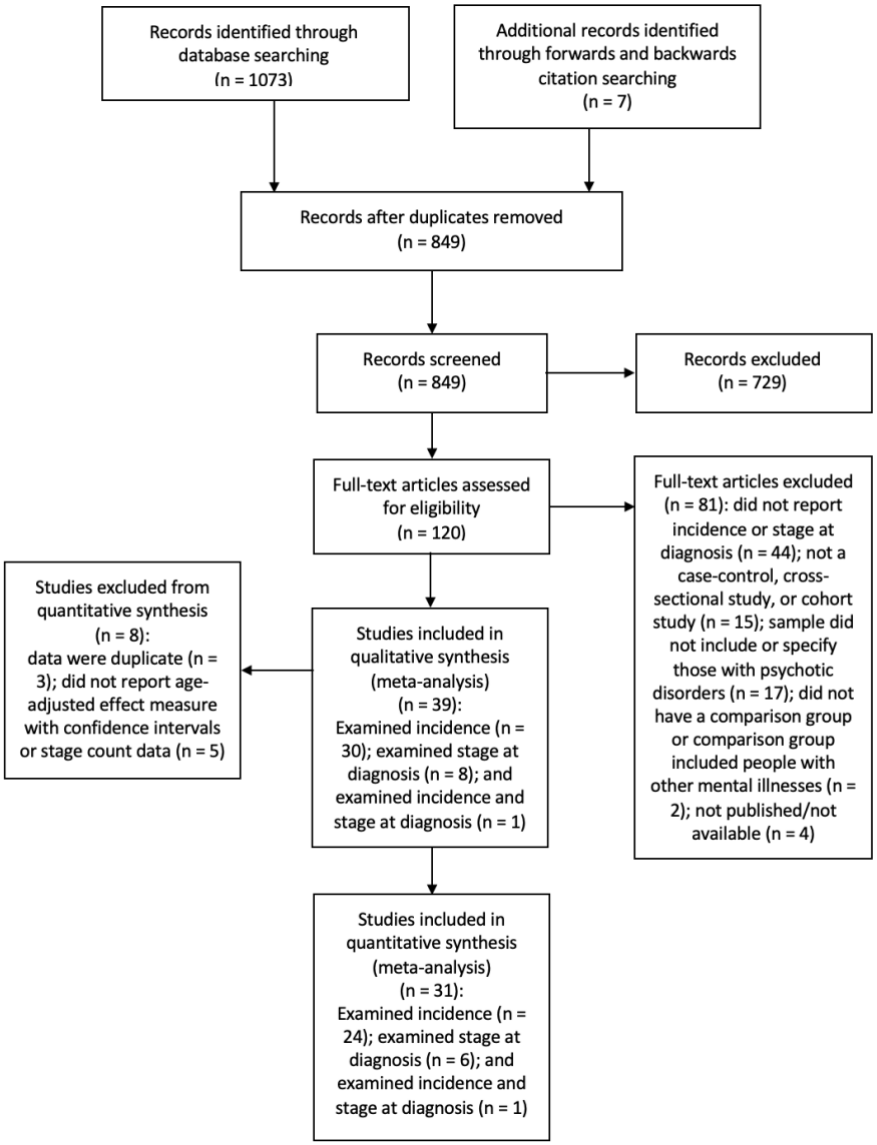

Figure 2.1: PRISMA flowchart

Table 2.2: Characteristics of studies included in qualitative synthesis

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Ahlgrén-Rimpiläinen et al., 2020[182]	Finland	A	non-affective psychotic disorders	S	breast	Retrospective cohort	1969 - 2013	78,079	Finnish Cancer Registry	without psychotic disorders
Arffman et al., 2019[176]	Finland	A	non-affective psychotic disorders	S	lung	Retrospective cohort	1990 - 2013	34,572	Finnish Cancer Registry	without psychotic disorders
Baillargeon et al., 2011[172]	USA	A	unspecified	S	colon	Retrospective cohort	1993 - 2005	63,547	Surveillance, Epidemiology, and End Results Program	without psychotic disorders
Barak et al., 2005[123]	Israel	A	schizophrenia, bipolar	I	all cancer	Retrospective cohort	1993 - 2003	3,226	Inpatients at Abarbanel Mental Health Center	general population
Barak et al., 2008[154]	Israel	A	schizophrenia	I	all cancer	Retrospective cohort	1960 - 2005	2,011	Inpatients at Abarbanel	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
									Mental Health Center	
Bergamo et al., 2014[183]	USA	A	schizophrenia	S	all cancer	Retrospective cohort	1992 - 2009	96,702	Surveillance, Epidemiology, and End Results Program	without psychotic disorders
Brink et al., 2019[184]	Denmark	A	schizophrenia	I	all cancer	Retrospective cohort	1980 - 2012	27,141	Danish National Patient Register	without psychotic disorders
Chang et al., 2013[173]	UK	A	schizophrenia, bipolar disorder, schizoaffective disorder	S	all cancer	Retrospective cohort	1999 - 2008	28,477	Clinical Record Interactive System (CRS) at South London and Maudsley (SLAM) and Biomedical Research Centre (BRC)	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Chen et al., 2018[153]	Taiwan	A	schizophrenia	I	all cancer	Retrospective cohort	2000 - 2010	32,731	Psychiatric Inpatient Medical Claims Database	general population
Chou et al., 2011[171]	Taiwan	A	schizophrenia	I	all cancer	Retrospective cohort	2000 - 2008	237,413	National Health Insurance Research Database	general population
Chou et al., 2017[185]	Taiwan	A	schizophrenia	I	breast	Retrospective cohort	1998 - 2008	21,454	National Health Insurance Research Database (NHIRD)	without psychotic disorders
Cunningham et al., 2015[175]	New Zealand	A	schizophrenia, bipolar disorder, schizoaffective disorder	S	all cancer	Retrospective cohort	2006 - 2010	8,434	New Zealand Ministry of Health	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Dalton et al., 2005[152]	Denmark	A	schizophrenia	I	all cancer	Retrospective cohort	1969 - 1995	22,766	Danish Psychiatric Central Register	general population
Dalton et al., 2008[186]	Denmark	A	schizophrenia and other psychoses	I	lung	Retrospective cohort	1994 - 2003	3,218,440	Danish Civil Registration System	general population
Dalton et al., 2008[187]	Denmark	A	schizophrenia and other psychoses	I	all cancer	Retrospective cohort	1994 - 2003	3,218,440	Danish Civil Registration System	general population
Goldacre et al., 2005[188]	UK	A	schizophrenia	I	all cancer	Retrospective cohort	1963 - 1999	9,649	National Health Service Hospitals Database	general population
Grinshpoon et al., 2005[151]	Israel	A	schizophrenia	I	all cancer	Retrospective cohort	1962 - 2001	33,372	Israeli Psychiatric Case Register	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Hippisley-Cox et al., 2007[189]	UK	A	schizophrenia, bipolar	I	breast, colon, rectal, gastroesophageal, prostate, and respiratory	Retrospective cohort	1995 - 2005	4,040,494	QRESEARCH database	without psychotic disorders
Ishikawa et al., 2016[170]	Japan	A	schizophrenia	S	gastric, colorectal	Retrospective cohort	2010 - 2013	12,475	Japanese Diagnosis Procedure Combination database	without psychotic disorders
Ji et al., 2013[8]	Sweden	A	schizophrenia	I	all cancer	Retrospective cohort	1965 - 2008	59,233	Swedish Hospital Discharge Register	general population
Kisley et al., 2013[174]	Australia	A	schizophrenia, affective psychosis,	I	all cancer	Retrospective cohort	1988 - 2007	135,451	Western Australia Data Linkage System	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
			other psychoses							
Kisley et al., 2016[135]	Australia	A	schizophrenia, affective psychosis, other psychoses	I	all cancer	Retrospective cohort	2002 - 2007	93,271	Queensland Hospital Admitted Patients' Data Collection	general population
Lawrence et al., 2000[177]	Australia	A	schizophrenia, affective psychosis, other psychoses	I	all cancer	Retrospective cohort	1982 - 1995	172,932	Western Australia Data Linkage System	general population
Levav et al., 2007[9]	Israel	A	schizophrenia	I	all cancer	Retrospective cohort	1960 - 2003	6,132	Israeli Psychiatric Case Register	general population
Levav et al., 2009[190]	Israel	A	schizoaffective	I	all cancer	Retrospective cohort	1980 - 2005	2,400	Israeli Psychiatric Case Register	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Liao et al., 2015[169]	Taiwan	A	schizophrenia	I	liver	Retrospective cohort	1998 - 2010	11,965	National Health Insurance Research Database	without psychotic disorders
Lichtermann et al., 2001[7]	Finland	A	schizophrenia, schizoaffective disorder	I	all cancer	Retrospective cohort	1969 - 1996	26,996	National Hospital Discharge Register, National Disability Pension Register	general population
Lin et al., 2013[155]	Taiwan	A	schizophrenia	I	all cancer	Retrospective cohort	1995 - 2007	102,202	National Health Insurance Research Database	general population
Lin et al., 2013[136]	Taiwan	A	schizophrenia, bipolar	I	all cancer	Retrospective cohort	1995 - 2009	91,884	National Health Insurance	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
									Research Database	
Manderbacka et al., 2017[191]	Finland	A	unspecified	S	all cancer	Retrospective cohort	1990 - 2013	600,052	Finnish Cancer Registry	without psychotic disorders
McGinty et al., 2012[178]	USA	A	schizophrenia, bipolar	I	all except non-melanoma skin cancer	Retrospective cohort	1996 - 2004	3,317	Maryland Medicaid Program	general population
Mortensen et al., 1989[192]	Denmark	A	schizophrenia	I	all cancer	Retrospective cohort	1957 - 1984	6,152	Inpatients at Danish psychiatric hospitals	general population
Mortensen, 1994[193]	Denmark	A	schizophrenia	I	all cancer	Retrospective cohort	1970 - 1988	9,156	Danish Psychiatric Case Register	general population
Osborn et al., 2013[194]	UK	A	schizophrenia, schizoaffective, bipolar,	I	all cancer	Retrospective cohort	1990 - 2008	136,784	The Health Improvement	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
			affective psychosis, brief psychoses, psychoses NOS						Network Database	
Pettersson et al., 2020[150]	Sweden	A	schizophrenia	I	all cancer	Retrospective cohort	1990 - 2013	111,306	National Patient Register	general population
Raviv et al., 2014[195]	Israel	A	schizophrenia	I	all cancer	Retrospective cohort	1990 - 2011	4,326	Inpatients at Abarbanel Mental Health Center	general population
Scheflen, 1951[196]	USA	C	schizophrenia, bipolar, affective psychosis, non-organic psychosis	I	lung	Case-control	1928 - 1942	NR	Inpatients at Worcester State Hospital	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Toender et al., 2018[168]	Denmark	A	schizophrenia, bipolar disorder, schizoaffective disorder	I, S	all cancer	Retrospective cohort	1978 - 2012	579,039	Danish Civil Registration System	without psychotic disorders
Truyers et al., 2011[197]	Belgium	A	schizophrenia, affective psychosis, other psychoses	I	all cancer	Retrospective cohort	1997 - 2007	4,904	Integro (general practice registration network)	without psychotic disorders

A = Administrative, C = Clinical, I = incidence, S = stage at diagnosis

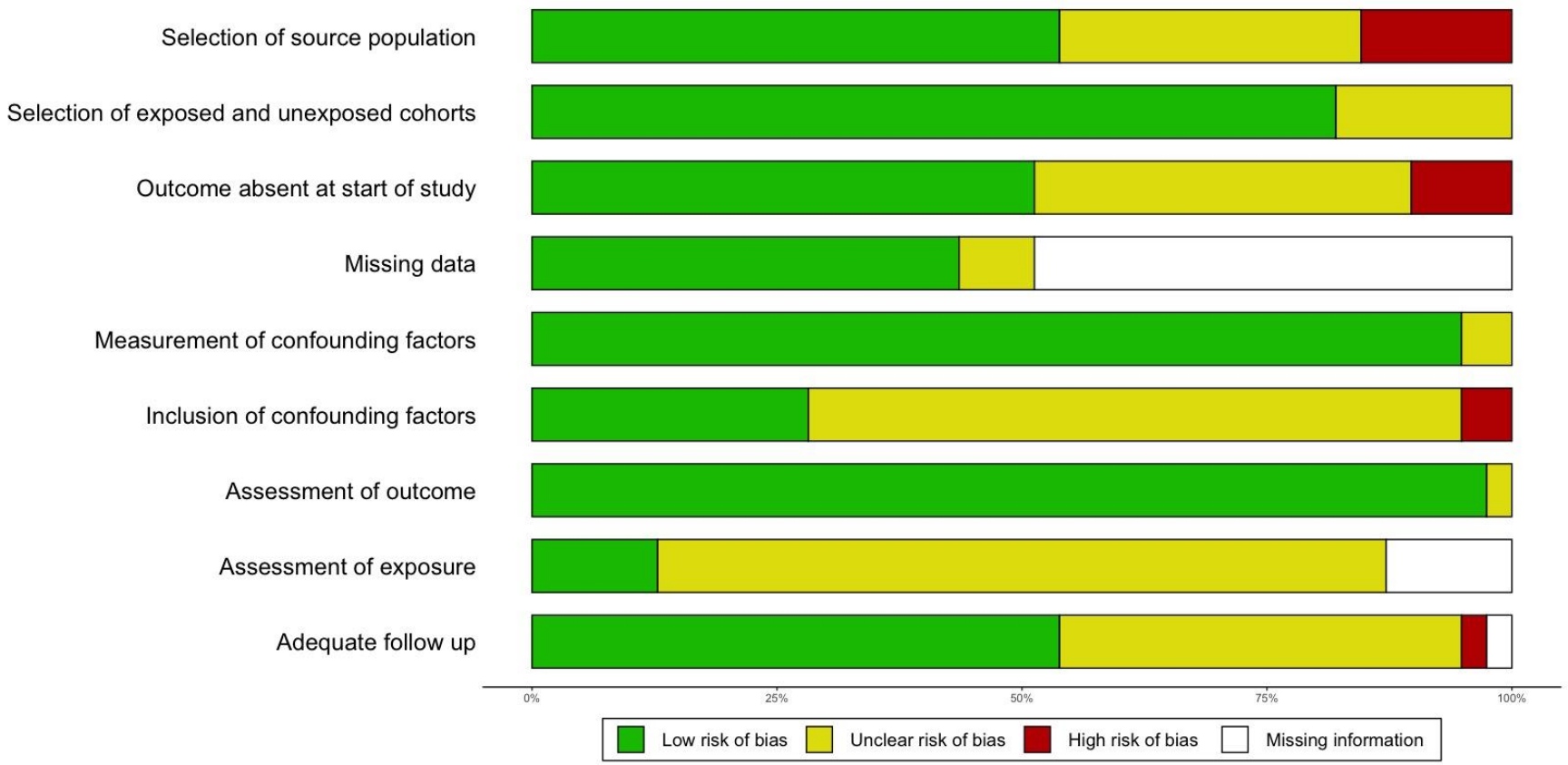

Figure 2.2: Risk of bias assessment summary

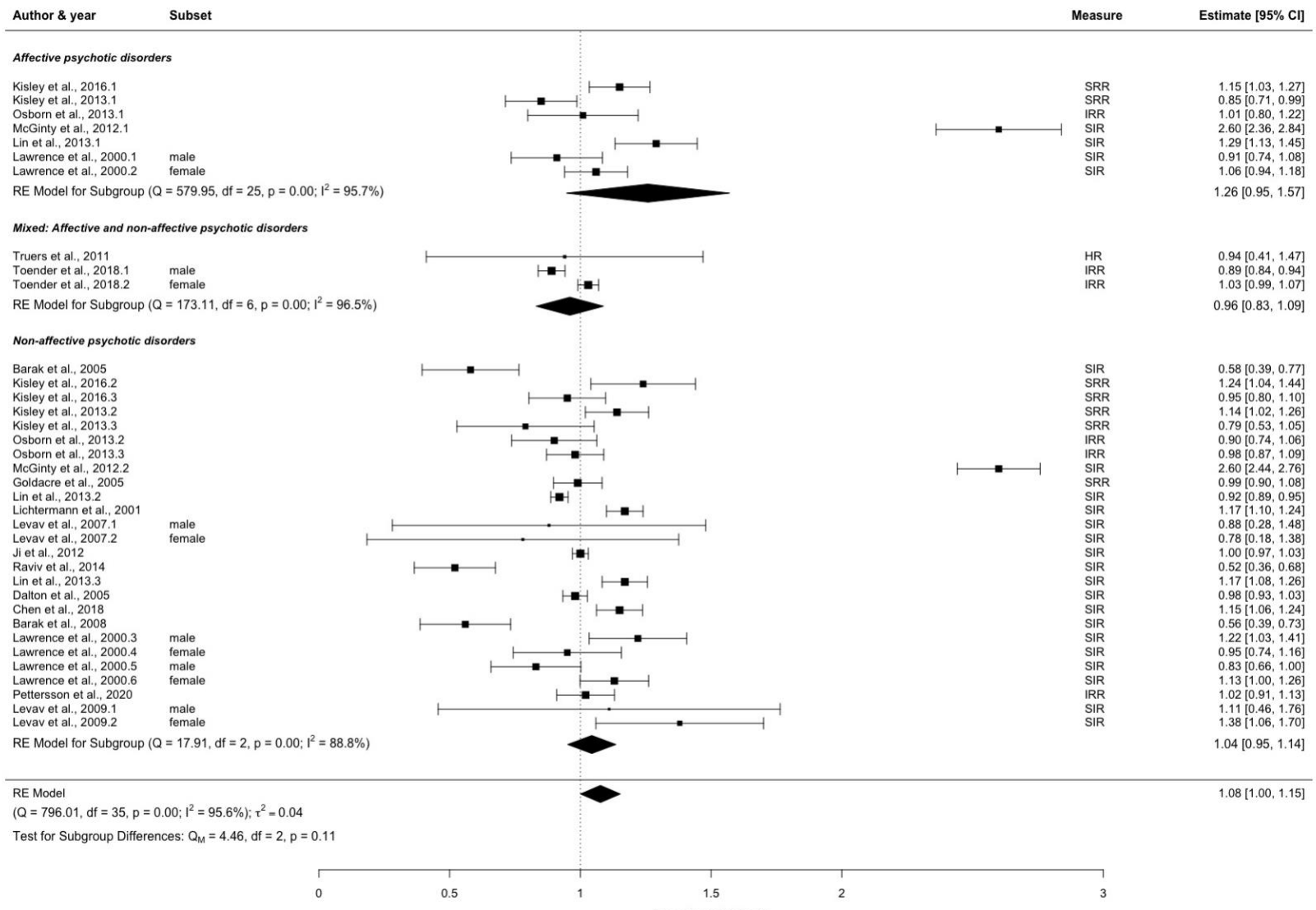

Figure 2.3: Forest plot of meta-analysis of age-adjusted incidence of cancer in people with psychotic disorders, relative to the general population, sub-grouped by psychiatric diagnosis

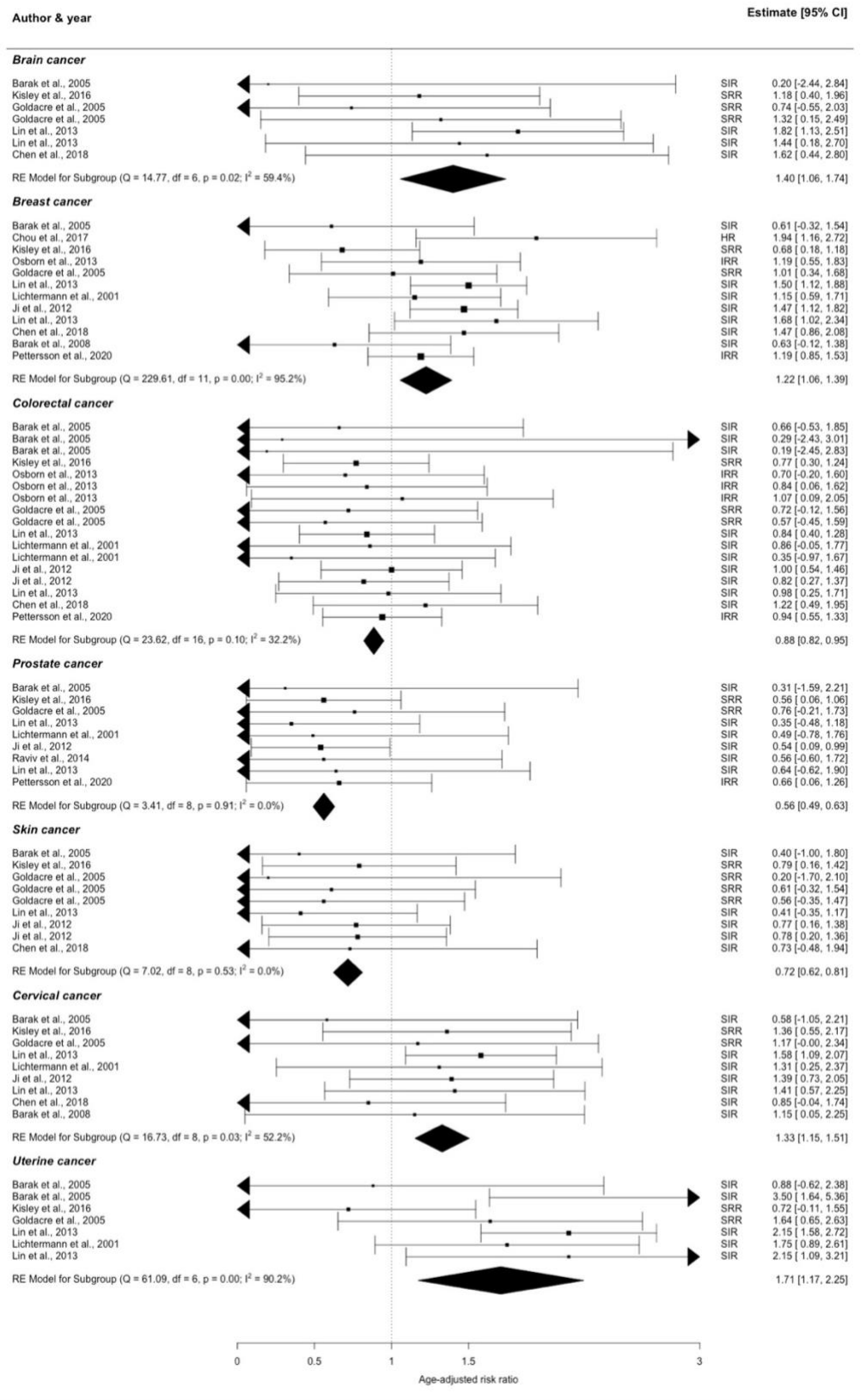

Figure 2.4: Forest plot of site-specific cancer incidence in people with PD, relative to the general population

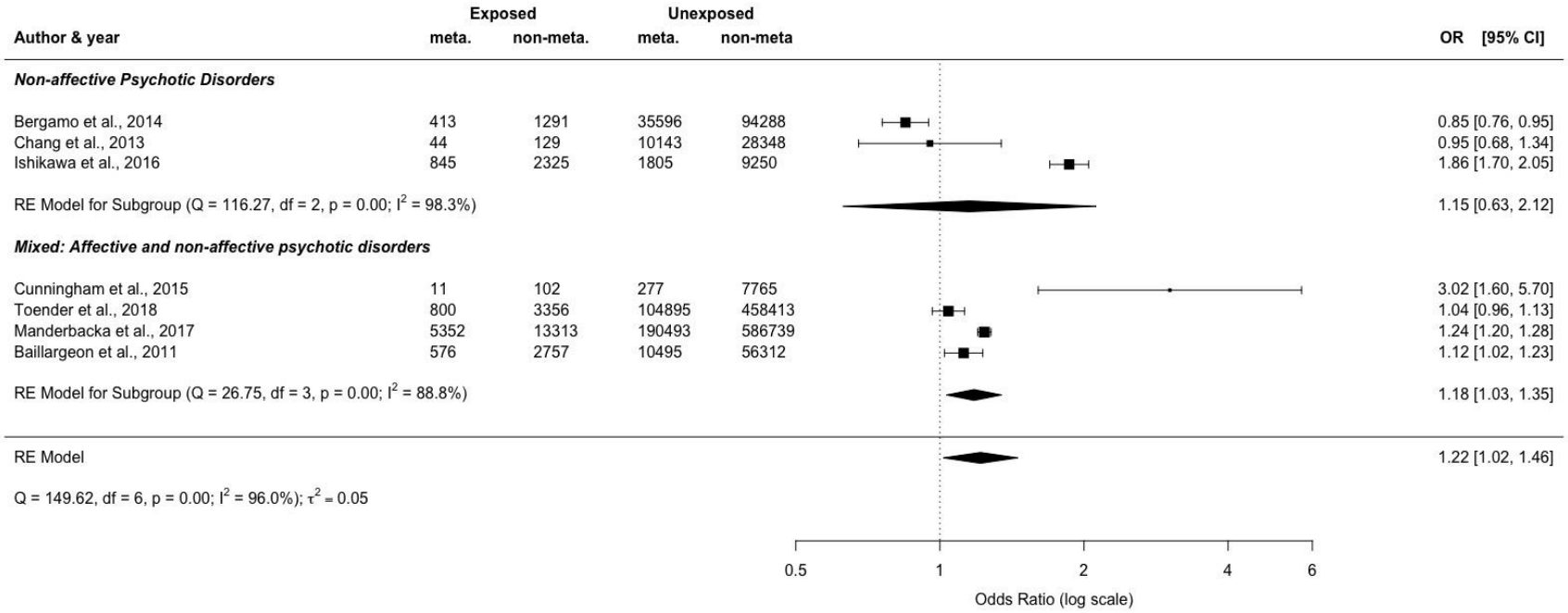

Figure 2.5: Forest plot of meta-analysis of odds of metastases in people with psychotic disorders, relative to the general population.

Chapter 3

3 Cancer incidence and stage at diagnosis among people with recent-onset psychotic disorders: A retrospective cohort study using Ontario health administrative data

3.1 Abstract

Background: Prior evidence on the incidence of cancer in people with psychotic disorders, compared to the general population, is equivocal, although those with psychotic disorders so have more advanced stage of cancer at the time of diagnosis. The objective of this study was to compare cancer incidence and stage at diagnosis for people with psychotic disorders, relative to the general population.

Methods: We used a retrospective cohort design to identify people with non-affective psychotic disorders diagnosed between 1995 and 2004, and a comparison group from the general population through linkage of Ontario health administrative databases held by the Institute for Clinical Evaluative Sciences (ICES). The cohort was followed until the end of 2019 for incident cases of cancer. We compared cancer incidence and stage at diagnosis between people with psychotic disorders and those without.

Results: People with psychotic disorders had an 8.6% higher incidence (IRR = 1.09, 95%CI: 1.05 to 1.12) of cancer overall, relative to the comparison group, adjusting for potential confounding factors. The incidence risk specific to individual cancer sites varied among people with psychotic

disorders, compared to those without. People with psychotic disorders had 23% greater odds (OR = 1.23, 95% CI: 1.13, 1.34) of being diagnosed with higher stage cancer, compared to those without psychosis.

Conclusions: This study found an elevated incidence of cancer in people with non-affective psychotic disorder, relative to the general population, with significant effect modification by sex. Additionally, we identified higher odds of more advanced stage at diagnosis in people with psychotic disorders, indicative of a significant diagnostic delay and a need to increase education and targeted access to care. Future research should examine the confounding effects of lifestyle factors and anti-psychotic medication, as well as potentially intermediary effects of cardiometabolic disorders.

3.2 Introduction

People with psychotic disorders – which can include schizophrenia, bipolar disorder, and depression with psychotic features – have mortality rates up to three times higher than the general population,[18,19,21] translating to a 15-year reduction in life expectancy.[22] It is estimated that 59% of this excess mortality is attributable to differences in concurrent medical illnesses.[128] Prior research suggests that people with psychotic disorders have a significantly higher incidence of at least 19 different medical illnesses, relative to the general population, which include liver disease, renal disease, diabetes, congestive heart failure, and myocardial infarction.[19] These concurrent medical comorbidities have been extensively researched, with particular focus on cardiometabolic disorders.[55,198,199]

This attention towards physical comorbidities among people with psychotic disorders has also led to a growing number of studies on cancer risk; however, this relationship presents an area

of significant controversy..[129,130] Prior evidence on the incidence of cancer in people with psychotic disorders, compared to the general population, is equivocal. A number of studies have found an elevated incidence of cancer among those with psychotic disorders,[7,124,187,189] whereas others have found a lower incidence.[123,171,193] The apparent lower incidence of cancer among people with psychosis was first noted in the Report of the Commissioners in Lunacy in 1909.[121] Since then, a series of hypotheses have been put forth as explanations for the lower incidence observed in many studies. These hypotheses include elevated natural killer cell activity, the protective effect of excess dopamine, an elevated rate of apoptosis, and the interaction of antipsychotic medication with cytochrome enzyme activity.[188] However, many of these hypotheses do not account for the wider range of behavioural and lifestyle factors affecting cancer risk,[129] which differ in prevalence between patients with psychotic disorders and the general population, thereby producing differences in site-specific cancers.[129]

Prior meta-analyses of the incidence of site-specific cancers in people with schizophrenia have found lower risk of prostate cancer, melanoma, and colorectal cancer, as well as higher incidence of breast, cervical, and uterine cancers.[1,2,131,200,201] Results of the cohort studies were found to vary significantly, depending on age of participants and duration of follow-up—two variables which are inconsistently reported. Furthermore, previous research has found the effect of psychotic disorder on cancer incidence to vary significantly across age categories and sex, suggesting effect modification, whereby females with psychotic disorders had a higher incidence of cancer compared to females without psychotic disorders and no difference was found for males with psychotic disorders.[150,155] Prior research has also found that people with serious mental illnesses (SMI), including psychotic disorders, are more likely to have more advanced stage of cancer at the time of diagnosis, suggesting disparities in prevention and treatment seeking

behaviour and access to care. A meta-analysis found that those with prior diagnoses of SMI had higher odds of advanced stage at diagnosis, higher odds of presenting with metastases, and worse survival, compared to those without SMI.[6] Psychotic disorders were also found to be associated with 60% increased risk of cancer-specific mortality.

There still remains significant debate regarding whether people with psychotic disorders have an elevated incidence of cancer compared to the general population. Furthermore, current evidence on stage-at-diagnosis is limited by a variety of methodological shortcomings and inconsistencies. Although studies examining cancer mortality and stage at diagnosis have been done in Canada,[3,202] there have been no Canadian studies to date on the incidence of cancer among people with psychotic disorders. Provincial health administrative data in the Canadian public healthcare system provides an opportunity to obtain population-based data on cancer incidence and stage at diagnosis in people with psychotic disorders.

The objective of this study was to use Ontario health administrative data to examine cancer incidence following the first diagnosis of non-affective psychotic disorder, relative to a general population comparison group. As a secondary objective, we also sought to compare stage at diagnosis for people with psychotic disorder and the general population. We hypothesized that we would observe significant heterogeneity of cancer incidence in people with NAPD, relative to those without NAPD by cancer site. Additionally, we hypothesized that people with NAPD would have greater odds of higher stage cancer at diagnosis.

3.3 Methods

3.3.1 Data sources

We followed the RECORD reporting guidelines for observational studies using health administrative data (Appendix A1).[203] The current study used population-based health administrative databases from Ontario, Canada, held by ICES (formerly known as the Institute for Clinical Evaluative Sciences). The following databases were linked using unique encoded identifiers and analyzed at ICES:

- The Registered Persons Database (RPDB) contains socio-demographic data for all Ontario residents registered for the Ontario Health Insurance Plan (OHIP).[204] Information in the RPDB includes date of birth, residential information, and dates of last contact with the healthcare system.[204]
- The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) contains data regarding separations from acute care, including discharges, deaths, sign-outs, and transfers, which are collected directly from acute care facilities and public health departments.[205] Each abstract contains data pertaining to hospital activity for each separation, including diagnostic, intervention, patient demographic, and administrative information.[205]
- The National Ambulatory Care Reporting System (NACRS) is a database created by CIHI for the purposes of capturing information regarding client visits to facility and community-based ambulatory care.[206] NACRS contains demographic, clinical, administrative, financial, and service-specific information for emergency department visits, day surgery procedures, diagnostic imaging, and clinic visits.[206]
- The OHIP Claims Database contains fee-for-service claims, as well as non-fee-associated (shadow billing) claims for physicians working under other payment models, submitted by physicians for

health services provided to Ontario residents under OHIP.[204] For each claim, information regarding date and location of service, type of service provider, diagnosis, and a service fee code is provided.[207] OHIP covers approximately 97% of all Ontario residents.[208]

- The Ontario Cancer Registry (OCR) compiles data on all cases of cancer diagnosed among Ontario residents.[209] This registry allows accurate reporting of cancer incidence, prevalence, and mortality. This reporting is facilitated through the compilation of data from the CIHI DAD and National Ambulatory Care Reporting System (NACRS) databases, as well data from regional cancer centres, pathology reports, death certificates, and out-of-province cancer diagnoses.
- The Primary Care Population dataset (PCPOP) includes all Ontario residents who have had contact with health services within any 7 to 9 year period, starting in the year 2000.[210] The PCPOP contains data on demographics, primary care, attachment status, and a number of variables specific to contact with healthcare services.[210]
- The ICES Physician Database (IPDB) contains demographic, specialty, and other information about physicians practicing in the province of Ontario.[211]

3.3.2 Study Design and Inclusion Criteria

We used a retrospective cohort design to identify people aged 14 to 59 at their index diagnosis of non-affective psychotic disorder, diagnosed between January 1995 and December 2004,[212] which formed our exposed group. To be classified as a case of psychotic disorder, people must have met at least one of the following criteria: (1) a primary discharge diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified (NOS) from an inpatient hospitalization (International Classification of Diseases, 9th Revision [ICD-9] code 295.x or 298.x; ICD-10 codes F20, F25, or F29) or (2) at least two OHIP billing claims or emergency

department visits with a diagnostic code for schizophrenia or schizoaffective disorder (ICD-9 code 295.x or 298.x; ICD-10 codes F20, F25, or F29) within a 24-month period. Psychosis NOS, replaced by "unspecified schizophrenia spectrum and other psychotic disorders" describes symptoms resulting in functional impairment and distress, characteristic of schizophrenia spectrum disorder while not meeting the full criteria of another condition.[213] In practice, this diagnosis is also applied to presentations which do not provide adequate information for a specific diagnosis.[213] This algorithm has been validated against medical chart diagnoses, and was found to have sensitivity of 93.9%, a specificity of 50.0%, a positive predictive value of 62.1%, and a negative predictive value of 90.4% for a diagnosis of schizophrenia, schizoaffective disorder, or psychosis NOS.[212] Diagnosis of affective psychoses requires four-digit ICD-10 codes, which are only available through emergency department and hospitalization billings, and are not available in OHIP billings. Therefore, for the purposes of maintaining external validity, we restricted our case definition to non-affective psychotic disorders.

The index event was defined as diagnosis with non-affective psychotic disorder, restricted to the first eligible date identified over the accrual period. A lookback window of five years prior to the index date for each person was used to identify and exclude chronic cases of psychosis. We selected the ten-year accrual period in order to accommodate a lookback window stretching back to 1990, the earliest date which we could collect billing data. We identified an unexposed group of people who had not previously received a diagnosis of non-affective psychotic disorder, frequency matched by age and sex at a ratio of 4:1. Index dates matched to the exposed group were assigned at random to the unexposed group. People were excluded from the comparison group if there was any evidence of schizophrenia, schizoaffective disorder, or psychosis NOS in the 5 years prior to the index date.

People were excluded from the study if they were under the age of 14 or over the age of 59 at the index date. This age range was chosen due to the low incidence of psychotic disorders prior to age 14, and to exclude possible cases of dementia after age 60. Non-residents of Ontario and those not eligible for OHIP in the year prior to the index date were excluded to improve continuity and completeness of data. Finally, we also excluded people who had been diagnosed with cancer prior to the index date.

3.3.3 Outcomes

Incident cases of cancer occurring after the index date were identified via linkage to the OCR. The cohort was followed until the end of the follow-up period (December 2019), death, or a new onset of non-affective psychotic disorder in the unexposed group, at which point censoring occurred among non-cases.

A detailed description of the derivation of the outcome variables can be found in Appendix A2. The primary outcome of this study was the time from the index date to the first date of cancer diagnosis, determined by the diagnosis date of the first appearance of an ICES Key Number (IKN) in the OCR. For this diagnosis, data pertaining to the stage and topography of the primary tumour were collected. Stage at diagnosis was classified using the Tumour, Node, and Metastases (TNM) stage at the first available primary site for that person. TNM staging is then grouped into stages I through IV.[71] Stage I describes a localized tumour which has not penetrated nearby tissues.[71] Stages II and III denote regional spread of the tumour to nearby tissues and lymph nodes.[71] Stage IV indicates that cancer has metastasized and spread to distant tissues in the body.[71] We did not include stage 0 tumors as part of our outcome definition, as these represent pre-cancerous lesions. The cancer site was based on ICD-O-3 topography codes for the primary tumor site, and grouped

into the following sites: bladder, brain, breast, cervical, colorectal, esophageal, Hodgkin's lymphoma, kidney, larynx, leukemia, liver, lung, melanoma, myeloma, non-Hodgkin's lymphoma, oral cavity, ovary, pancreas, prostate, stomach, testis, thyroid, uterus, and other.

3.3.4 Other Variables

The following confounding variables, with demonstrated associations with cancer incidence, were controlled for in the analyses: age, sex, neighborhood-level income quintile, rurality of residence, and access to a family physician. All confounding variables were assessed at baseline.[120,214–216] Age and sex were obtained from the RPDB, and age was used as a continuous variable. Neighborhood-level income quintile was obtained from the RPDB and was based on the average household income for each postal code, computed using census data. Rurality was defined using the Rurality Index of Ontario. Access to a family physician was based on whether a person was assigned to a family physician as of the index date, defined using the PCPOP database.

3.3.5 Statistical Analyses

We summarized descriptive characteristics of the cohort using frequency tables and calculated standardized differences to compare baseline characteristics between the exposed and unexposed groups. Standardized differences greater than 10% are indicative of significant between-group differences.[217]

The primary objective of this study was to compare the incidence of cancer between people with psychotic disorders and the general population comparison group. We presented the crude incidence rates of all cancer, as well as site-specific cancer for the exposed and unexposed group. We used univariate and multivariable Poisson regression models to compare the time from the

index date to the first cancer diagnosis among people with psychotic disorders and those in the comparison group. We adjusted for age, sex, neighbourhood income quintile, access to a family physician, and rurality of residence. Although the comparison group was frequency matched by age and sex during the cohort build, age and sex were also included in the multivariable analysis to adjust for residual confounding. We also conducted *post-hoc* stratified analyses by age group and sex, as previous research has suggested that age and sex act as effect modifiers in the relationship between schizophrenia and overall cancer risk.[150]

Additionally, we ran separate Poisson regression models for the incidence of cancer at each specific site. Those who developed cancer at sites other than the site of interest were censored at the time of that cancer diagnosis. Analyses of sex-specific cancers – including cervical, ovarian, uterine, testicular, and prostate cancer – were restricted to their respective sex. Additionally, breast cancer was treated as a sex-specific cancer occurring in females, as males account for only 1% of all breast cancer case,[218] however sensitivity analyses were performed to examine the effect of including males in the analysis of breast cancer incidence.

To examine the influence of sex-specific cancers on the overall incidence of cancer in people with psychotic disorders, we performed post-hoc sensitivity analyses by excluding sex-specific cancers from the model of overall cancer incidence, including breast, cervical, uterine, ovarian, prostate, and testicular cancer.

Our secondary objective was to compare stage at diagnosis between people with psychosis who developed cancer, and those who developed cancer in the comparison group. A proportional odds model for stage at diagnosis was fit on the binary variable of psychotic disorder diagnosis, adjusting for age, sex, neighbourhood income quintile, access to a family physician, and cancer site. Cancer site was included as a potential confounding factor to control for the varying

aggressiveness of cancer at different sites, which would influence the likelihood of presenting with more or less advanced staging at diagnosis.[219,220] People with missing data on stage at diagnosis were excluded from this analysis.

We found a large proportion of missing data on stage at cancer diagnosis; therefore, we performed a post-hoc analysis to examine whether people with psychotic disorders had higher odds of having missing data. A logistic regression model of missing stage at diagnosis was fit on the binary variable of diagnosis with psychotic disorder, adjusting for age, sex, neighbourhood income quintile, access to family physician, and cancer site.

All statistical analyses were performed using STATA v16, and results are presented as incidence rate ratios (IRR) or odds ratios (OR), with corresponding 95% confidence intervals (CI).

3.4 Results

We identified 63,410 cases of non-affective psychotic disorder between 1995 and 2004 who met the study inclusion criteria, and these cases were frequency matched on age and sex to 260,539 people from the general population. A complete breakdown of the derivation of the study cohort can be found in Appendix A3.

The characteristics of the study cohort at the index date are presented in Table 1. The mean age for both groups was 36.0 years (SD = 11.9), and 45% of the sample were females. As the comparison group was sampled from the general population, there was an even distribution across the neighborhood-level income quintiles, whereas a higher proportion of people in the exposed group were in the lowest neighborhood-level income quintile (31%). Similar proportions of the exposed group (13%) and comparison group (10%) lived in rural areas. Eighty-nine percent of people in the exposed group had access to a family physician, compared to 84% in the comparison

group. With respect to psychiatric diagnoses among the exposed group, 60% had an index diagnosis of schizophrenia spectrum disorder and 40% had an index diagnosis of psychosis NOS.

3.4.1 Incidence

The total observation time among the unexposed group was 1,814 billion person-years with a mean observation time of 19 years. The total observation time among the exposed group was 425.4 million person-years and the mean observation time was 18 years. Over the follow-up period, a total of 5,069 people with psychotic disorder developed cancer, for an incidence rate of 4.5 cases per 1,000 person-years. In the unexposed group, 20,175 people developed cancer for a rate of 4.2 cases per 1,000 person-years. People with psychotic disorder had an 8.6% higher incidence (IRR = 1.09, 95% CI: 1.05 to 1.12) of cancer overall, relative to the comparison group, adjusting for age, sex, income, rurality of residence, and access to a family physician (Table 2).

The results of the Poisson regression models for site-specific cancers can be found in Table 2. People with psychotic disorder had a higher incidence of breast cancer (IRR = 1.09, 95% CI: 1.01 to 1.17), cervical cancer (IRR = 1.43, 95% CI: 1.10 to 1.87), esophageal cancer (IRR = 1.72, 95% CI: 1.29 to 2.29), leukemia (IRR = 1.23, 95% CI: 1.08 to 1.40), liver cancer (IRR = 1.70, 95% CI: 1.31 to 2.21), lung cancer (IRR = 1.52, 95% CI: 1.40 to 1.65), and uterine cancer (IRR = 1.19, 95% CI: 1.02 to 1.38). People with psychotic disorder had a lower incidence of melanoma (IRR = 0.66, 95% CI: 0.55 to 0.79), thyroid cancer (IRR = 0.84, 95% CI: 0.72 to 0.98), and prostate cancer (IRR = 0.59, 95% CI: 0.53 to 0.66). Including males in the analysis of breast cancer incidence did not significantly alter results.

The results of the post-hoc stratified analyses by age and sex can be found in Appendix A4. Sex was found to be an effect modifier on the association between psychotic disorders and

incidence of cancer. Females with psychotic disorder had a higher incidence of cancer overall, compared to females without psychosis (IRR = 1.15, 95% CI: 1.11 to 1.20), adjusting for age, income, rurality of residence, and access to a family physician. Exclusion of female-specific cancers, including breast, cervical, uterine, and ovarian cancer, did not significantly alter the estimate. In contrast, there was no difference in cancer incidence for males with psychotic disorder, compared to males without, adjusting for age, income, rurality of residence, and access to a family physician. Removal of male-specific cancers, testicular and prostate cancer, produced an IRR indicating an increased incidence of remaining cancers in males with psychotic disorders, compared to those without (IRR = 1.14, 95% CI: 1.08 to 1.20). No significant differences were found in the IRR by age category for either males or females.

3.4.2 Stage at Diagnosis

The frequencies and percentages of people diagnosed with each stage can be found in table 3. The results of the proportional odds model of stage at diagnosis and the logistic regression model of missing stage at diagnosis can be found in table 4. More than half of people diagnosed with cancer had unknown stage at diagnosis (exposed group: 56%; unexposed group: 51%) and were excluded from the analysis. People with psychotic disorder had 23% greater odds (OR = 1.23, 95% CI: 1.13, 1.34) of being diagnosed with higher stage cancer, compared to those without psychosis. Our post-hoc analysis suggests that people with psychotic disorder also had 24% greater odds (OR = 1.24; 95% CI: 1.17 to 1.32) of missing stage at diagnosis data, relative to those in the comparison group.

3.5 Discussion

This study identified a higher incidence of cancer in people with non-affective psychotic disorders, relative to the general population, with substantial variation by cancer site. We also found that people with psychotic disorder had a more advanced stage at diagnosis. Our findings are strengthened by the use of a population-based health administrative dataset in a country with universal healthcare, which allows for a large, representative sample in a county with a publicly funded universal health care system. Furthermore, the use of health administrative data allowed for a longer follow-up period, and the present study represents one of few longitudinal studies to examine both incidence and stage at diagnosis within the same cohort.

Previous meta-analyses have produced conflicting results regarding excess risk of cancer among people with psychotic disorders, with one finding a lower incidence of cancer,[2] and two showing no difference in incidence between people with psychotic disorder and the general population.[1,201] However, these prior meta-analyses have found heterogeneity in both the direction and magnitude of effect by cancer site,[1,2,201] which is similar to the findings from the current study. It is possible that the small but significantly elevated risk of cancer overall that we observed among people with psychotic disorders is driven by higher rates of more common cancers in this population, such as breast cancer, colorectal cancer, and lung cancer.

The present study identified significant effect modification in overall cancer risk by sex. Similar to previous studies, we found that females with psychotic disorders had a significantly higher incidence of cancer, compared to females without psychosis,[150,155] which was not driven by a higher risk of female-specific cancers. In contrast, we did not find a difference in cancer risk between males with psychotic disorder and those without;[150,155] however, after excluding prostate cancer, males with psychotic disorder were found to be at a higher risk of cancer overall, similar

to the IRR observed in females with psychotic disorder. Similar patterns were observed in previous studies, where removing prostate cancer led to an excess risk of cancer overall in males with psychotic disorder, compared to men without.[150,155]

It was initially hypothesized that people with psychotic disorders have a lower incidence of cancer.[121] One theory posits that genetic factors associated with schizophrenia decrease the risk of developing cancer.[8] It has been suggested that polymorphisms of Tp53 increase neuronal apoptosis during embryonic development, which is associated with both the development of schizophrenia as well as greater regulation of tumorigenesis, thereby reducing the risk of developing cancer.[221] A number of studies have identified an association between Tp53 polymorphisms and schizophrenia.[222–224] Furthermore, several cohort studies have examined cancer risk in the siblings and parents of people with schizophrenia,[7–9,225] with a meta-analysis of these data showing a lower risk of all site cancer in close relatives of people with schizophrenia, despite finding no difference in cancer risk for people with schizophrenia.[1] Opponents of this theory have argued that in addition to cohort studies producing inconsistent results, there are too many unknown factors influencing cancer risk in this population which must be accounted for.[226] However, it is possible that the protective effects conferred by genetics are overcome by exposure to environmental and lifestyle factors among people with psychotic disorders,[227] thus explaining the lower incidence of cancer in relatives of people with schizophrenia, and the similar risk of cancer among people with schizophrenia, relative to the general population.

Smoking has a demonstrated causal association with lung, bladder, and head/neck cancers.[66,67,96,97] Despite higher rates of smoking among people with psychotic disorder, prior research has produced mixed results regarding lung cancer risk; however, adjustment for smoking has been shown to attenuate the relative risk of lung cancer in people with psychosis.[1,2,127,201] The

present study identified an elevated risk of lung cancer among people with psychotic disorder and no difference for the incidence of bladder cancer, consistent with previous research.[1,2,201] However, our interpretation of these results is limited, given that we are unable to adjust for smoking or other environmental exposures.

Additionally, people with psychotic disorders are more likely to have poor eating habits and a sedentary lifestyle, resulting in higher rates of cardiometabolic disorders, including cardiovascular disease, obesity, and diabetes,[5,24,44–48] all of which have demonstrated associations with breast and colorectal cancer.[104,105] The present study identified a higher incidence of colorectal cancer among people with psychotic disorders, inconsistent with the results of prior meta-analyses; however, the 95% CI included 1, indicating the possibility of a null effect.[2,201]

Additionally, diabetes mellitus is associated with a lower risk of prostate cancer.[162] This inverse association is thought to be the product of lower levels of testosterone, low responsiveness to insulin, as well as downregulation of insulin growth factors.[162] Therefore, higher risk of diabetes among males with psychotic disorders may lead to a lower risk of prostate cancer. In agreement with prior meta-analyses, the present cohort study identified a lower incidence of prostate cancer among males with psychotic disorders.[1,2,201]

The risk of these cardiometabolic disorders is further exacerbated by treatment with antipsychotic medications, with a significantly greater effect on females, compared to males.[28,29] Additionally, anti-psychotic medications (dopamine antagonists) have demonstrated highly heterogenous effects on oncogenesis depending on cancer site, increasing the risk of liver, breast, and uterine cancer, while decreasing the risk of prostate cancer,[144,146–148,157] which is consistent with our findings and with previous literature.[1,2,126,131,200,201] It has been proposed that hyperprolactinemia resulting from antipsychotic medication is responsible for the higher risk of

breast and uterine cancer among females with PD and a lower incidence of prostate cancer among males with PD, all of which are hormonally sensitive.[146–148] Males with schizophrenia who are prescribed phenothiazines have also been found to have markedly lower prostate cancer incidence.[157]

Additionally, people with schizophrenia spectrum disorders have three times the odds of having hepatitis B (HBV) or hepatitis C (HCV) infections compared to those without.[228] Globally, it is estimated that 78% of all hepatocellular carcinoma is attributable to infection with HBV and HCV.[229] The increased prevalence of HBV and HCV infection among people with psychotic disorders is largely driven largely by injection drug use and risky sexual behaviour.[230] Furthermore, people with serious mental illnesses have been found to have low rates of vaccination for hepatitis.[231]

We observed a higher odds of advanced stage at diagnosis in people with psychotic disorders, which is also consistent with a prior meta-analysis, which found that in countries with universal healthcare, people with mental illnesses had higher odds of advanced stage cancer at diagnosis.[6] This has also been shown for psychotic disorders specifically.[201] These trends may be indicative of a diagnostic delay due to disparities in healthcare-seeking behaviour and access to screening and treatment.[6,201] It has been previously shown that people with schizophrenia are less likely to participate in screening for breast, cervical, prostate, and colorectal cancer.[164,167,179–181]

Lower screening uptake may have variable impacts on cancer incidence, depending on the effectiveness of cancer screening programs. In Canada and the USA, successful initiatives for pap-smears and colorectal cancer screening – both of which allow for early detection and removal of pre-cancerous lesions – have translated into dramatic reductions in cervical cancer and colorectal cancer over time, as well as reduced mortality.[77,80–82,232] On the other hand, significant increases

in prostate and mammography screening have increased the observed incidence of prostate and breast cancer, mainly through overdiagnosis, resulting in unnecessary treatment and little difference in mortality.[83–85,232,233] Therefore, low uptake of screening among people with psychotic disorders, restricting their ability to benefit from these programs, may explain the higher incidence of cervical and colorectal cancer, while significantly underestimating the incidence of prostate and breast cancer in people, relative to the trends in the general population.[126,155,234]

Furthermore, while evidence regarding melanoma screening uptake among people with psychotic disorders is limited, it is likely the pattern of lower screening uptake for other cancers applies, thereby potentially reducing the observed incidence of melanoma among people with psychotic disorders.[150,235] It has been previously suggested that the observed reduced incidence of melanoma among people with psychotic disorders is the result of reduced sun exposure; however, there is limited evidence to support this theory.[1]

Important to the discussion regarding stage at diagnosis is the availability of accurate staging data. A large proportion of people who developed cancer in the present study had an unknown stage at diagnosis, and people with psychotic disorder had higher odds of having an unknown stage at diagnosis, which has been shown previously.[3,172] This demonstrates that patients with psychotic disorders may not have had adequate staging performed, resulting from either lack of access or refusal of services. In turn, this may limit the availability of diagnostic information pertinent to informing cancer treatment and prognosis among people with psychotic disorders. It is important to note that these differences persist in studies like this one, conducted in countries with a universal healthcare system,[3,170,172,191] suggesting that cost remains only one of many factors influencing access to care for marginalized populations, such as people with psychotic disorders.

Some of the trends we observed may be due to diagnostic overshadowing, whereby physical symptoms reported by a person with mental illnesses are misattributed to the mental illness by clinicians.[236] People with psychotic disorders have a higher prevalence of cardiometabolic disorders, viral infections, musculoskeletal diseases, sexual dysfunction, and pregnancy complications, which are often dismissed or attributed to the psychiatric diagnosis, consequently making them less likely to receive specialized treatment and screening for these conditions.[237] It is possible that a similar dismissal of symptoms in relation to malignancy may contribute to delayed diagnosis and intervention.

3.5.1 Limitations

We are limited by the data available in the ICES databases; therefore, we were unable to adjust for important confounding variables, such as smoking, obesity, antipsychotic medication exposure, and a number of other lifestyle factors with known associations with cancer risk.[1,5,24,44–48,144] The case definition that we used to identify people with psychotic disorder has high sensitivity, which increases the potential for false positives, and some people in our exposed group may be misclassified, although we expect this to be nondifferential. Additionally, the cancer registry used to define our outcome does not include cases of basal and squamous cell carcinomas of the skin,[238] which limits our ability to draw conclusions about some cancer types.[238] Furthermore, the incidence of certain cancers, including Hodgkin's lymphoma, laryngeal cancer, and myeloma, were particularly low, thereby limiting the validity of our estimates for those particular cancers.

As previously mentioned, there was a large proportion of missing data for stage at diagnosis for people who developed cancer during the follow-up period. This may limit the generalizability

of the findings if people with missing data differ systematically from those with available data on stage at diagnosis, and our post hoc analyses do suggest that people with psychotic disorders are more likely to have missing stage data. Moreover, low rates of cancer screening in people with psychotic disorders may have resulted in detection bias for some types of cancer, such as breast and prostate cancer.[164,167,179–181]

Finally, our cohort was restricted to people aged 15 to 59 at their respective index dates. Therefore, the conclusions drawn from our analyses are limited to those within this age range and may differ for elderly people with psychotic disorders. This age restriction may limit our conclusions to those cancers which commonly occur in younger people including, brain, breast, cervical, colorectal, leukemia, lymphoma, melanoma, testicular, and thyroid.[239]

3.6 Conclusions

This retrospective cohort study identified a small but significantly elevated incidence of cancer in people with non-affective psychotic disorder, relative to the general population; however, both the direction and magnitude of effect varied significantly by cancer site. Furthermore, we identified effect modification by sex. We also found evidence of more advanced stage at diagnosis in people with psychotic disorders, potentially indicative of diagnostic delay. Further efforts should be made to improve the quality and granularity of population-based health administrative data, such that future cohort studies may control for lifestyle factors such as smoking, obesity, diabetes, and medication use. Future research should aim to evaluate the effects of a broader array of confounding factors involved in cancer incidence and stage at diagnosis, as well as potential intermediary effects of antipsychotic medication and cardiometabolic comorbidities. Lastly, efforts should be made to improve education surrounding cancer screening and diagnosis targeting

this population, as well as programs which improve access to care and increasing uptake of vaccinations for HPV and hepatitis among people with psychotic disorders.

3.7 Acknowledgements

The data used in the current study were accessed through ICES, which is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation, and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. Additionally, parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

3.8 Tables and Figures

Table 3.1: Descriptive characteristics of exposed and unexposed groups at the index date

Characteristic		Exposed n (%) (N = 63,410)	Unexposed n (%) (N = 250,539)	Standardized Difference (%)
Age (years)	**mean (standard deviation)**	36.0 (11.9)	36.01 (11.9)	0.1
	15 – 20	6,090 (9.6)	24,010 (9.6)	0.1
	20 – 29	14,686 (23.2)	58,210 (23.2)	0.2
	30 – 39	17,183 (27.1)	67,628 (27.0)	0.2
	40 – 49	15,382 (24.3)	60,766 (24.25)	0.0
	50 – 59	10,069 (15.9)	39,925 (15.94)	0.2
Sex	Female	28,394 (44.8)	112,030 (44.7)	0.1
	Male	35,016 (55.2)	138,509 (55.3)	0.1
Neighbourhood-level Income Quintile	1 (lowest)	19,818 (31.3)	49,954 (19.9)	26.1
	2	14,065 (22.2)	49,889 (19.9)	5.6
	3	11,133 (17.6)	49,918 (19.9)	6.1
	4	9,793 (15.4)	50,033 (20.0)	11.9
	5 (highest)	8,601 (13.6)	50,745 (20.3)	17.9
Access to a family physician	Yes	56,326 (88.8)	209,218 (83.5)	17.3
	No	7,084 (11.2)	41,321 (16.5)	14.7
Rurality of residence	Urban	57,186 (90.2)	218,776 (87.3)	9.1
	Rural	6,224 (9.8)	31,763 (12.7)	9.1
Psychiatric Diagnosis	Schizophrenia spectrum disorder	38,004 (59.9)	--	--
	Psychosis NOS	25,406 (40.1)	--	--

Table 3.2: Incidence cancer cases by site and results of adjusted and unadjusted Poisson regression models of all-site and site-specific cancer incidence among people with psychotic disorders

	Exposed (n = 63,410)		**Unexposed (n = 250,539)**		**Incidence Rate Ratios (IRR)**	
	Events	**IR (95% CI) (per 1000 person-years)**	**Events**	**IR (95% CI) (per 1000 person-years)**	**IRR (95% CI) (unadjusted)**	**IRR (95% CI) (adjusted)***
All Cancer	5,069	4.47 (4.35, 4.59)	20,175	4.22 (4.17, 4.28)	1.06 (1.03, 1.09)	**1.09 (1.05, 1.12)**
Bladder	151	0.13 (0.11, 0.16)	639	0.13 (0.12, 0.14)	1.00 (0.83, 1.19)	1.04 (0.87, 1.25)
Brain	82	0.07 (0.06, 0.09)	356	0.07 (0.07, 0.08)	0.97 (0.76, 1.23)	0.99 (0.78, 1.26)
Breast (female only)	888	1.71 (1.60, 1.83)	3498	1.63 (1.58, 1.68)	1.05 (0.98, 1.13)	**1.09 (1.01, 1.17)**
Cervix (female only)	76	0.15 (0.12, 0.19)	212	0.10 (0.09, 0.11	1.49 (1.14, 1.93)	**1.43 (1.10, 1.87)**
Colorectal	484	0.43 (0.39, 0.47)	1,968	0.41 (0.39, 0.43)	1.04 (0.94, 1.14)	1.11 (1.00, 1.23)
Esophagus	66	0.06 (0.05, 0.07)	171	0.04 (0.03, 0.04)	1.63 (1.22, 2.16)	**1.72 (1.29, 2.29)**
Hodgkin's Lymphoma	33	0.03 (0.02, 0.04)	104	0.02 (0.018, 0.03)	1.34 (0.90, 1.98)	1.33 (0.89, 1.97)
Kidney	165	0.15 (0.12, 0.17)	614	0.13 (0.12, 0.14)	1.13 (0.95, 1.34)	1.12 (0.94, 1.34)
Larynx	24	0.02 (.01, 0.03)	112	0.02 (0.02, 0.03)	0.90 (0.58, 1.40)	0.93 (0.59, 1.45)
Leukemia	298	0.26 (0.23, 0.29)	1,065	0.22 (0.21, 0.24)	1.18 (1.04, 1.34)	**1.23 (1.08, 1.40)**
Liver	83	0.07 (0.06, 0.09)	188	0.04 (0.03, 0.05)	1.86 (1.44, 2.41)	**1.70 (1.31, 2.21)**
Lung	793	0.70 (0.65, 0.75)	2,173	0.45 (0.44, 0.47)	1.54 (1.42, 1.67)	**1.52 (1.40, 1.65)**
Melanoma	134	0.12 (0.10, 0.14)	942	0.20 (0.18, 0.21)	0.60 (0.50, 0.72)	**0.66 (0.55, 0.79)**
Myeloma	<6	0.00 (0.00, 0.01)	17	0.00 (0.00, 0.01)	0.74 (0.22, 2.54)	0.81 (0.23, 2.81)
Non-Hodgkin's Lymphoma	209	0.18 (0.16, 0.21)	800	0.17 (0.16, 0.18)	1.10 (0.94, 1.28)	1.11 (0.95, 1.30)

Oral cavity	147	0.13 (0.11, 0.15)	562	0.12 (0.11, 0.13)	1.10 (0.92, 1.32)	1.12 (0.94, 1.35)
Ovary (female only)	83	0.07 (0.06, 0.09)	391	0.18 (0.17, 0.20)	0.88 (0.70, 1.12)	0.90 (0.71, 1.14)
Pancreas	85	0.07 (0.06, 0.09)	402	0.08 (0.08, 0.09)	0.89 (0.70, 1.13)	0.90 (0.71, 1.14)
Prostate (male only)	321	0.28 (0.25, 0.32)	2,519	0.95 (0.91, 0.99)	0.54 (0.48, 0.61)	**0.59 (0.53, 0.66)**
Stomach	77	0.07 (0.05, 0.08)	317	0.07 (0.06, 0.07)	1.02 (0.80, 1.31)	1.03 (0.80, 1.33)
Testis (male only)	56	0.09 (0.07, 0.12)	189	0.07 (0.06, 0.08)	1.26 (0.94, 1.70)	1.27 (0.94, 1.72)
Thyroid	192	0.17 (0.15, 0.19)	930	0.19 (0.18, 0.21)	0.87 (0.74, 1.02)	**0.84 (0.72, 0.98)**
Uterus (female only)	227	0.44 (0.39, 0.50)	800	0.38 (0.35, 0.40)	1.18 (1.02, 1.36)	**1.19 (1.02, 1.38)**
Other	392	0.85 (0.79, 0.90)	1,206	0.99 (0.96, 1.02)	0.85 (0.80, 0.92)	**0.90 (0.84, 0.96)**
Person-time at risk	425,400,000		1,814,000,000			

* adjusted for age, sex, income, rurality of residence, and access to a family physician

Table 3.3: Stage at diagnosis for people diagnosed with cancer in the exposed and unexposed groups

Stage	Exposed n (%) (n = 5,069)	Unexposed n (%) (n = 20,175)
I (early)	688 (13.6)	3,285 (16.3)
II	531 (10.5)	2,733 (13.6)
III	424 (8.4)	1,823 (9.0)
IV (metastatic)	565 (11.2)	1,974 (9.8)
Unknown	2,861 (56.4)	10,360 (51.4)

Table 3.4: Results of adjusted and unadjusted proportional odds models of stage at diagnosis excluding people with missing stage data, and logistic regression model of the odds of missing stage at diagnosis among people with psychotic disorders are reported

Stage at diagnosis		OR (95% CI)
Diagnosis with NAPD (unadjusted)		1.23 (1.13, 1.34)
Diagnosis with NAPD (adjusted)*		1.16 (1.06, 1.27)
Diagnosis with NAPD (unadjusted)		1.24 (1.17, 1.32)
Diagnosis with NAPD (Adjusted)*		1.23 (1.15, 1.32)

* adjusting for age, sex, income, rurality of residence, access to a family physician, and primary cancer site

Chapter 4

4 Integrated Discussion

This chapter will discuss the findings of the two manuscripts of this thesis together in the context of literature on cancer incidence and stage at diagnosis in people with psychotic disorders. Importantly, we will consider the methodological limitations of this thesis and the potential impact on our findings. Lastly, we will describe how our findings should shape future investigations into this topic and specifically, which questions remain to be answered.

4.1 Key Findings

The objective of this thesis was to use systematic review methodology, as well as Ontario health administrative data, to study the incidence of cancer and stage at diagnosis among people with psychotic disorders, relative to the general population. Our systematic review and meta-analysis presented in chapter 2 synthesized the existing literature on cancer incidence and stage at diagnosis in people with psychotic disorders – including both affective and non-affective – to the general population, identifying methodological strengths and shortcomings of the current literature. The findings from this review helped to inform the retrospective cohort study in chapter 3, which compared cancer incidence and stage at diagnosis in people with non-affective psychotic disorder to a comparison group sampled from the general population, using population-based health administrative data from Ontario.

The systematic review found that the incidence of all-site cancer among people with psychotic disorder was slightly elevated (RR: 1.08, 95% CI: 1.00, 1.16), although the 95% CI

includes the possibility of a null effect. Differences in incidence were identified by cancer site. People with psychotic disorder were found to have a higher risk of developing brain, breast, nasopharyngeal, cervical, and uterine cancers; while having a lower risk of colorectal, prostate, and skin cancer. Additionally, we found that people with psychotic disorder had a higher odds of metastases at diagnosis, compared to people without psychotic disorders. Common sources of bias identified across the included studies were the inability to ensure the outcome of interest was absent at the start of the study, failure to include important confounding factors, and variable reporting regarding the case definition used to identify people with psychotic disorders.

The cohort study found that the incidence of all-site cancer was elevated among people diagnosed with non-affective psychotic disorder, relative to those without psychotic disorder (IRR: 1.09, 95% CI: 1.05, 1.12), adjusting for age, sex, income, rurality of residence, and access to a family physician. Similar to the systematic review, we found that people with psychotic disorders had a higher incidence of breast, cervical, and uterine cancer, and a lower incidence of prostate and skin cancer. We additionally identified an elevated incidence of lung cancer, esophageal cancer, and leukemia, and a lower incidence of thyroid cancer, which was not found in the systematic review. We also found evidence of significant effect modification by sex. Specifically, females with psychotic disorder were found to have a higher incidence of cancer overall, compared to females without psychotic disorder, but no difference was found for males. However, after excluding prostate cancer in males, the effect of psychotic disorder on overall cancer incidence was the same for both sexes.

Our cohort study also identified a greater odds of more advanced stage cancer at diagnosis, consistent with the results of our meta-analysis. These findings could indicate the presence of a diagnostic delay for people with psychotic disorder. Additionally, our post-hoc

analysis of missing stage at diagnosis found that people with psychosis had a higher odds of having a missing stage at diagnosis.

4.2 Results in Context

The results of this thesis suggest that the higher incidence of cancer in people with PD is largely driven by higher rates of common cancers, including breast, colorectal, cervical, and lung cancer. The higher incidence of cancer at these specific sites highlights a number of inequities in health outcomes faced by those with psychotic disorder, driven by exposure to risk factors, as well as differences in screening behavior and access of treatment, and increased risk of other comorbidities. Therefore, the presence of any genetic factor which may be associated with lower cancer risk in people with psychotic disorders, is likely overcome by these other risk factors, should it exist at all. Furthermore, this hypothesized genetic factor may provide very little utility in our understanding of this relationship until all other environmental, lifestyle, and behavioral factors influencing cancer incidence can be accounted for and adequately addressed.

In chapter 3, we explored how a number of risk factors for cancer could have influenced our results. Firstly, people with psychotic disorder are more likely to smoke, and smoke at higher rates compared to the general population,[65,240–244] thereby contributing to higher incidence of lung, head/neck, and esophageal cancers,[1,2,127,201] among others. Secondly, treatment with antipsychotic medication has been shown to exhibit highly variable effects on the risk of specific cancers.[144,146–148,157] Hyperprolactinemia resulting from treatment with this class of medications has been hypothesized to increase the risk of developing breast and uterine cancer and decrease the risk of prostate cancer, due to the hormone-sensitivity of these cancers.[146–148] We found that a lower incidence of prostate cancer in males with psychotic disorder was responsible for the effect measure modification by sex that we observed. Thirdly, people with psychotic disorder are more

likely to have poor eating habits and a sedentary lifestyle, which contribute to increased risk of cardiometabolic disorders, such as diabetes mellitus and obesity, which are identified risk factors for breast and colorectal cancer, while diabetes may provide a protective effect against the development of prostate cancer.[5,24,44–48,161,162] This risk is worsened by exposure to antipsychotic medications through the overstimulation of appetite and increased risk of insulin resistance.[56,58,59] Furthermore, exposure to factors such as smoking, obesity, and insulin resistance among people with psychotic disorders are driven, in part, by stressful living environments and limited access to financial resources,[245,246] as people with psychotic disorders are likely to be of lower SES compared to the general population.[247] Finally, people with psychotic disorders have higher odds of having hepatitis infections compared to the general population, driven by injection drug use, risky sexual behaviour, and low vaccination rates, which is known to account for a majority of hepatocellular carcinoma worldwide.[228–231]

Differences in screening behaviour and uptake may also be responsible for our findings. People with psychotic disorder are far less likely to participate in screening for breast, cervical, prostate, and colorectal cancer, compared to the general population, resulting in later stage at diagnosis.[164,167,179–181] Widespread screening for cervical and colorectal cancer, along with the ability to remove pre-cancerous lesions, has translated into dramatic reductions in the incidence of these cancers over time.[77,80–82,232] Because people with psychotic disorder are less likely to participate in these programs, it is possible that we would not see the same reductions in incidence over time as we have seen in the general population. Conversely, prostate and breast cancer have been over-diagnosed in the general population as the result of excessive screening.[83–85,232,233] Therefore, low adherence to these screening programs may result in under detection of breast and prostate cancer, relative to the general population. Additionally, this lack

of screening uptake for other cancers could apply to melanoma, potentially explaining the lower incidence observed in people with NAPD.[150,235]

Although later stage at diagnosis does contribute to higher mortality rates among people with psychotic disorder, this does not account for the entirety of the excess mortality.[168] Physicians' perceptions of patients with psychotic disorder have further health consequences in this population, through diagnostic and treatment overshadowing.[236] Diagnostic overshadowing refer to the phenomena whereby physicians misattribute symptoms of physical illnesses to a person's pre-existing mental illness diagnoses, such that the physical illnesses may be overlooked.[236] Although difficult to quantify, the effects of diagnostic overshadowing can be seen in the disparities in receipt of treatment by people with mental illnesses.[236] An example can be found in treatment for ischemic heart disease, where people with psychotic disorder were less likely to receive revascularization procedures compared to people without psychotic disorder.[248,249] A cohort study using Ontario health administrative data found that people with serious mental illnesses (SMI), including schizophrenia, schizoaffective disorder, major depression, and other bipolar disorder, were significantly less likely to receive surgical resection or adjuvant treatment for colorectal cancer, compared to those without SMI, translating to a higher mortality risk.[202] Furthermore, people with psychotic disorders are less likely to receive adequate medical management of physical illnesses, as physicians may doubt a patient's ability to adhere to treatment and lifestyle interventions, in a phenomenon termed 'nihilistic overshadowing'.[245]

4.3 Strengths and Limitations

This thesis must be considered within the larger body of literature examining cancer incidence and stage at diagnosis among people with psychotic disorders. Our meta-analysis provided a comparison of cancer risk among people with psychosis by synthesizing data from a broader array of studies than has been done previously. Our retrospective cohort study is the first to examine cancer incidence and stage at diagnosis among people with psychotic disorders in Ontario. The use of population-based health administrative data in a country with universal healthcare allows for a substantial follow-up period of a large, representative sample. Furthermore, our retrospective cohort study represents one of very few studies which examine incidence and stage at diagnosis within the same cohort.

The systematic review in chapter 2 should be considered in light of its limitations. Firstly, there was a high degree of statistical heterogeneity present in our meta-analyses. This was likely because our meta-analyses included a variety of effect estimates with varying levels of adjustment for confounding factors. These estimates were included in order to analyze a wider range of studies with varying methodology; however, this may have introduced a substantial degree of statistical heterogeneity. Secondly, our literature search did not include unpublished literature or grey literature. Therefore, introducing potential publication bias as well as excluding a body of potentially relevant literature. Furthermore, our Egger's test was underpowered to detect publication bias for studies examining stage at diagnosis. As such, it is unclear whether publication bias was present in our meta-analysis of stage at diagnosis.

This thesis was limited by the availability of data within the health administrative databases. The OCR does not contain cases of basal or squamous cell carcinomas of the skin, thereby minorly limiting our ability to examine a number of cancer types.[238] Additionally, the

incidence of myeloma, laryngeal cancer, and Hodgkin's lymphoma were low within our cohort. Therefore, the validity of estimates and conclusions drawn about these particular cancers is limited. Moreover, there was a large proportion of missing data for stage at diagnosis among people diagnosed with cancer over the follow-up period, with people in the exposed group being more likely to have missing stage data. If people with missing stage data differ systematically from those with complete stage data, this may limit the generalizability of our analyses of stage at diagnosis. Furthermore, there are low rates of screening for colorectal, breast, prostate, and cervical cancer among people with psychotic disorders,[164,167,179–181] which may introduce detection bias for these cancers.

There was a potential for misclassification among our exposed group as a result of a high sensitivity of our case definition used to identify people with psychotic disorders. However, we expect that this misclassification was nondifferential by outcome status. Additionally, our case definition was limited to people diagnosed with nonaffective psychotic disorder, therefore our conclusions may not be generalizable to people with affective psychoses.

Because our cohort was restricted to people aged 15 to 59 at the index date, the conclusions drawn from our cohort study may only apply to those within this age range. Additionally, our conclusions may be limited to cancers which commonly occur in younger people.[239]

Finally, because health administrative data is designed for billing rather than research purposes, we were not able to adjust for a number of important confounding factors such as antipsychotic medication exposure, obesity, smoking, and a number of other lifestyle factors which contribute to cancer risk.[1,5,24,44–48,144] As we explored in the discussion of chapters 2 and 3, factors associated with obesity and cardiometabolic disorders likely have a substantial influence on the risk of a number of cancers, including breast, colorectal, and prostate cancer.[104,105,161]

Therefore, we are not able to understand the pathway from psychotic disorder diagnosis to cancer incidence without adjustment for these factors.

4.4 Future Directions

Future research regarding this topic should be more transparent in the reporting of case definitions used to identify people with psychotic disorders and the extent to which missing data may have had an influence on the results. Additional studies should be conducted using population-based health administrative data in countries with universal healthcare in order to improve the representativeness of samples to the general population and improve comparability of study populations.

Future research should work to quantify the effects of antipsychotic medication exposure and comorbidities such as obesity and diabetes, which occur in higher rates among people with psychotic disorders,[5,24,44–48] and are demonstrated risk factors for a number of cancers.[104,105] In addition to the varying effects of antipsychotic medication on cancer risk by site,[144,146–148,157] treatment with anti-psychotic medication has been found to worsen the risk of cardiometabolic disorders.[28,29] The intermediary effects of these variables in the relationship between psychotic disorder diagnosis and cancer, should be examined along with screening uptake and vaccination coverage.

In the future, we will use the cohort identified in chapter 3 in order to examine how treatment decisions, following a cancer diagnosis, influence cancer-specific and all-cause mortality among people with PD. Mahar et al. have suggested that disparities in reception of treatment by patients with colorectal cancer, may account for a portion of the 69% higher

mortality risk among people with severe psychiatric illnesses, as patients with severe mental illnesses were less likely to receive surgical resection or adjuvant treatment.[202]

Furthermore, efforts should be made to educate and improve awareness regarding cancer screening programs and increase uptake of vaccinations for HPV and hepatitis among this vulnerable population.

4.5 Conclusion

This thesis identified a significantly elevated cancer incidence among people with nonaffective psychotic disorders, relative to people without psychotic disorders. The magnitude and direction of this effect varied significantly by cancer site. Additionally, we observed effect modification by sex, which was likely driven by the lower incidence of prostate cancer among people with NAPD. These differences in cancer incidence are likely the product of environmental, lifestyle, and socioeconomic risk factors among people with psychotic disorders, along with poor screening behaviour.

The evidence of more advanced stage cancer at diagnosis is reflective of a diagnostic delay and differential access to care for people with psychosis. These differences are likely driven, in part, by misperceptions, stigma, and diagnostic overshadowing on the part of healthcare providers, as well as health-seeking behaviours of people with psychotic disorders.[237] It is important to note that these differences are observed in a country with universal healthcare, wherein cost barriers in access to care are minimal.

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Appendices

Appendix 2A: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	15
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	15
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	16 – 17
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	18
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	18 – 19
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	18
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2B (page 115)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	18 – 19
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	19
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	19
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	19
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	19
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	19 – 20

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	20 – 21
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	20 – 21
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	21
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	21
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	20 – 21
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	21
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	20 – 21
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	21 – 22
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	22
Study characteristics	17	Cite each included study and present its characteristics.	Table 2.1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2.3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendices 2H and 2I
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix 2C
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2.4 – 2.6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figures 2.4 – 2.6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	23 – 25
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	23 – 25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	23 – 25

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	25 – 29
	23b	Discuss any limitations of the evidence included in the review.	29 – 30
	23c	Discuss any limitations of the review processes used.	30 – 31
	23d	Discuss implications of the results for practice, policy, and future research.	31 – 32
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	32
Competing interests	26	Declare any competing interests of review authors.	32
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	32

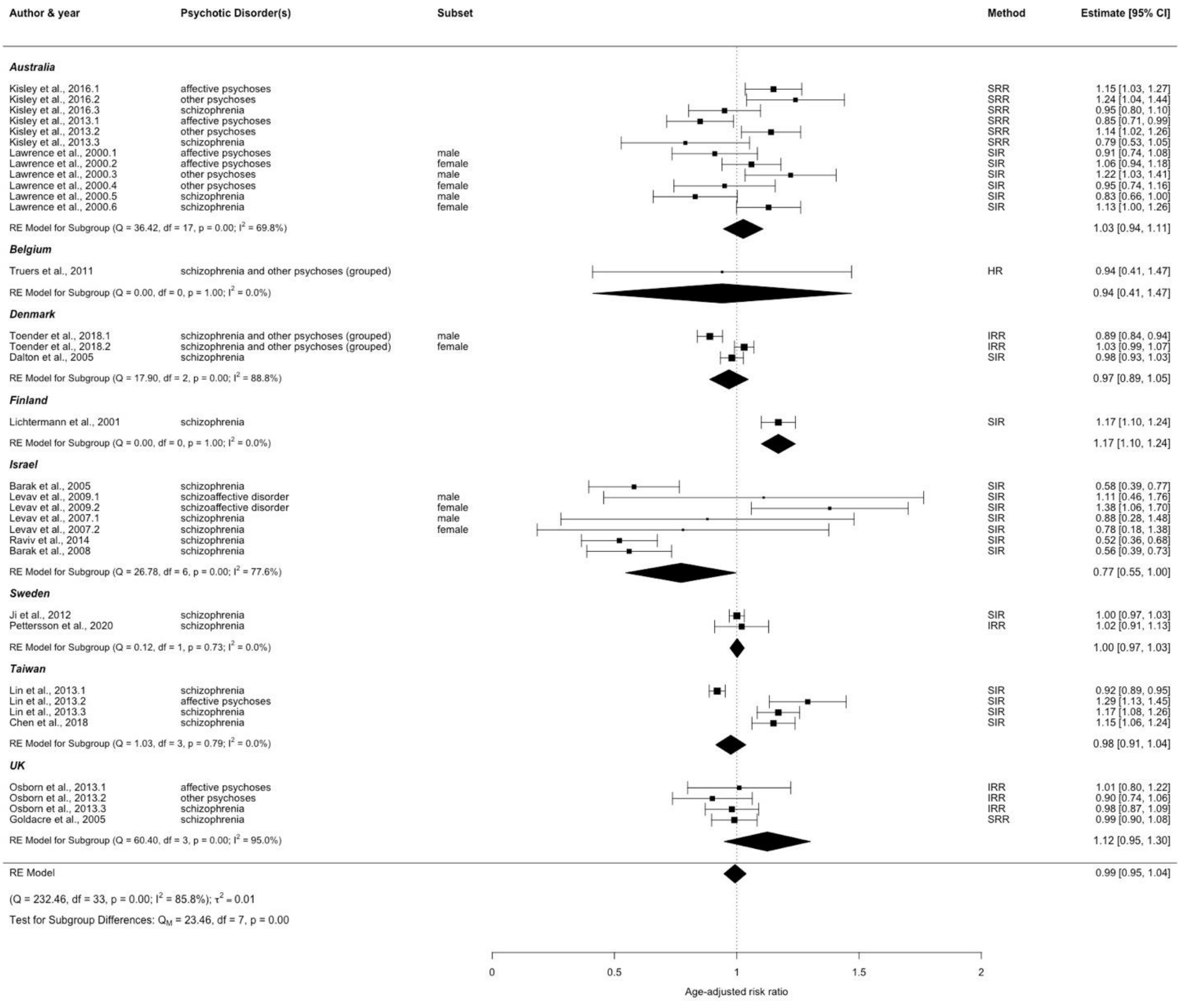
Appendix 2B: Search strategy

	Database				
Concept	Medline (via Ovid)	PsychNFO (via Ovid	EMBASE (Via Ovid)	CINAHL	Keywords
cancer	exp neoplasms/ or cancer.mp.	exp neoplasms/ or cancer.mp.	Cancer.mp. or exp malignant neoplasm/	(MH "Neoplasms+") OR cancer	Cancer or neoplasms
Psychotic disorders	exp "schizophrenia spectrum and other psychotic disorders"/ or (Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder*).mp.	exp psychosis/ or (Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder*).mp.	exp psychosis/ or (Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder*).mp.	(MH "Psychotic Disorders+") OR "psychosis" OR "psychotic" OR schizophreni* OR "sever* mental ill*" OR "sever* mental disorder"	Psychotic disorders or schizophrenia or severe mental illnesses
Incidence and staging	cancer staging.mp. or exp Neoplasm Staging/ or incidence.mp. or exp Incidence/	exp morbidity/ or morbidity.mp. or incidence.mp. or (cancer staging or staging).mp.	exp cancer staging/ or exp staging/ or staging.mp. or cancer staging.mp. or cancer incidence.mp. or exp cancer incidence/	(MH "Neoplasm Staging") OR "cancer staging" OR "staging" OR (MH "Incidence") OR inciden*	Cancer incidence or cancer staging
Results	231	139	374	323	

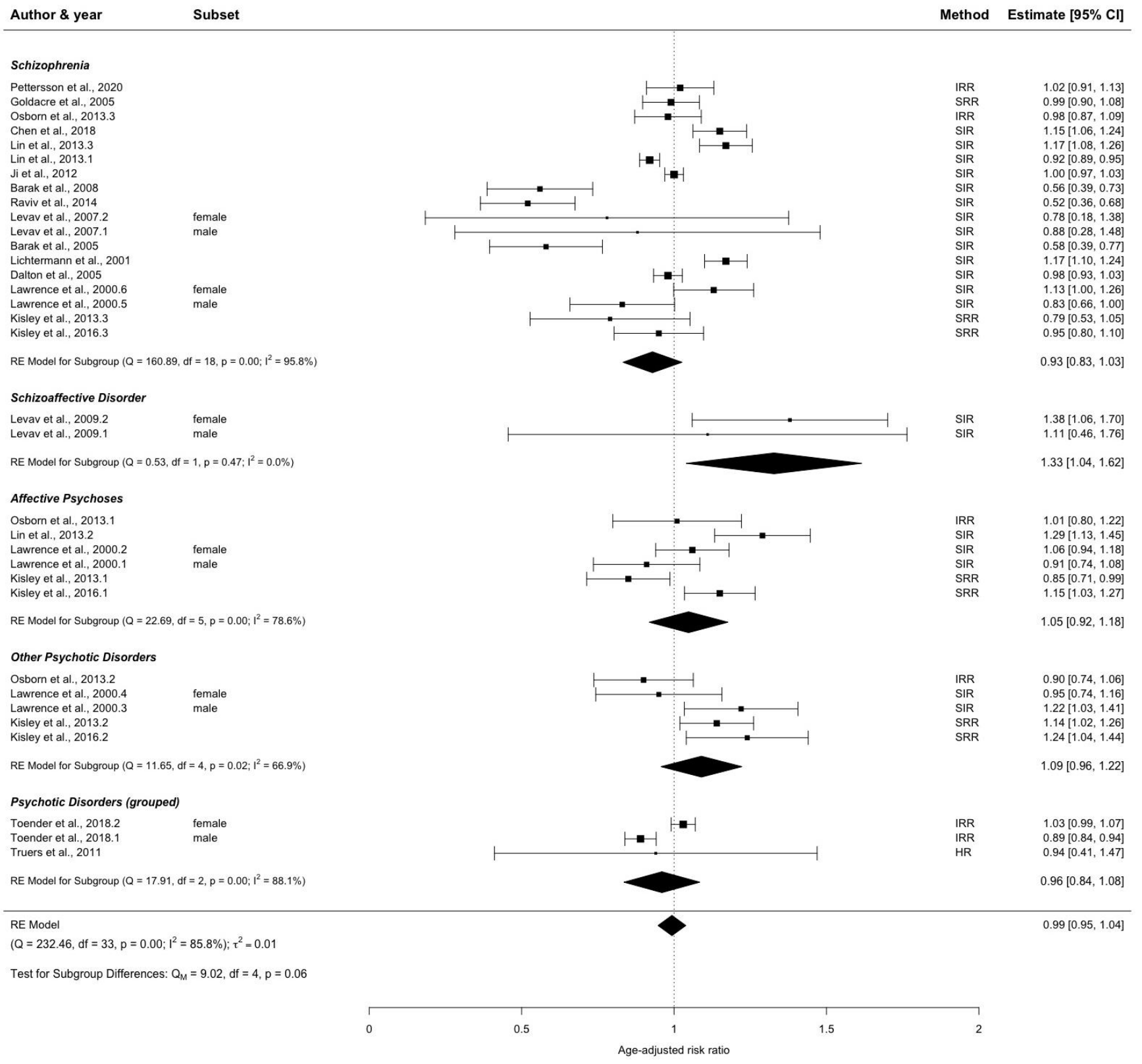
Appendix 2C: Results of Risk of Bias Assessment

Citation	1. Is the source population representative of the general population?	2. Was selection of exposed and non-exposed cohorts drawn from the same population?	3. Can we be confident in the assessment of exposure?	4. Can we be confident in the assessment of outcome?	5. Can we be confident that the outcome of interest was not present at start of study?	6. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	7. Can we be confident in the assessment of the confounding factors?	8. Was the follow up of cohorts adequate?	9. Is there little missing data?
Chen et al., 2018	low risk	intermediate risk	intermediate risk	low risk	low risk	intermediate risk	low risk	intermediate risk	not reported
Dalton et al., 2005	low risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	not reported
Chou et al., 2011	intermediate risk	low risk	low risk	low risk	high risk	intermediate risk	low risk	intermediate risk	intermediate risk
Lin et al., 2013	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	intermediate risk	low risk
Goldacre et al., 2005	intermediate risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	not reported
Grinshpoon et al., 2005	intermediate risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	not reported
Levav et al., 2009	intermediate risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	not reported
Liao et al.2015	intermediate risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	intermediate risk	not reported
Kisley et al., 2016	intermediate risk	low risk	intermediate risk	low risk	high risk	high risk	low risk	high risk	not reported
Lin et al., 2013	low risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	intermediate risk	not reported
McGinty et al., 2012	high risk	intermediate risk	not reported	low risk	high risk	intermediate risk	low risk	intermediate risk	not reported
Mortensen et al., 1989	intermediate risk	intermediate risk	not reported	low risk	high risk	intermediate risk	low risk	low risk	low risk
Kisley et al., 2013	low risk	low risk	low risk	low risk	intermediate risk	intermediate risk	low risk	low risk	low risk
Dalton et al., 2008	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	intermediate risk	low risk
Truers et al., 2011	low risk	low risk	low risk	low risk	intermediate risk	intermediate risk	low risk	intermediate risk	not reported
Chou et al., 2017	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	low risk	low risk
Barak et al., 2005	intermediate risk	intermediate risk	low risk	low risk	intermediate risk	intermediate risk	low risk	intermediate risk	intermediate risk
Mortensen, 1994	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	intermediate risk	not reported
Lichtermann et al., 2001	low risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	not reported
Ishikawa et al., 2016	intermediate risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	intermediate risk	low risk
Ahlgrén-Rimpiläinen et al., 2020	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	low risk	low risk
Arffman et al., 2019	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	low risk	not reported
Baillargeon et al., 2011	high risk	low risk	intermediate risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk
Barak et al., 2008	intermediate risk	intermediate risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	not reported
Brink et al., 2019	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	low risk
Bergamo et al., 2014	high risk	low risk	intermediate risk	low risk	intermediate risk	low risk	low risk	low risk	not reported
Chang et al., 2013	intermediate risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	intermediate risk	low risk
Osborn et al., 2013	intermediate risk	low risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	low risk
Raviv et al., 2014	high risk	low risk	not reported	low risk	intermediate risk	intermediate risk	low risk	intermediate risk	not reported
Levav et al., 2007	high risk	intermediate risk	intermediate risk	low risk	intermediate risk	intermediate risk	low risk	low risk	not reported
Ji et al., 2012	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	low risk
Manderbacka et al., 2017	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	not reported
Dalton et al., 2008	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	intermediate risk	low risk
Cunningham et al., 2015	low risk	low risk	not reported	low risk	low risk	low risk	low risk	intermediate risk	low risk
Scheflen, 1951	high risk	intermediate risk	intermediate risk	intermediate risk	intermediate risk	high risk	intermediate risk	not reported	not reported
Toender et al., 2018	low risk	low risk	intermediate risk	low risk	low risk	low risk	low risk	low risk	intermediate risk
Lawrence et al., 2000	low risk	low risk	intermediate risk	low risk	low risk	intermediate risk	low risk	low risk	low risk
Pettersson et al., 2020	low risk	low risk	low risk	low risk	low risk	intermediate risk	low risk	low risk	low risk
Hippisley-Cox et al., 2007	low risk	low risk	not reported	low risk	low risk	low risk	intermediate risk	low risk	low risk

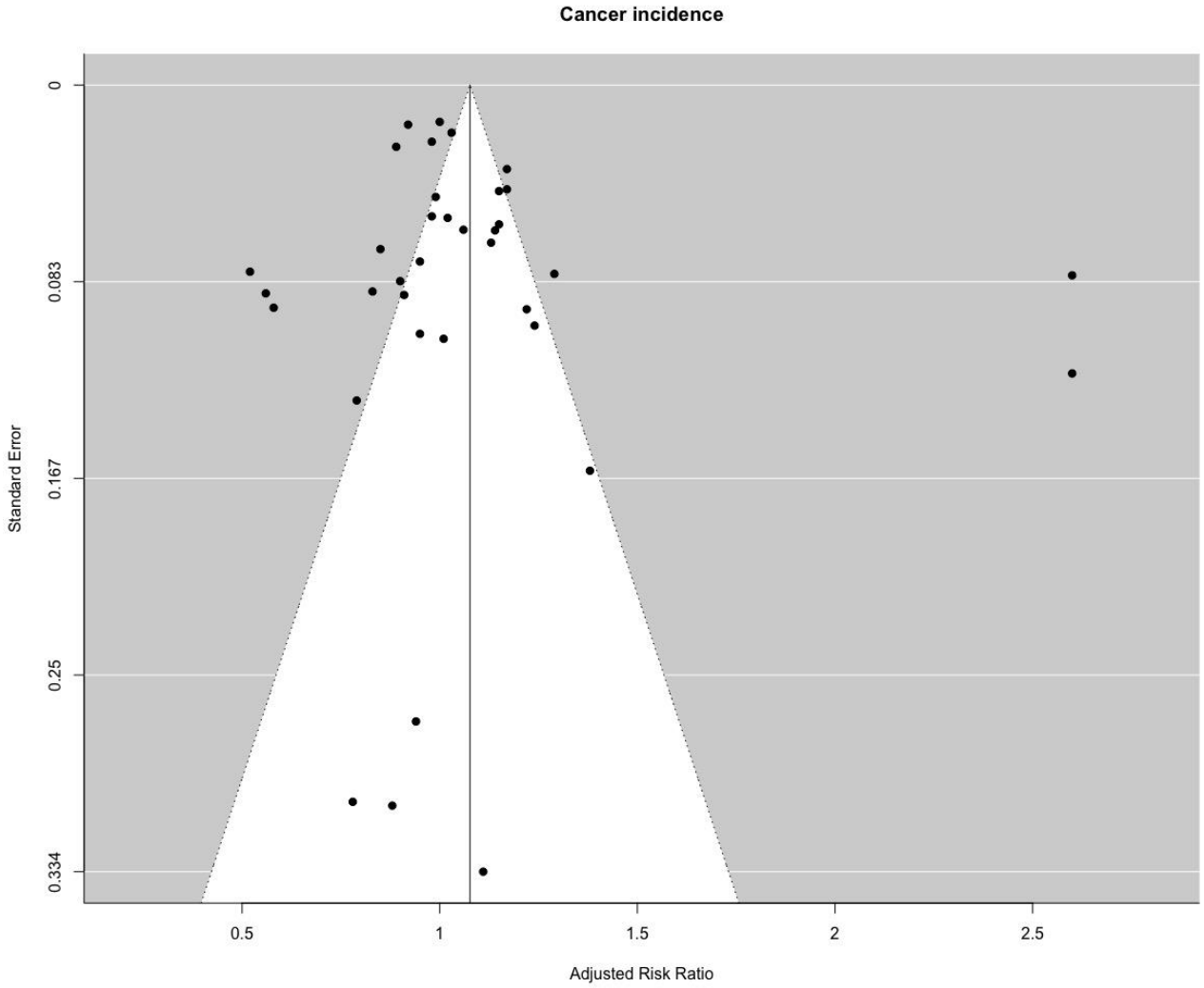
Appendix 2D: Meta-analysis of overall cancer incidence sub-grouped by country



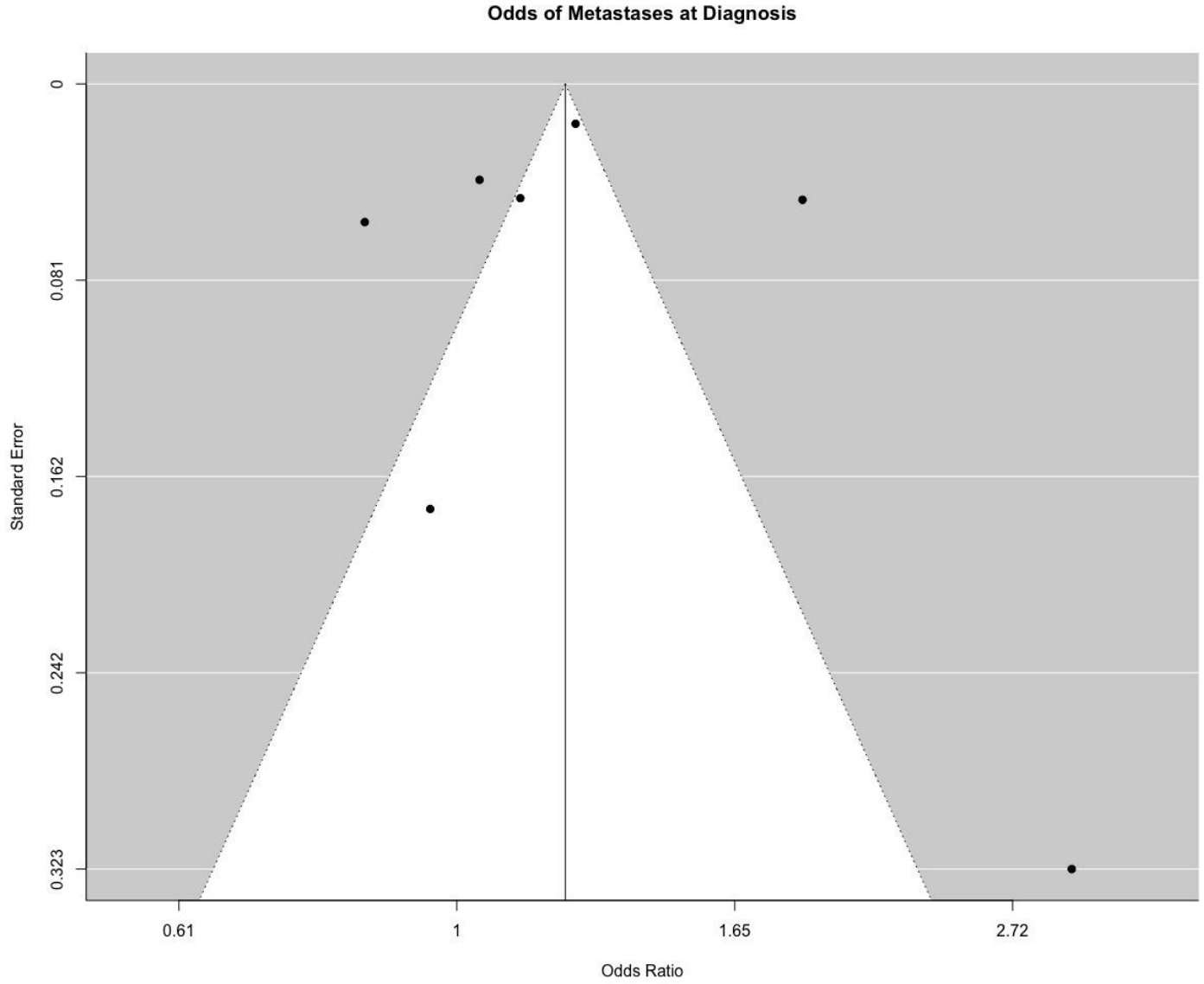
Appendix 2E: Meta-analysis of overall cancer incidence sub-grouped by specific psychotic disorder



Appendix 2F: Funnel Plot of cancer incidence



Appendix 2G: Funnel Plot of odds of metastases at diagnosis



Appendix 2H: Summary of findings table for studies which reported on cancer incidence

Citation	Psychotic Disorder	sub-sample	Cancers	Exposed				Unexposed				Crude				Adjusted					Other Findings
				Outcome	No Outcome	Total	Person Time (P-Y) (IR)	Outcome	No Outcome	Total	Person Time (IR)	Crude incidence measure	Point Estimate	lower (95%)	upper (95%)	Adjusted Measure	Point Estimate	lower (95%)	upper (95%)	Covariates	
Barak et al., 2005	schizophrenia		all cancer	120	3106	3226	NR	NR	NR	NR	NR					SIR	0.58	0.48	0.69	age	Significantly reduced risk of all cancers overall. Significantly reduced risk of stomach and rectal cancer. Reduced risk of prostate cancer
Barak et al., 2008	schizophrenia		all cancer	139	1872	2011	NR	NR	NR	NR	NR					SIR	0.56	0.47	0.66	age	Women with schizophrenia had a reduced incidence of cancer overall compared to the general population. Women with schizophrenia had a reduced incidence of breast cancer compared to the general population. Increased risk of cervical uteri cancer among women with schizophrenia.
Breen, 1981	schizophrenia		all cancer	24	38	62	NR	25	37	62	NR										more patients in control group died of lung cancer compared to the patients with schizophrenia.
Brink et al., 2019	schizophrenia		all cancer	632	3912	4544	107833	3605	18992	22597	623822										People with schizophrenia between the ages of 50-59 had an increased risk of cancer, compared to the general population.
Chen et al., 2018	schizophrenia		all cancer	514	32217	32731	238509									SIR	1.15	1.06	1.26	age	higher incidence of cancer overall in people with schizophrenia, relative to the general population. Females with schizophrenia had a higher incidence of breast and bladder cancer compared to the general population. Males with schizophrenia had a higher incidence of colorectal cancer.
Chou et al., 2011	schizophrenia		Lung, stomach, liver, colorectal, esophagus, prostate, breast, cervical/uterine, other	1145	58112	59257	NR	5294	172862	178156	NR	Cox (HR)	0.64	0.6	0.69	HR	0.71	0.66	0.75	gender, urbanization, Charlson Comorbidity Index Score (CCIS), monthly income, age	people with schizophrenia had an increased risk of cancer, compared to those without schizophrenia.
Chou et al., 2017	schizophrenia		breast	119	10608	10727	87114	65	10662	10727	88811	HR	1.88	1.39	2.54	HR	1.94	1.43	2.63	age, occupation, monthly income, comorbidities, medications	females with schizophrenia were 1.88 (95% CI: 1.39–2.54) times more likely to develop breast cancer, even after adjusting for confounding factors (aHR: 1.94, 95% CI: 1.43–2.63). Risk of breast cancer significantly higher in females receiving combination of FGAs and SGAs. Compared with the non-schizophrenia cohort, the aHRs of breast cancer were nearly 2-fold regardless of the mean FGA exposure dosage
Dalton et al., 2005	schizophrenia		all cancer	1394	21372	22766	292230									SIR	0.98	0.93	1.02	age	No difference in cancer incidence for people with schizophrenia, relative to the general population. Elevated SIR during the first year of follow-up. Decreased risk of rectal cancer, prostate cancer, and non-melanoma skin cancers among males with schizophrenia. Female patients with schizophrenia had an increased risk of breast cancer.
Dalton et al., 2008	schizophrenia and other psychoses	males	lung	143	14841	14984	139396	11496	1486926	1498422	24915314	IRR	1.67	1.42	1.97	IRR	3.03	2.57	3.58	education, disposable income, employment status, social class, housing tenure, size of dwelling, cohabiting status, district type, ethnicity, charston comorbidity index, depression	incidence rates of lung cancer decreased with increasing social advantage (education, income, closer affiliation to work market, housing tenure, larger housing). Presence of somatic or psychiatric disorders increased IRR.
		females		153	13787	13940	140218	8997	1457779	1466776	12414122	IRR	1.54	1.31	1.81	IRR	2.51	2.14	2.94	education, disposable income, employment status, social class, housing tenure, size of dwelling, cohabiting status, district type, ethnicity, charston comorbidity index, depression	
Dalton et al., 2008	schizophrenia and other psychoses	males	all cancer	NR	NR	NR	NR	NR	NR	NR	NR					IRR	1.47			age, period, education, disposable income	In persons with schizophrenia, the incidence rates of lung, breast, and cervix cancer were increased and the incidence rate of prostate cancer was reduced.
		females		NR	NR	NR	NR	NR	NR	NR	NR					IRR	1.4			age, period, education, disposable income	
Goldacre et al., 2005	schizophrenia		all cancer	486	9163	9649	NR	26926	NR	~600000	NR					standardized RR	0.99	0.9	1.08	age, gender, year	No difference in cancer risk overall among people with schizophrenia, compared to the reference group. Incidence of esophageal cancer elevated in those with schizophrenia. Skin cancer, rectal cancer, colon cancer lower in people with schizophrenia.
Grinshpoon et al., 2005	schizophrenia	males	lung, breast, melanoma, brain, corpus uteri, prostate	602	NR	NR	336109	NR	NR	NR	NR					SIR	0.86	0.8	0.93	age	incidence of cancer overall was lower for both males and females with schizophrenia, compared to the general population. Males with schizophrenia had an increased risk of lung cancer. Females with schizophrenia had an increased risk of cancers of corpus uteri and breast.
		females		902	NR	NR	288755	NR	NR	NR	NR					SIR	0.91	0.85	0.97	age	
Hippisley-Cox et al., 2007	schizophrenia		all cancer																		people with schizophrenia had significantly increased risk of breast and colon cancer, but a lower risk of respiratory cancer. Increased breast cancer risk not affected by antipsychotic medication use.
Ji et al., 2012	schizophrenia		all cancer	5101	53096	58197	NR	NR	NR	NR	NR					SIR	1	0.97	1.03	age, gender, calendar period, SES, residential area, comorbidity	people with schizophrenia had a decreased incidence of cancer overall, compared to the general population. Decrease was more pronounced before the first diagnosis of schizophrenia. Increased risk of liver, breast, cervix, and endometrium cancer and unknown primary after first diagnosis. adjusting for smoking reduced incidence of urinary and bladder cancers, but increased breast and endometrium cancer. When restricting to cancer after first diagnosis, male patients with schizophrenia had lower incidence than the general population, while female patients had a higher risk. overall risk was significantly reduced among unaffected parents and siblings. Breast cancer had increased risk irrespective of follow-up time and period after first diagnosis--in attempts to evaluate effects of antipsychotic treatment.
Kisley et al., 2013	schizophrenia		all cancer	129	NR	NR	NR	NR	NR	NR	NR					standardized RR	0.79	0.61	1.02	age	overall incidence of cancer lower in people with psychiatric illnesses. Statistically significantly lower cancer incidence in males with affective psychoses, stress or adjustment reactions, and non-specific psychiatric diagnoses.
	affective psychoses			358	NR	NR	NR	NR	NR	NR	NR					standardized RR	0.85	0.75	0.98	age	
	other psychoses			302	NR	NR	NR	NR	NR	NR	NR					standardized RR	1.14	1.01	1.28	age	

Citation	Psychotic Disorder	sub-sample	Cancers	Exposed				Unexposed				Crude				Adjusted					
				Outcome	No Outcome	Total	Person Time (P-Y) (IR)	Outcome	No Outcome	Total	Person Time (IR)	Crude incidence measure	Point Estimate	lower (95%)	upper (95%)	Adjusted Measure	Point Estimate	lower (95%)	upper (95%)	Covariates	Other Findings
Kisley et al., 2016	schizophrenia		all cancer	236	NR	NR	NR	NR	NR	NR	NR					standardized RR	0.95	0.81	1.08	age	cancer incidence lower in people with psychotic disorders compared to the general population.
	affective psychoses			319	NR	NR	NR	NR	NR	NR	NR					standardized RR	1.15	1.02	1.28	age	
	other psychoses			185	NR	NR	NR	NR	NR	NR	NR					standardized RR	1.24	1	1.48	age	
Lawrence et al., 2000	schizophrenia	males	all cancer	223	NR	NR	NR	NR	NR	NR	NR					SIR	0.83	0.7	0.98	age, gender	lower cancer incidence rates were observed in males with schizophrenia and dementia and both male and female patients with non-specific psychiatric diagnoses.
	schizophrenia	females		273	NR	NR	NR	NR	NR	NR	NR					SIR	1.13	0.99	1.28	age, gender	
	affective psychoses	males		211	NR	NR	NR	NR	NR	NR	NR					SIR	0.91	0.76	1.07	age, gender	
	affective psychoses	females		401	NR	NR	NR	NR	NR	NR	NR					SIR	1.06	0.94	1.19	age, gender	
	other psychoses	males		118	NR	NR	NR	NR	NR	NR	NR					SIR	1.22	1.02	1.47	age, gender	
	other psychoses	females		149	NR	NR	NR	NR	NR	NR	NR					SIR	0.95	0.78	1.17	age, gender	
Levav et al., 2007	schizophrenia	males	all cancer	28	4045	4073	NR	NR	NR	NR	NR					SIR	0.88	0.55	1.78	age, gender, country of origin	Both parents, including those with schizophrenia had a reduced cancer risk compared to the general population. When excluding parents with schizophrenia, this remained unchanged. Lower ratios were found for gender-concordant pairs of offspring and parents.
		females		14	2045	2059	NR	NR	NR	NR	NR					SIR	0.78	0.37	1.19	age, gender, country of origin	
Levav et al., 2009	schizoaffective disorder	males	all cancer	12	1191	1203	13445	NR	NR	NR	NR					SIR	1.11	0.48	1.73	age	People with schizoaffective disorder did not have significantly different incident rates for cancer than the general population or people with bipolar disorder. Cancer incidence among female patients with schizoaffective disorder significantly higher than among female patients with schizophrenia.
		females		42	1155	1197	13445	NR	NR	NR	NR					SIR	1.38	0.96	1.8	age	
Liao et al., 2015	schizophrenia		hepatocellular carcinoma	16	2521	2537	16351	35	9393	9428	68452	IRR	1.91	1.67	2.19	HR	1.93	1.07	3.49	age, diabetes mellitus, cirrhosis, alcoholic liver damage, other chronic hepatitis, hepatitis B	higher incidence of hepatocellular carcinoma in those with schizophrenia than those without schizophrenia. Schizophrenia group aged 40-64 had the highest incidence of HCC, but the schizophrenia group aged 20-39 had the highest risk of HCC (IRR: 4.03, 95% CI: 3.42 to 4.75).
Lichtermann et al., 2001	schizophrenia		all cancer	724	26272	26996	446653	NR	NR	NR	NR					SIR	1.17	1.09	1.25	age, calendar period	increased overall incidence of cancer in people with schizophrenia. Increased for cancers of lung, pharynx, gallbladder. Decreased incidence of rectal cancer. Decreased incidence of cancer for relatives, compared to the general population. Cancer incidence in siblings and parents of those with schizophrenia was lower than the general population.
Lin et al., 2013	schizophrenia		all cancer	1738	100464	102202	774691	NR	NR	NR	NR					SIR	0.92	0.9	0.96	age, sex, follow-up time	patients with schizophrenia had a significantly lower risk of cancer overall, compared to the general population. Elevated risk of cancers in nasopharynx, brain, breast, uterine cervix (invasive), uterine corpus, ovary, and other uterine adnexa. Decreased incidence of cancer in lip, oral cavity and pharynx, stomach, colorectum, liver, pancreas, lung, thyroid, other skin, and prostate. female patients with schizophrenia had a higher incidence of cancer overall, compared to the general population, whereas male patients with schizophrenia had a lower incidence of cancer overall. When female-specific cancers were excluded, female patients with schizophrenia had similar incidence to the general population. relative risk of cancer in patients with schizophrenia is highest among patients aged 20-29. Effect is seen across all cancer types. higher cancer risk for those with earlier age of onset.
Lin et al., 2013	schizophrenia		all cancer	1129	70188	71317	NR	NR	NR	NR	NR					SIR	1.17	1.08	1.28	age, sex, follow-up time	Females with schizophrenia and females with bipolar both had a higher incidence of cancers overall, compared to the female general population. Overall cancer SIR for people with schizophrenia reduced gradually as age of onset increased, and SIR became protective from age 50. Same decrease with females but no protective effect after a certain age. Females with schizophrenia had an increased risk of breast and body of uterus cancers.
	bipolar disorder			367	20200	20567	NR	NR	NR	NR	NR					SIR	1.29	1.11	1.51	age, sex, follow-up time	
McGinty et al., 2012	schizophrenia		all except non-melanoma skin cancer	155	2160	2315	19855	NR	NR	NR	NR					SIR	2.6	2.2	3	age	elevated incidence of cancer observed in people with schizophrenia and bipolar disorder, compared to the SEER population. Observed in all subgroups with the exception of men with bipolar disorder. Elevated incidence of colorectal and breast cancer. Men with schizophrenia had an increased risk of prostate cancer--not observed in men with bipolar
	bipolar disorder			75	927	1002	8405	NR	NR	NR	NR					SIR	2.6	2	3.2	age	
Mortensen et al., 1989	schizophrenia		all cancer	1028	5124	6152	NR	NR	NR	NR	NR					SIR	0.9			age	male patients with schizophrenia had significantly reduced incidence of cancer, especially for cancers of the respiratory, genital, and urinary systems. Overall, cancer incidence in female patients with schizophrenia was not different from the general population. Male and female patients with schizophrenia together, had a lower incidence of cancer. Elevated risk of developing breast cancer in patients with schizophrenia. In female patients, increased incidence of non-Hodgkin lymphoma. lower incidence of lung cancer.
Mortensen, 1994	schizophrenia		all cancer	133	9023	9156	NR	NR	NR	NR	NR					SIR	0.79			age, gender, calendar period	Male patients with schizophrenia had a significantly reduced incidence of cancer. Reduction for females but not statistically significant. Reduced incidence of skin and testicular cancer in male patients with schizophrenia.
Osborn et al., 2013	schizophrenia and other psychoses		all cancer	380	20252	20632	NR	2356	113796	116152	NR	IRR	0.95	0.85	1.06	IRR	0.98	0.88	1.09	age, sex, period, deprivation	no difference in overall cancer incidence in people with SMI, compared to those without SMI. No difference in specific cancers either
Pettersson et al., 2020	schizophrenia		all cancer	11670	99636	111306	424829	NR	NR	NR	NR					IRR	1.02	0.91	1.13	age, sex, calendar period	no significant difference in the overall incidence of cancer. No differences found by age group or period. Slightly decreased incidence of overall cancer in males with schizophrenia and a slightly increased incidence of overall cancer in females with schizophrenia. People with schizophrenia had a significantly higher incidence of cancers of the lung, esophagus, pancreas, and breast. Males with schizophrenia had a lower incidence of prostate cancer.
Raviv et al., 2014	schizophrenia		all cancer	181	4145	4326	NR	NR	NR	NR	NR					SIR	0.52	0.45	0.61	age	significantly reduced incidence of cancer among people with schizophrenia, compared to the general population.
Scheflen, 1951	schizophrenia, bipolar, affective psychosis, non-organic psychosis		all cancer	NR	NR	NR	NR	NR	NR	NR	NR										no difference in cancer incidence between people with psychotic disorders and people without
Toender et al., 2018	schizophrenia, bipolar disorder, schizoaffective disorder	males	all cancer	NR	NR	NR	NR	NR	NR	NR	NR					IRR	0.89	0.85	0.94	age, calendar period, somatic comorbidity, substance abuse	Slightly lower cancer incidence in males with SMI. Females with SMI had similar incidence of cancer overall to females without SMI.

Citation	Psychotic Disorder	sub-sample	Cancers	Exposed				Unexposed				Crude				Adjusted					
				Outcome	No Outcome	Total	Person Time (P-Y) (IR)	Outcome	No Outcome	Total	Person Time (IR)	Crude incidence measure	Point Estimate	lower (95%)	upper (95%)	Adjusted Measure	Point Estimate	lower (95%)	upper (95%)	Covariates	Other Findings
		females		NR	NR	NR	NR	NR	NR	NR	NR					IRR	1.03	0.99	1.07	age, calendar period, somatic comorbidity, substance abuse	
Truers et al., 2011	schizophrenia and other psychoses		all cancer	NR	NR	894	NR	NR	NR	4010	NR	HR	0.85	0.51	1.42	HR	0.94	0.56	1.58	age, gender	no significantly higher risk for cancer

Appendix 2I: Summary of findings table for studies which reported on cancer stage at diagnosis

Citation	Psychotic Disorder	Notes	Cancers	Staging	stage I (local)	stage II	stage III (regional)	stage IV (metastasized)	missing	Total	stage I (local)	stage II	stage III	stage IV (metastasized)	missing	Total	Crude Measure	Point Estimate	lower (95%)	upper (95%)	Adjusted Measure	Point Estimate	lower (95%)	upper (95%)	Covariates	Other Findings
Ahlgrén-Rimpiläinen et al., 2020	non-affective psychotic disorders		breast	local-metastasized	1774			269	202	2245	65218			5308	5308	75834										
Arffman et al., 2019	non-affective psychotic disorders	Male	lung	local-metastasized	125			592	238	955	3589			15314	5025	23928									age, time of diagnosis	
		Female		local-metastasized	45			259	101	405	1393			5849	2042	9284										
Baillargeon et al., 2011	psychotic disorders		colon	I-IV	662	933	586	576	819	3576	13133	18831	13853	10495	3718	60030										
Bergamo et al., 2014	schizophrenia		all cancer	I-IV	398	57	423	413	12	1303	24899	4292	29501	35596	1111	95399										Elderly patients with schizophrenia were less likely to receive stage-appropriate NSCLC treatment compared to those without schizophrenia. When analyzed according to stage, patients with schizophrenia were less likely to undergo surgery for stages I-IIIA, receive combined RT and chemotherapy for stage IIIB or chemotherapy for stage IV NSCLC.
Chang et al., 2013	schizophrenia		all cancer	local-metastasized	57			36		93	18205			10143		28348	OR	1.13	0.75	1.72	logistic (OR)	1.23	0.81	1.88	age, gender	No association between diagnosis with any SMI and advanced stage at diagnosis, adjusting for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity and deprivation score for income.
	bipolar disorder			local-metastasized	24			7		31	18205			10143		28348	OR	0.52	0.22	1.22	logistic (OR)	0.55	0.24	1.3	age, gender	
	schizoaffective			local-metastasized	4			1		5	18205			10143		28348	OR	0.45	0.05	4.02	logistic (OR)	0.47	0.05	4.38	age, gender	
Cunningham et al., 2015	schizophrenia, bipolar disorder, schizoaffective disorder		all cancer	local, regional, meta	53		38	11	10	112	4467	3021		277	557	8322										
Ishikawa et al., 2016	schizophrenia		gastric, colorectal	I-IV	595	402	483	845	170	2495	4347	1476	1622	1805	730	9980					ordinal logistic regression (RR)	1.86	1.72	2	age, gender, comorbidity, income, smoking, type of cancer	People with schizophrenia had a higher proportion of stage IV cancer (33.9%) compared to those without schizophrenia (18.1%)
Manderbacka et al., 2017	psychotic disorders	Male	all cancer	local-metastasized	3088			2237		5325	183311			90288		273599										
		Female		local-metastasized	4873			3115		7988	212935			100205		313140										
Toender et al., 2018	schizophrenia, bipolar disorder, schizoaffective disorder	Male	all cancer	local, regional, meta	528	301		355	449	1633	97435	50908		58186	69511	276040										
		Female		local, regional, meta	974	753		445	502	2674	123050	82125		46709	46808	298692										

Appendix 3A: 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	RECORD items	Location in manuscript where items are reported
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	Pages 48 – 49	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.	Page 48 Page 48 Page 48
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 49 – 51		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 51		
Methods					
Study Design	4	Present key elements of study design early in the paper	Pages 52 – 55		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 52 – 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	Pages 53 – 54	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.	Pages 53 – 54 Pages 53 – 54

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		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	Page 54	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.	Appendices 3C, 3D
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Pages 55 - 56	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.	Appendix 3B
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	Appendix 3B Appendix 3B		
Bias	9	Describe any efforts to address potential sources of bias	Pages 53 - 58		
Study size	10	Explain how the study size was arrived at	Appendices 3C, 3D		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 56 – 57		
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	Pages 56 – 57 Pages 56 – 57 Pages 56 – 57 Pages 56 – 57 Pages 56 – 57		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Pages 53 – 54

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Pages 53 – 54
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	Appendices 3C, 3D Appendices 3C, 3D	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.	Appendices 3C, 3D
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)	Page 58 and table 3.1 Appendices 3C, 3D Page 59		
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	Pages 59 – 60		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Pages 59 – 60		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Pages 59 – 60		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Pages 60 – 65		
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	Pages 66 – 67	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.	Pages 66 – 67
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 60 – 65		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 66 – 67		
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	Pages 67 – 68		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Appendix 3

Appendix 3B: Derivation of exposure, outcome, and confounding variables

Variable Name	Source of Data	Description	Variable Name in Database	Values and Database Codes
Main Comparison Groups				
Exposed	DAD, OHIP	Binary group membership - To be classified in the exposed group as a case of psychotic disorder, people must meet at least one of the following criteria: (1) at least one primary discharge diagnosis (dxtype=M, dx10code) of schizophrenia, schizoaffective disorder, schizophreniform, or psychosis NOS in the DAD database (see appendix B1 for diagnostic codes) OR (2) at least two OHIP billings within 24 months with a diagnostic code (DXCODE) for schizophrenia, schizoaffective disorder, schizophreniform, or psychosis NOS in the OHIP claims database (see appendix B1 for diagnostic codes)	N/A	Exposed (1) vs unexposed (0)
Index Date	DAD, OHIP	Date of first diagnosis of non-affective psychotic disorder	N/A	Date (DDMMYYYY)
Baseline Socio-Demographic Characteristics				
Age at Index Date	RPDB	Age at index date	BDATE	Continuous variable calculated based on index date and birth date
Gender	RPDB	Recorded sex	SEX	1 = Male 2 = Female
Rural Residence	RPDB	Rural place of residence, defined using the Rurality Index of Ontario. Areas with score of 40 or above are considered rural.	RIO2008	1 = Rural 0 = Non-Rural
Income Quintile	RPDB	Neighbourhood-level income quintile	INCQUINT	1 = Lowest Income Quintile 5 = Highest Income Quintile
Access to a family physician	PCPOP	Person is assigned to a FP in PCPOP database closest to the index date	R_TYPE	0 = no regular FP 1 = regular FP
Censoring events				

Variable Name	Source of Data	Description	Variable Name in Database	Values and Database Codes
Censored	N/A	Censored at end observation time	N/A	1 = censored 0 = not censored
Censored date	N/A	Date of first censoring event	N/A	Date (DDMMYYYY)
Reason for Censoring	RPDB, OHIP, DAD	Reason for censoring at the end of the observation time	N/A	0 = not censored developed cancer at the end of the observation time 1 = death as recorded in RPDB 2 = Maximum follow-up date (December 31, 2019) 3 = New onset of non-affective psychotic disorder (unexposed group only)
Observation Time	N/A	Time (in days) between index and end of observation (first of cancer_dxdate or censored_date).	N/A	Time in days
Outcomes				
Cancer	OCR	Person identified in the OCR during the follow-up	N/A	1 = incident cancer case identified in OCR during follow-up 0 = No incident cancer case identified in OCR during follow-up
Cancer diagnosis date	OCR	First date of incident cancer diagnosis	DXDATE	Date (DDMMYYYY)
Cancer site	OCR	Site of primary tumour	CURR_TOPOG_CD	OCR ICD-O-3 Topography Code (see appendix B2)
Cancer stage	OCR	Stage of cancer at diagnosis	BEST_STAGE_GRP	Roman numeral staging (I, II, III, IV) derived from TNM staging

Appendix 3C: Cohort Build for exposed group

Cohort build: Exposed group		**DAD**	-	**Ambulatory**	-
Step	**Description**	**#Excluded**	**# Patients remaining**	**#Excluded**	**# Patients remaining**
1	Diagnosis of non-affective psychosis identified using case definition between 1995 and 2005	-	116,982	-	15,392
2	Total BEFORE exclusions	-	116,982	-	15,392
3	Age <18 or >=60 at index	31,620	85,362	7,149	8,243
4	Invalid/missing data in age and sex variables	0	85,362	0	8,243
5	Non-Ontario resident	1,241	84,121	34	8,209
6	Not eligible for OHIP in past year	572	83,549	114	8,095
7	Death date < index date	<=5	NR	0	8,095
8	Presence of IKN in OCR from 1964 to index date	1,223	82,323	202	7,893
9	evidence of non-affective psychosis (diagnostic codes listed in appendix A) within 5 years prior to beginning of accrual period	23,803	58,520	1,239	6,654
10	After frequency match	0	58,520	0	6,654
11	Total AFTER cohort build exclusions	**58,459**	**58,520**	**8,738**	**6,654**
12	Remaining patients from **BOTH** databases	65,174			
	Excluded for cancer diagnosis on index date, diagnosis with stage 0 cancer, or invalid/missing data in income, rurality, and access to family physician variables	63,410	1,764		
	Total AFTER exclusions	**63,410**			

Appendix 3D: Cohort build for unexposed group

Cohort build: Unexposed group		**RPDB**	
Step	**Description**	**#Excluded**	**# Patients remaining**
1	Individuals in RPDB who are alive, in Ontario and born after 1935 as of Jan 1, 1995	-	18,218,136
2	Total BEFORE exclusions	-	18,218,136
3	Age <18 or >=60 at index	7,709,580	10,508,556
4	Invalid/missing data in age and sex variables	0	10,508,556
5	Non-Ontario resident	607,467	9,901,089
6	Not eligible for OHIP in past year	2,249,342	7,651,747
7	Death date < index date	1,389	7,650,358
8	Presence of IKN in OCR from 1964 to December 2004	93,225	7,557,133
9	In the exposed cohort	57,281	7,499,852
10	Evidence of schizophrenia, schizoaffective disorder, or psychosis NOS within 5 years of index date	24,425	7,475,427
11	After frequency match	7,214,731	260,696
	Total AFTER cohort build exclusions	**17,957,440**	**260,696**
	Excluded for cancer diagnosis on index date, diagnosis with stage 0 cancer, or invalid/missing data in income, rurality, and access to family physician variables	**10,157**	**250,539**

Appendix 3E: Results of age- and sex-stratified Poisson models of cancer incidence in people with NAPD, relative those without NAPD

Category	IRR	95% CI lower limit	95% CI upper limit
Ages 15 —19	0.92	0.71	1.21
Ages 20 – 29	1.00	0.89	1.14
Ages 30 –39	1.10	1.03	1.19
Ages 40 –49	1.08	1.03	1.14
Ages 50 – 59	1.10	1.04	1.15
Remove all gender specific	1.17	1.13	1.22
Male			
All ages male	1.01	0.97	1.06
15 – 19	1.08	0.77	1.51
20 – 29	1.05	0.88	1.26
30 – 39	1.05	0.94	1.17
40 – 49	1.00	0.93	1.09
50 – 59	0.99	0.92	1.06
Males with all male-specific cancers removed: testes, prostate	1.15	1.09	1.21
Males, excluding prostate cancer	1.15	1.10	1.21
Males, excluding testicular cancer	1.01	0.96	1.05
Female			
All ages female	1.15	1.11	1.20
15 – 19	0.73	0.47	1.14
20 – 29	0.96	0.80	1.15
30 – 39	1.14	1.04	1.26
40 – 49	1.15	1.07	1.23
50 – 59	1.19	1.12	1.28
Females, excluding breast	1.19	1.13	1.25
Females, excluding cervical	1.15	1.10	1.20
Females, excluding ovarian	1.16	1.12	1.21
Females, excluding uterine	1.15	1.10	1.20
All ages female (female-specific cancers removed: breast, cervix, ovary, uterus)	1.20	1.13	1.27

Curriculum Vitae

Education

University of Western Ontario—MSc student, Epidemiology and Biostatistics, September 2019 - Present

University of Guelph, Guelph ON — BSc. majoring in Biomedical Science, 2019

St. Marcellinus Secondary School, Mississauga ON—High School Diploma, 2015

Research Experience

Master's Student, Supervised by Dr. Kelly K. Anderson, PhD, Department of Epidemiology & Biostatistics, Western University—2019-2021

Thesis: Incidence of cancer, stage at diagnosis, treatment, and mortality among people with recent onset psychotic disorder

- Examined the incidence of cancer, stage at diagnosis, cancer-specific mortality, and treatment among those with recent onset, non-affective psychotic disorders, compared to the general population using Ontario health administrative data held by the Institute for Clinical Evaluative Sciences (ICES)
- Performed systematic review and meta-analysis on the incidence of cancer and stage at diagnosis among those with psychotic disorders

Summer Studentship, University of Guelph—2019

- Andrea Leger-Dunbar Summer Studentship in the Department of Population Medicine, Ontario Veterinary College (OVC)
- Performed meta-analysis and risk of bias assessment as continuation of fourth-year research project
- Reference screening for scoping review in population medicine regarding goat kid mortality

Fourth-year research project, Supervised by Dr. A. Jones-Bitton, Department of Population Medicine, OVC, University of Guelph—2018-2019

- Systematic review and meta-analysis to estimate of prevalence of depression among farming populations
- Protocol for a systematic review and meta-analysis: prevalence of depression among farmers and agriculturalists worldwide currently available at the University of Guelph Library Online Repository

Laboratory Assistant, university of Guelph, Guelph on—2018

- Assistance with lab work pertaining to molecular and cellular biology specific to plants
- Experience performing DNA extraction, Polymerase Chain Reactions (PCR), as well as gel electrophoresis

Contributions

Publications

Briana NM Hagen *, Charlotte B Winder, Jared C. Wootten, Carrie McMullen, Andria Jones-Bitton (*Submitted for review*). A systematic review and meta-analysis of depression among farming populations worldwide.

Manuscripts in preparation or under review

Jared C. Wootten, Joshua C. Wiener, Phillip Blanchette, MD, Kelly K. Anderson, PhD (*In preparation*). Cancer incidence and stage at diagnosis among people with psychotic disorders: A systematic review and meta-analysis.

Jared C. Wootten, Lucie Richard, Phillip Blanchette, MD, Yayuan Zhu, PhD, Kelly K. Anderson, PhD (*In preparation*). Incidence of cancer, stage at diagnosis, and mortality among people with psychotic disorders.

Janica Adams, Emily Constance Dawson, Tavleen Dhinsa, Jared C. Wootten, Piotr Wilk, PhD (*In preparation*). Differences in mental health service use among white and non-white immigrants to Canada.

Poster presentations

Jared C. Wootten, Joshua C. Wiener, Kelly K. Anderson, PhD. Cancer incidence and stage at diagnosis among people with psychotic disorders: A systematic review and meta-analysis. Mental Health Research & Innovation Day. 2020.

Jared C. Wootten, Joshua C. Wiener, Kelly K. Anderson, PhD. Cancer incidence among people with psychotic disorders: A systematic review and meta-analysis. Annual Scientific Meeting of the Canadian Academy of Psychiatric Epidemiology. 2020.

Teaching Experience

Graduate Teaching Assistantship, Epi 2200B: Introduction to Epidemiology—2021

- Leading tutorial sessions weekly
- Grading and assessment of exams and assignments

Awards & Achievements

Western Graduate Research Scholarship, 2019 - 2021

Andrea Leger Dunbar summer studentship

- Continuation of fourth-year research project into the summer

College Role of Distinction Award, University of Guelph—Winter 2019

- Awarded to students with an average of 85 or higher in semester 5 or later