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Sex Differences in Health Service Use for Mental and Substance Use Disorders Among Methamphetamine Users

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Abstract

Methamphetamine and associated health service use are rising globally, with psychiatric complications that may impact women and men differently. However, there are no recent population-level estimates of mental health and addictions (MHA) service use among methamphetamine users. This thesis explores the relationship between methamphetamine use and MHA service use across Ontario from 2017 to 2019 by identifying methamphetamine users through drug screen results and identifies differences in psychiatric health service use between women and men who use methamphetamine. Service use was higher in people with a positive test compared to those with a negative test, sex affected the relationship between methamphetamine use and MHA service use differently across psychiatric diagnostic categories, and men were at higher risk of MHA ED visits and hospitalizations compared to women. Sex did not affect the risk of outpatient visits or length of hospitalization. These findings can guide health system planning and harm reduction efforts.

Keywords

Methamphetamine; amphetamine; mental health and addictions; sex; health service utilization; Ontario

Summary for Lay Audience

Methamphetamine is a stimulant with significant health harms and its use is on the rise in Canada and internationally. This is also accompanied by a rise in mental health and addictions (MHA) service use for methamphetamine-related harms, including psychiatric complications such as depression and psychosis. Furthermore, evidence suggests that psychiatric complications of methamphetamine users can vary by sex, with authors of studies reporting that women who use methamphetamine may experience higher levels of mood and anxiety disorders, whereas more men may experience psychotic disorders. However, no studies report population-level findings on the rates of MHA service use associated with methamphetamine in Ontario and whether sex affects the rate of use. Therefore, this thesis aimed to understand: 1) the rate of mental health service use – including outpatient visits, ED visits, hospitalizations, and diagnostic categories 2) effect modification by sex on the rates of MHA service use, and 3) the sociodemographic and clinical factors associated with MHA use and total length of inpatient stay, within 12 months following a positive methamphetamine screen. Ontarians who had a methamphetamine/amphetamine urine/serum screen in 2017 or 2018 were identified through the Ontario Laboratory Information System (OLIS), a database with lab results for patients across Ontario. These individuals were included in the cohort and followed for 365 days to determine their rate of MHA service use, and for women and men in the cohort separately. Overall, service use was higher in people with a positive test compared to those with a negative test. Sex was identified as an effect modifier in the relationship between methamphetamine use and MHA service use across different psychiatric diagnostic categories. Men were at higher risk of MHA ED visits and hospitalizations compared to women. Sex did not affect the risk of outpatient visits or length of hospitalization. More information is needed on the effect of other sociodemographic on service use, including rurality and income quintile. These findings highlight the need for more research on the needs of methamphetamine users to guide health programming and interventions for harm reduction.

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Chapter 1

1 Introduction

This chapter provides a brief introduction to the thesis that provides an overview of the thesis topic, outlines its rationale and objectives, and describes the structure of the thesis and role of the student, supervisors, and committee members.

1.1 Overview of Thesis Topic

Methamphetamine use contributes to some of the most significant health harms associated with stimulants in Canada, and its use is on the rise.[1] Inpatient hospitalizations due to central nervous system stimulants (including methamphetamine) nearly doubled across Canada between 2007 and 2014[1]. Between 2003 and 2020, Crispo et al.[2] reported a 15-fold increase in the population-based rate of amphetamine-related emergency department (ED) visits in Ontario. Similarly, a recent Manitoba-based study[3] reported that health service contacts in the province due to methamphetamine increased between 2013 and 2018, noting seven-fold increase in methamphetamine-related emergency department (ED) visits and nearly a two-time increase in the rate of hospitalizations. In 2017, an estimated $200 million in direct health care costs in Canada were due to stimulant use, including methamphetamine.[1]

Increasing trends have also been seen in the United States (US): The National Surveys on Drug Use and Health (NSDUH) found that from 2015 to 2019, methamphetamine use in the US doubled among men and tripled among women.[4] Furthermore, from 2015 to 2019, there was a 43% increase in the number of people reporting past-year methamphetamine use and a 66% increase in the number of methamphetamine users who reported frequent use.[4]

In addition to physical harms such as arrhythmias, tooth decay, blood infections, and skin abscesses,[5–8] methamphetamine use is associated with increased psychiatric harms such as depression, suicidality, self-neglect, hostility, and symptoms of psychosis, including

hallucinations and delusions.[9,10] These psychiatric harms lead to increased methamphetamine-related mental health service use.[11–17]

Although the scientific literature broadly describes the risks of methamphetamine use in different population subgroups, these studies often have predominantly male participants, and few explore sex differences in prevalence of use and psychiatric diagnoses of methamphetamine users. Studies that do investigate sex differences in mental health presentations among methamphetamine users report conflicting findings, with some finding no differences in mental disorders between male and female users and others reporting more severe psychiatric symptoms among females than males.[18,19]

1.2 Thesis Rationale and Objectives

Despite the mental health effects of methamphetamine use and documented increases in methamphetamine use in recent years, there is a lack of recent literature estimating mental health and addictions (MHA)-related health service use by methamphetamine users. Furthermore, there is minimal information investigating sex differences in mental health service use among methamphetamine users. Therefore, this thesis had the following objectives:

1) What was the rate of mental health service use – including outpatient visits, ED visits, hospitalizations, and diagnostic categories – within 12 months following a positive methamphetamine screen?

2 Was there effect modification by sex on the rates of mental health service use within 12 months following a positive methamphetamine screen?

3) What were the sociodemographic and clinical factors associated with mental health outpatient visits, ED visits, hospitalizations, and total length of inpatient stay within 12 months following a positive methamphetamine screen?

1.3 The Role of the Student, Supervisors, and Committee Members

The data for this project was obtained from ICES, formerly known as the Institute of Clinical Evaluative Sciences, which is a not-for-profit organization that houses clinical and administrative health service data of patients across Ontario. This thesis is part of a larger project aimed at identifying methamphetamine users in the health administrative data and describing their medical, psychiatric, and health service-related outcomes. I created a project proposal and dataset creation plan – based on the methods of the larger project – where I outlined the background and rationale behind the project, outlined the required databases, defined the outcome measures and exposures, and described my analysis plan. My supervisors and committee members evaluated these documents and provided important feedback which guided my project design. My co-supervisor, Dr. Silverman, provided clinical expertise which helped me describe the background and rationale of the project, define my objectives, and select clinically relevant inclusion and exclusion criteria, exposure variables, and outcomes of interest. My co-supervisor, Dr. Coleman, provided expertise and feedback throughout my project, from project design and proposal creation to statistical analysis. As the responsible ICES scientist on my project, Dr. Anderson also provided key information and feedback on the design of my project and proposal submission to ICES. Upon consultation with Dr. Choi to ensure the appropriateness and feasibility of my statistical methods, I proposed a data analysis plan that was approved my co-supervisors and Dr. Anderson. Melody Lam, an analytic epidemiologist at ICES, created the dataset necessary for completion of this project. Upon receiving feedback from my co-supervisors and committee members, I ran the statistical analyses and described the results. All supervisors and committee members gave feedback on the writing and content of this thesis.

Chapter 2

2 Background and Literature Review

This chapter will explore methamphetamine's pharmacology, followed by its adverse effects and epidemiology of use. Section 2.1 explains its mechanism of action on the central nervous system (CNS), followed by section 2.2 which explains the common methods of administration. Section 2.3 explores the epidemiology of methamphetamine use globally, in Canada, and in the United States. Section 2.4 describes physical and psychiatric harms of methamphetamine use. Section 2.5 describes the correlates of methamphetamine use identified in prior research studies, and finally, section 2.6 details systematic literature search to understand the current knowledge on mental health service use among methamphetamine users and identify the current gaps in literature.

2.1 Mechanism of Action

Methamphetamine is a potent psychostimulant used medically as a treatment for attention-deficit hyperactivity disorder (ADHD), weight loss, and narcolepsy. However, it is also known for its euphoric and addictive properties. As a derivative of amphetamine, methamphetamine is sometimes referred to by the generic term 'amphetamine' or 'amphetamine-type stimulant'.[20] Methamphetamine acts on nerve endings to promote the release of neurotransmitters dopamine, serotonin, and norepinephrine, and prevents their reuptake into cells, causing intense euphoria.[21,22] Once its effects wear off, methamphetamine must be retaken to experience its highs.

2.2 Methods of Administration

Methamphetamine comes in three forms: powder, pills, and crystals, and can be administered for illicit use through smoking, injecting, snorting, or oral ingestion.[23] Smoking, injection, and snorting are the most common methods of illicit administration, reported by 66%, 24%, and 10% of users, respectively.[23] Smoking and injection provide

the most rapid, intense, and short-lived highs, while snorting and oral ingestion provide slower, less intense highs.[23]

2.3 Epidemiology of Use

According to the United Nations (UN) World Drug Report 2022, there were an estimated 34 million people aged 15 to 64 years around the world who used amphetamine-type stimulants in 2020, the majority of whom used amphetamines or methamphetamines.[24] According the UN report, amphetamine use (including methamphetamine and prescription amphetamine stimulants) is estimated to be most prevalent in North America (3.9% of the population), followed by Australia and New Zealand (1.3%), Europe (~ 0.5%), Asia, and Africa (both ~ 0.4%).[24] While the global prevalence of past-year use in 2020 was similar to past-year use in 2010, (34 million versus 33 million, or 0.7% of the global population in both years), North American past-year use of amphetamine has increased from 1.3% of the population in 2010 to 3.9% in 2020.[24]

Recent population surveys suggest that the prevalence of methamphetamine use has been increasing among Canadians: the Canadian Alcohol and Drugs Survey reported that the past-year use of methamphetamine among people aged 15 years and older increased from 0.2% in 2015 to 0.5% in 2019.[25] Furthermore, among the general Canadian population aged 15 years and older, 2019 estimates indicated that both past-year and lifetime prevalence of methamphetamine use was higher among men compared to women (past year-use: 0.8% of all males versus 0.1% of all females; lifetime use: 4.1% of males versus 2.3% of females).[25] Methamphetamine is also a commonly used drug used among persons who inject drugs (PWIDs): authors of the Tracks Survey of people who inject drugs in Canada, 2017-2019 reported that 43% of PWIDs reported methamphetamine use within the past six months.[26]

Surveys also suggest that prevalence of methamphetamine use in the US has increased between 2015 and 2020. The results of the 2015 and 2021 NSDUH surveys indicate that the prevalence of past-year methamphetamine use among Americans aged 12 and older increased from 0.6% (0.9% of men and 0.4% women) in 2014 to 0.9% (1.2% of men and

0.7% of women) in 2020.[27] Past-year use also increased with older age – in 2020, 0.1% of youth aged 12 to 17 years reported methamphetamine use, while this estimate increased to 0.5% of adults aged 18 to 25 and 1.1% of adults aged 26 years and older.[27]

Harms arising from methamphetamine use are also on the rise. In Canada, methamphetamine use was associated with 44% and 53% of apparent stimulant toxicity-related deaths in 2018 and 2022, respectively.[28] In Ontario, the Office of the Chief Coroner for Ontario estimated that methamphetamine contributed to 14 deaths in 2012, which increased to 217 deaths in 2017.[29] Similarly, methamphetamine overdose deaths doubled from 2.1 per 100,000 Americans in 2015 to 5.6 per 100,000 in 2019 as per data from the Centers for Disease Control.[30] Notably, it is thought that increases in fentanyl contaminants in the methamphetamine supply may have contributed to the increase in methamphetamine-related deaths.[31, 32]

2.3.1 Sex-Specific Trends

The Canadian Centre on Substance Use and Addiction telephone survey estimated that women made up 11% of all methamphetamine users in 2019. However, in other Canadian studies that recruiting from harm reduction sites or health care centres, women made up 35% of methamphetamine users.[33,34] This difference may be due to differences in study designs, with women being reluctant to disclose use on a telephone survey. It is also possible that a larger proportion of female drug users use harm reduction services and health services compared to men, leading to a larger proportion of women users being represented in these studies. Bach et al.[35] reported that methamphetamine use is also on the rise in both men and women. Their Vancouver study of 1,030 crystal methamphetamine users (women=34.5%) identified a significant increase in methamphetamine use between 2006 and 2017 (19% to 36% $p<.001$). Women reported a significant 22% increase in crystal methamphetamine use (14% of women in 2006 versus 36% in 2016, $p <.001$), while men reported a smaller but still statistically significant 15% increase (22% to 37%, $p <.001$).

Notably, in younger age groups, women may represent a larger proportion of methamphetamine users. In Manitoba between 2013 and 2018, nearly all

methamphetamine users aged 10 to 14 were female.[3] This trend continued in other age groups: females aged 15 to 19 years made up over 5% of methamphetamine users, while males in the same age group only made up 3% of users. Females aged 20-24 years made up over 10% of all methamphetamine users while males in the same age bracket made up less than 10%.[3] However, males accounted for the majority of users aged 25 years and older. In the US, the 2021 NSDUH surveyed 279,844 adults (51% women) regarding drug use and reported that among all Americans aged 12 years and older, women made up 37% of people who reported past-year methamphetamine use.[27] However, women made up 41% of methamphetamine users between the ages of 12 and 17 and 53% of methamphetamine users aged 18 to 25, and this percentage decreased to women only making up 33% of users among adults 18 and older, and 35% of adults 26 years and older. This potential trend between sex and age of methamphetamine users should be further studied.

2.4 Effects of Methamphetamine Use

This section describes the effects of methamphetamine use beginning with its medicinal uses, followed by brief descriptions of physical effects, focusing on cardiovascular harms, blood-borne infections and sexually transmitted infections, and tooth decay. Finally, the psychiatric harms that arise from illicit methamphetamine use will be described in further detail.

2.4.1 Medicinal Use

While well-known for their recreational uses, amphetamines can be prescribed to treat ADHD. For example, methamphetamine is prescribed as a treatment for ADHD in the United States under the brand name Desoxyn.[36] Besides Desoxyn, other amphetamines are also prescribed by health care providers for ADHD, including Adderall (amphetamine salts), and Vyvanse (lisdexamfetamine).[36] Amphetamines can be used to treat obesity and promote weight loss: two examples of drugs used for this purpose include Desoxyn (approved to treat obesity, although rarely prescribed today) and Phentermine.[37] Finally, amphetamines like Adderall and Vyvanse can also be prescribed to treat excessive

daytime sleepiness experienced by patients with narcolepsy.[38] These drugs' side effects include decreased appetite, decreased fatigue, increased heart rate, dry mouth, and anxiety.[36]

2.4.2 Physical Harms

2.4.2.1 Cardiovascular Harms

Methamphetamine use is associated with cardiovascular harms. Excluding overdose and accident-related deaths, the number one cause of death among methamphetamine users is cardiovascular complications. Short-term use of methamphetamine increases heart rate and blood pressure, causes vasoconstriction, and can also lead to cardiac arrythmias.[6,5] Young people with a history of methamphetamine abuse have an elevated risk of myocardial infarction compared to their counterparts who do not use methamphetamine.[5] Chronic methamphetamine use is also associated with other serious cardiovascular conditions such as atherosclerotic plaque formation, pulmonary hypertension, and dilated cardiomyopathy, [5] as well as a 2-5-time increased risk of hemorrhagic stroke.[39, 40] Swor et al. found that compared to patients who had experienced an intracerebral hemorrhage, methamphetamine use was associated with significantly younger age of stroke onset and longer hospital stays.[41]

2.4.2.2 Blood-Borne Infections (BBIs) and Sexually Transmitted Diseases (STDs)

Illicit methamphetamine use is associated with an increased risk of acquiring blood-borne infections (BBIs) due to unsafe injection practices and increased risky behaviour among users. Unsafe needle sharing and unsterile injections can increase the risk of BBIs including human immunodeficiency virus (HIV), and hepatitis B and hepatitis C virus (HBV and HCV) among methamphetamine users.[42] Bacterial and fungal contaminants in the drug supply increase the risk of acquiring infectious diseases like infective endocarditis and methicillin-resistant *Staphylococcus aureus* (MRSA) soft tissue and skin infections among persons who inject methamphetamine.[43] Tactile hallucinations can cause users to have a sensation of insects crawling over their skin, leading to persistent

itching and scratching, open wounds, and skin abscesses that become infected with bacteria including MRSA and methicillin-susceptible *S. aureus*.[7] Methamphetamine's effects on mood also increases users' risky sexual behaviour (such as sex without a condom and multiple sexual partners),[44] increasing the risk of acquiring sexually transmitted infections and diseases (STIs and STDs) such as HIV, chlamydia, syphilis, and gonorrhea.[45, 46]

2.4.2.3 Tooth Decay

Methamphetamine misuse causes severe tooth decay informally known as 'meth mouth'. One key feature of this condition is dry mouth. The reduction in saliva and its enzymes are thought to leave teeth vulnerable to cavities and decay.[8] 'Meth mouth' also involves severe teeth grinding which wears down enamel and can lead to cracked, loose, or missing teeth.[8] Methamphetamine's acidic components can also dissolve enamel, leaving teeth vulnerable to cavities and infections.[47] Methamphetamine use also causes sugar cravings and consequent increased consumption of high sugar foods and drinks, leading to greater acid secretion by oral bacteria that further damages enamel.[8, 47] Gum disease is commonly seen in people who use methamphetamine; chronic methamphetamine use leads to severe gum disease, black, rotting teeth, and ultimately, tooth loss.[8, 47]

2.4.3 Psychiatric Harms

Through its stimulation of the CNS, methamphetamine causes intense euphoria, alertness, and energy for 6 to 12 hours after use.[6] Acute use of the drug can cause irritability, agitation, aggression, violence, and increased sex drive.[2024-09-26] 11:59:00 AM

Chronic methamphetamine use is associated with anxiety, depression, insomnia, hallucinations, and paranoia.[48] Methamphetamine use can also cause significant damage to episodic memory and executive function, causing problems in long-term memory recall, distractedness, and impulsive behaviour.[49]

2.4.3.1 Methamphetamine Use Disorder

Methamphetamine use disorder is diagnosed by a set of criteria for substance use disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The DSM-5 classifies methamphetamine as a general "amphetamine-type substance". Furthermore, methamphetamine use disorder falls under the larger category of "stimulant use disorders" outlined by the DSM-5. Unlike the DSM-IV that separated diagnoses of stimulant abuse and stimulant dependence, the DSM-5 combined these two categories into a single diagnosis referred to as stimulant use disorder.[50,51]

Stimulant use disorder is defined in the DSM-5 by the following criteria:

1) "The stimulant is often taken in larger amounts and over a longer period than was intended.
2) There is a persistent desire or unsuccessful efforts to cut down or control stimulant use.
3) A great deal of time is spent in activities necessary to obtain the stimulant, use the stimulant, or recover from its effects.
4) Craving, or a strong desire to use the stimulant.
5) Recurrent stimulant use resulting in a failure to fulfil major role obligations at work, school, or home.
6) Continued stimulant use despite having persistent or recurrent social or interper-sonal problems caused or exacerbated by the effects of the stimulant.
7) Important social, occupational, or recreational activities are given up or reduced be-cause of stimulant use.
8) Recurrent substance use in situations in which it is physically hazardous.
9) Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10) Tolerance.
11) Withdrawal."

The presence of 2-3 of these criteria over a 12-month period meets the threshold for diagnosis with a mild stimulant use disorder, meeting 4-5 of these criteria is classified as moderate stimulant use disorder, and 6 or more is classified as having a severe stimulant use disorder.[51]

For the purposes of describing studies in this literature review, the use of the terms "methamphetamine dependence" and "methamphetamine abuse" will be used as they appeared in their original publications and defined if necessary.

2.4.3.2 Methamphetamine-Induced Psychosis

A well-known consequence of methamphetamine use is methamphetamine-induced psychosis, which affects an estimated 26% to 46% of methamphetamine-dependent users.[52] According to the DSM-5,[50] substance-induced psychotic disorder can be diagnosed when an individual reports:

1) "Prominent hallucinations or delusions;
2) Hallucinations or delusions develop during or within a month of intoxication or withdrawal from a substance or medication known to cause psychotic symptoms;
3) Psychotic symptoms are not actually part of a psychotic disorder (such as schizophrenia, schizophreniform disorder, schizoaffective disorder) that is not substance-induced (i.e., if psychotic symptom onset was prior to substance or medication use, or persists longer than one month after substance intoxication or withdrawal, then another psychotic disorder is likely);
4) Psychotic symptoms do not only occur during a delirium; and
5) The symptoms cause significant social, occupational, or other forms of distress or impairment that impact important areas of functioning."

Methamphetamine-induced psychosis can lead to violence, delusions, and visual and tactile hallucinations.[48,53] More specifically, methamphetamine users can experience 1) paranoid delusions, the belief that a group or person is attempting to harm them; or 2) grandiose delusions, the belief that they have unique, important powers, wealth, or identity. While less commonly reported, methamphetamine-induced psychosis can also

involve negative affective symptoms including lack of facial expressions and minimal body language.[54]

2.4.3.3 Correlates of Methamphetamine-induced Psychosis

A systematic review by Arunogiri et al.[55] of 20 studies looking at risk factors of methamphetamine-induced psychosis found that both quantity of methamphetamine use and severity of dependence were correlated with psychosis among users.

There is also conflicting evidence regarding the association between a family history of psychosis or substance abuse and the risk of developing methamphetamine-induced psychosis. A study of 37 stimulant users (81% of whom primarily used methamphetamine) found that having a family history of psychosis or family history of schizophrenia is thought to increase an individual's risk of developing methamphetamine-induced psychosis. Ding et al. carried out interviews of 189 adult methamphetamine users in a rehabilitation centre and identified 35.4% who had experienced methamphetamine-related psychosis in their lifetime.[56] They found that adverse childhood experiences – which includes physical abuse, sexual abuse, or having a battered mother, incarcerated household member, or family members experiencing substance abuse – were significantly associated with increased risk of methamphetamine-induced psychosis in adulthood.[56] However, Arunogiri et al. found that 3 out of 5 studies in their systematic review that examined the relationship between family history of psychiatric illness and psychosis found no link, while 2 other studies each identified that family history of psychotic illness and family history of schizophrenia were correlated to persistent psychosis and lifetime substance-induced psychotic disorder, respectively.

2.4.3.4 Comorbid Psychiatric Diagnoses Among Methamphetamine Users

The prevalence of comorbid psychiatric conditions (mood disorders, anxiety disorders, and non-substance-related psychotic disorders) among methamphetamine users may be as high as 36% to 48%.[57,58] Among 100 methamphetamine users interviewed in a study by Akindipe et al., 16% reported a current mood disorder.[57] Similarly, Lisa et al.[59]

interviewed 93 methamphetamine users and reported that 14% of them met the DSM-IV criteria for current major depressive disorder. Comparative rates of current depression were found by Glasner-Edwards et al.,[58] who reported that 15% of methamphetamine users met the criteria for current major depressive disorder.

Comorbid anxiety disorders and symptoms have also been reported among people who use methamphetamine. Akindipe et al.[57] found that 7% of methamphetamine users in their study had an anxiety disorder. Other studies have found a higher prevalence of anxiety disorders: for example, Lisa et al.[59] identified that 11.8% of users had comorbid anxiety disorder, 12% had post-traumatic stress disorder (PTSD), and 5% had obsessive-compulsive disorder (OCD). Glasner-Edwards et al.[58] reported an even greater prevalence: 23% of methamphetamine users had a current anxiety disorder, which included generalized anxiety disorder (12% of users), PTSD (6%), and OCD (8%). Despite each of these studies using structured interviews and DSM-IV criteria to identify anxiety disorders, the differences in prevalence estimates indicate the need for further studies to understand the prevalence of anxiety disorders in methamphetamine users.

The prevalence of primary psychotic disorders (such as schizophrenia, schizophreniform disorder, schizoaffective disorder) may range from 4.9% to 13.0%.[58, 57] However, estimating prevalence of primary psychotic disorders in methamphetamine users is challenging due to their similarity in presentation to methamphetamine-induced psychosis – both primary and substance-induced psychotic disorders can involve hallucinations, paranoia, and delusions.

2.4.3.5 Sex Differences in Psychiatric Harms

The 2021 NSDUH[27] reported that 0.6% of Americans aged 12 years and older reported methamphetamine-related substance use disorder. Females were less likely than males to have a substance use disorder of any kind.[27]

Some studies suggest that there are sex differences in psychiatric harms arising from methamphetamine use. Among a sample of 103 men and 25 women in sober living homes who were dependent on methamphetamine, significantly more women reported

experiencing symptoms of post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), panic disorder, psychosis, somatization, and bulimia than men.[60] Similarly, an interview and survey-based study of methamphetamine-dependent men and women found that significantly more women had PTSD, mental stress disorder, and substance use disorder at discharge compared to men.[61]

Impulsivity is another characteristic associated with methamphetamine use. Cservenka & Ray[62] found that among a community sample of 133 men and 44 women who used methamphetamine, women reported higher levels of impulsivity than men as measured by the Barratt Impulsiveness Scale, although this difference was not statistically significant (p=.07). However, another study found that there were no sex differences in impulsivity among 62 methamphetamine users.[63]

2.4.4 Treatment

Treatment of the psychiatric harms of methamphetamine use can range from verbal reassurance by health care providers or cognitive behavioural therapy (CBT), to pharmaceutical treatments that include the use of anxiolytic and antipsychotic prescription medications. Benzodiazepines can be used to manage anxiety and irritation that arises from methamphetamine use. Recent preliminary data suggests that a tapering dose of lisdexamfetamine may be helpful in treating acute methamphetamine withdrawal.[64] Although there are currently no standardized treatments or evidence-based guidelines for the treatment of methamphetamine-induced psychosis, randomized controlled trials have shown that antipsychotics such as haloperidol, olanzapine, risperidone, and quetiapine may be effective at reducing its symptoms.[65, 66, 67]

Addressing symptoms of psychosis in the long-term focuses on reducing methamphetamine use. There are no approved pharmacological treatments for methamphetamine dependence; however, recent studies suggest that mirtazapine, bupropion, and naltrexone may potentially be effective in reducing methamphetamine use.[68, 69, 70] One evidence-based approach to treating methamphetamine dependence is the Matrix Model – a comprehensive outpatient program that includes a combination of individual and family counselling, 12-Step Facilitation, CBT, education, and support

groups for addiction.[71, 72, 73] However, it is resource-intensive, requires a rigid schedule, and is specialist-run.[74] Nevertheless, it is an effective program that is proven to help reduce methamphetamine use among those dependent on the drug.

2.5 Correlates of Methamphetamine Use

While there are many studies examining the factors associated with general substance use, there are few that examine the sociodemographic and clinical correlates and factors associated with methamphetamine use. Among youth under 19 years of age, studies report that history of opiate use, alcohol use, smoking, family history of drug use, family history of alcohol abuse, and risky sexual behaviour are associated with methamphetamine use.[75,76] A longitudinal birth cohort study by Boden et al.[77] examined childhood and adulthood predictors of methamphetamine use. Among children and adolescents, being male, reporting attention problems, alcohol use disorder, and deviant peer affiliations were identified as predictors of methamphetamine use in adulthood. Boden et al. identified history of substance use disorder, stress, and unemployment as adult correlates of methamphetamine use.

Similarly, Radatz et al.[78] identified other sociodemographic and behavioural characteristics as factors associated with methamphetamine use. In their 2014 study, they identified that male sex was associated with adolescent methamphetamine use. Another factor associated with adolescent methamphetamine use that they identified was ‘community risk’: a composite risk factor that includes perceived ease of access to drugs and neighbourhood crime. Furthermore, they identified ‘individual risk’ as a predictor of methamphetamine use, a composite factor that includes perceived harms of drug use, antisocial behaviour, attitudes towards drug use, and age at initiation into drug use.

Correlates of methamphetamine use among men and women have been identified by various studies. A study of 1,056 PWIDs in Tijuana, Mexico identified a significantly higher proportion of women reported methamphetamine compared to men.[79] Being younger than 35 years of age was correlated with methamphetamine use among women, while being homeless, having sex with another male, and being younger than 35 years of

age were correlates of methamphetamine use among men.[79] One study of 1,984 PWIDs[35] in Vancouver identified sex work, shared syringes, having unprotected sex, and history of experiencing physical violence as being associated with crystal methamphetamine use in both men and women. Past experiences of sexual violence were correlated with methamphetamine use among women, whereas homelessness, having sex with men, and being HIV positive were associated with methamphetamine use among males. In their Chicago-based study, Garofalo et al.[80] reported that risky sexual behaviour, lower self-esteem, and psychological distress were correlates of methamphetamine use among men aged 16 to 24 years who have sex with men.

2.6 Mental Health Service Use Among Methamphetamine Users

2.6.1 Literature Search

To understand what is known about mental health service use among methamphetamine users and identify knowledge gaps, a systematic literature search was conducted in June 2023 using PubMed, EMBASE, CINAHL, and PsycINFO databases via the OVID platform. Articles about methamphetamine were identified through the search terms (methamphetamine OR amphetamine). Studies focusing on the psychiatric effects of methamphetamine use were identified through the search terms (mental illness OR mental health OR psych*). Finally, studies investigating health service use were identified through the search terms (hospitaliz* OR hospitalis* OR inpatient OR admission OR outpatient OR visit OR emergency department OR urgent care). These groups of search terms were linked using the AND operator.

All studies focused on methamphetamine/amphetamine-type stimulant users that examined mental health service use outcomes (including history of health service use, number of visits, hospitalizations, and length of stay) were included. The health care settings that were the focus of this search were outpatient clinics, emergency departments (EDs), hospitalizations, and rehabilitation centres.

Studies with a pediatric population with a mean participant age less than 12 years were excluded. Interventional studies, case reports, case studies, case series, and studies with animal models were excluded. Studies that focused on non-methamphetamine stimulant use only (eg ecstasy, synthetic cathinones, etc) were excluded. Finally, studies that focused on specific sub-populations such as veterans, infants, or pregnant women only were excluded.

2.6.2 Findings

Seventy-two articles met the inclusion criteria. The majority of studies were based in the United States (n=32) or Australia (n=14). Only 4 studies were Canadian. Other countries represented included Switzerland, Iran, Germany, England, India, and Japan. Most studies relied on diagnostic codes in chart reviews, databases, or self-reported drug use to identify methamphetamine-related presentations. Only 23 studies involved the use of laboratory toxicology screens to identify/confirm methamphetamine use.

Overall, methamphetamine-related mental health service use has been increasing over the past 20 years. Generally, males made up the majority of methamphetamine users in the included studies, whereas female methamphetamine users accounted for larger proportions among younger age groups who used methamphetamine.[81,82] The mean/median ages of methamphetamine users in these studies were between the ages of 30 to 35 years. No studies investigated sex difference in mental health and addictions (MHA) service use specifically or the association between rurality and MHA service use. Factors that were commonly associated with methamphetamine use included younger ages (approximately 20 to 30 years of age), being male, and having low income.[83–85]

2.6.2.1 Outpatient MHA Service Use

Five studies reported outpatient mental health service use-related outcomes. Generally, authors of these studies reported the proportion of the sample with prior outpatient mental health and addiction service use. Population-level rates of outpatient health care use were not reported in any of the included studies, nor were sex differences or trends in outpatient health service use.

Among people with methamphetamine use disorder, authors of one study[86] in a single-payer public health care system in Taiwan reported that outpatient mental health service use significantly increased post-diagnosis compared to pre-diagnosis. Outpatient mental health service use may also vary among methamphetamine users based on medical specialty: one study of 484 people with methamphetamine dependence found that 34% of patients had seen an outpatient counsellor or psychologist, while only 23% had seen an outpatient psychiatrist.[87] Similarly, among people with amphetamine-related psychosis, only 36% reported past use of community mental health services.[85] Outpatient mental health referrals were only reported by one study: Chivaurah et al.[88] reported that 32.8% of people who presented to an ED with amphetamine-related symptoms were referred to community mental health services.

Use of outpatient mental health services may also vary based on methamphetamine use and prevalent mental health disorders: McKetin et al.[87] found that outpatient mental health service use decreased during periods of high frequency of methamphetamine use.[85] Similarly, those with amphetamine-induced psychosis were less like to have accessed outpatient mental health care compared to those with non-drug psychosis.[85] However, in another study by Lee et al.[89], methamphetamine users who died by suspected suicide were found to be more likely to have used outpatient psychiatric services in the 3 months prior to their death compared to their living counterparts.

2.6.2.2 Emergency Department Use

The included studies reported that both the proportion of methamphetamine-related ED visits and the proportion of mental health-related ED visits among methamphetamine users are increasing.[83,12,90,86,91]

The included studies found that methamphetamine-related ED visits and MHA-related ED among methamphetamine users have been on the rise. One Australian study[87] of 484 methamphetamine users estimated that methamphetamine led to an additional 29700 to 151800 ED visits in 2013, and that comorbid MHA disorders among methamphetamine users was an important predictor of presentation to EDs. Tardelli et al.[11] reported a 5.5-fold increase in the percentage of amphetamine-related ED visits in Toronto between

2014 and 2021 (1.5% and 8.3%, respectively). The proportion of these visits with a co-occurring MHA disorder increased from 25% to 55%. Authors of a similar study of by Harnett et al. of two EDs in London, England found that the percentage of patients who self-reported methamphetamine use increased 8.5-fold from 2% in 2005 to 16% in 2018.[92] Neuropsychiatric symptoms were the most commonly reported among the cases in this study: agitation (42%), anxiety (35%), hallucinations (17%), and psychosis (15%). An increasing trend in ED visits was also seen in an American study[91] using national ambulatory data: the rate of psychostimulant-related ED visits increased between 2008 and 2018 from 2.2 visits/10,000 population to 12.9 visits/10,000 population, ,with psychiatric concerns accounting for 50% of visits. In Hawaii, there was a significant increase in the percentage of amphetamine-positive patients vising an ED (13% in 2007 to 19% in 2011, $p<.001$).[83] Importantly, an Australian study also reported a seven-fold increase in the number of amphetamine-related presentations between 2011 and 2015 (24 cases versus 175 cases), with the majority of cases related to psychiatric symptoms/disorders; however, the percentage of cases were not reported by the authors.[93]

The average age of people in these studies typically included individuals who were 30 to 35 years old. Men made up the majority of methamphetamine users who visited the ED and generally, methamphetamine users were more likely to be male.[84,85,94] However, women made up larger proportions of ED visits among younger age groups. For example, McFaull et al.[82] reported that among methamphetamine-related injuries and poisoning cases that presented to a Canadian ED, females made up 71% of visits among those aged 10-14 years, and 64% of those aged 15-19 years.[82] Similarly, in one study[81] of 100 methamphetamine-related presentations to the ED in Australia, over one-quarter of women were in the 21-25 years age group, compared to only 10% of men.

Mental health and addiction-related visits made up an estimated 18% of all methamphetamine-related ED encounters.[95,96,97] The majority of studies only reported demographics of methamphetamine users, however, Indig et al.[98] reported that men with amphetamine-related ED visits were significantly more likely to have an MHA diagnosis compared to women (aOR, 95% CI = 7.9, 6.5-9.7 versus 6.4, 4.8-8.5, respectively). In the included studies, symptoms and disorders most frequently associated with

methamphetamine-related ED presentations included psychotic disorder (12-13%)[84, 93], psychosis (16-46.6% of presentations)[71,74,78,79], agitation (28-48% of presentations)[92,95,99,100], aggression (8-65.7% of presentations)[88,95,98,99,101], and suicidal ideation (10.5-47% of presentations).[12,95] Common prior mental health diagnoses included personality disorders, schizophrenia, depression, ADHD, bipolar disorder, and anxiety.[81,88,90,96,99,102] The risk of ED presentation was significantly higher among those with previous psychiatric health service use or a documented psychiatric diagnosis.[103,104]

Notably, studies[12,105] report that suicidal ideation and suspected suicide attempts may be significantly increasing among methamphetamine users who present to the ED. Murphy et al.[84] found that among patients with methamphetamine-related presentations, 29% had a history of a suicide attempt. Interestingly, in a study by Pasic et al.[94] of adult methamphetamine users and non-users, self-harm and suicide attempts made up 40% of methamphetamine-related psychiatric ED visits and 67% of non-related visits. In this same study, Pasic et al. found that methamphetamine users who presented to the psychiatric ED were less likely to have a history of suicide attempts compared to patients who did not use methamphetamine. The reasons for this difference were unclear, although it may be due differences in the characteristics of the convenience sample of users and non-users included in the study: significantly more users were male compared to non-users (85% versus 62%), users were significantly younger than non-users (mean age 31.4 years versus 36.9 years, respectively), and significantly fewer users had a past psychiatric diagnosis or hospitalization compared to non-users. In a nested-case control study by Lee et al.,[89] nearly 30% of 745 methamphetamine users who died by suicide reported use of ED services within 3 months prior to their deaths – a significantly higher proportion compared to their living age- and sex-matched counterparts. Importantly, women may represent a larger proportion of cases of suicide and self-harm in younger ages: McFaull et al. found that women made up 75% of cases of self-harm among methamphetamine users aged 10-19 years old.[82] This was despite the fact that females only made up 71% and 64% of users between 10 to 14 years of age, and 15 to 19 years of age, respectively. However, among those aged 20-49 years, men made up 70% of methamphetamine users, and correspondingly, male methamphetamine users represented 67% of cases of self-harm in this age group.

2.6.2.3 Hospitalizations

Studies[11,12,14–16] across different countries generally showed an increase in mental health-related hospitalizations by methamphetamine users. McKetin et al.[87] estimated that methamphetamine use accounted for an 28,400 to 80,900 psychiatric admissions in Australia in 2013. In a retrospective chart review, Nathani et al.[14] reported an increase in the number of psychiatric admissions associated with amphetamine use from 352 (11% of total psychiatric admissions) in 2006 to 528 admissions (15% of total psychiatric admissions) in 2015. Similarly, a South African study by Sara et al.[15] described an increase in admissions for amphetamine-induced psychosis between 2000-2009 from 2 to 24 admissions/day. At a California medical centre, however, Richards et al.[12] reported that the percentage of psychiatric admissions decreased from 58.1% of methamphetamine presentations in 1996 to 41.2% in 2016. Looking at Canadian data, Callaghan et al.[16] detailed a rise in methamphetamine-related hospitalizations from approximately 30-50 admissions/month in 1996 to over 200/month by early 2005, a third of which had a primary diagnosis of mental and behavioural disorders. In a Toronto hospital, Tardelli et al.[11] reported that total inpatient admissions for amphetamine use increased from 76 in 2014 (63% with a co-occurring mental disorder) to 303 in 2021 (72% with a co-occurring mental disorder). They also reported that amphetamine-related hospitalizations with co-occurring psychotic disorder increased from 16% of admissions to 35% of admissions.[11] Among presentations to psychiatric EDs, one-third[106,107] to one-half[12,95] of methamphetamine-related presentations led to psychiatric admissions. Studies that reported methamphetamine MHA-related hospitalizations varied in duration: some studies reported hospitalization over a 1-month window while the longest study reported methamphetamine-related hospitalization trends over 15 to 20 years.

Common causes of MHA hospitalization among methamphetamine users were management of psychosis, psychotic disorder, depression, and suicidality.[83,93] Low income, drug treatment, and comorbid mental disorders were found to be associated with of psychiatric admission.[87] More frequent methamphetamine use was also associated with increased presentation to psychiatric hospitals.[87]

Few studies investigated trends in admission by sex or sex differences in mental health symptoms. Two studies reported sex differences in admission and had conflicting findings: Leamon et al.[107] found that female methamphetamine users were significantly more likely than men to be admitted to the psychiatric ward, while McKetin et al.[87] reported that sex was not associated with psychiatric admission. However, both these studies differed greatly in geographic region (Australia versus United States), sample size (60 versus 484), and year (1996 versus 2013). Plüddeman et al.[96] reported that among methamphetamine users who presented to psychiatric hospitals, men were twice as likely to present with aggression compared to females, while women were significantly more likely to present with mood issues.

Two American studies[94,97] reported no differences between the rates or proportion of psychiatric hospitalization of methamphetamine users and non-users, while one study[108] in Iran found that methamphetamine users were significantly more likely to be admitted to a psychiatric hospital compared to people who do not use methamphetamine. Conversely, another study by Schultz et al.[83] in Hawaii reported that significantly fewer methamphetamine users underwent psychiatric hospitalization compared to patients who did not use methamphetamine. Although patients' mean ages in these studies were similar (early to mid 30s), three of these settings looked at proportions or rates of hospital admission from an ED, while another looked at hospital admissions among those receiving outpatient drug treatment. Another reason for differences in findings between these studies could be due to regional differences in treatment practices, such as encouraging symptom resolution while waiting in an ED rather than being hospitalized soon after symptom onset to decrease health resource use.

Prior psychiatric admissions were reported by 25-41% of methamphetamine users who were admitted to hospital.[109,110] Common prior psychiatric diagnoses among people who were hospitalized included personality disorders, psychotic disorders (including schizophrenia), depression, ADHD, and anxiety.

Average length of stay in psychiatric ward/hospital reported in studies ranged from 2.5 days to 2.5 months. These five studies focused on patients being treated in public

hospitals with methamphetamine/amphetamine-induced psychoses and despite all using the DSM-IV or DSM-5 criteria for diagnosis and similar sample demographics (~ 65-77% male, mean age 30-35 years), there was a wide range in mean duration of stay. For example, Herbst et al.[111] found that the mean length of stay among patients with amphetamine-induced psychosis was 2.5 days. Thomas et al. and Medhus et al.[112] reported similar mean duration of treatment, respectively, of 7.4 days[113] and 6 days. Ali et al.[114], however, found that among 150 inpatients with methamphetamine-induced psychosis, the mean length of stay was 16.7 days. In Fasihpour et al.'s 2013 study,[115] authors found that average length of stay for methamphetamine users after admission was on average, 21.4 days. However, Iwanami et al.[116] found that mean length of stay for people with methamphetamine-induced psychosis was much longer at 2.5 months. Being male, current hospitalization with first-episode methamphetamine-induced psychosis, and having more severe symptoms of psychosis were associated with significantly longer lengths of stay.[114]

2.6.2.4 Rehabilitation Settings

Seven articles were based in rehabilitation settings, four of which were based in the United States, two in Germany, and one in England. Information pertaining to patients' MHA symptoms experienced and age and sex trends in symptoms was extracted. Information detailing the number of admissions and discharges was not extracted.

Five studies reported the percentages of patients admitted to rehabilitation centres for methamphetamine use who experienced psychiatric symptoms. These symptoms included depression (19.3-57% of users)[117–119,120], anxiety (9-40.4%)[118,120], suicidality (6-9%)[117,119–121], psychotic disorder (5.4-7%)[118,119], and hallucinations (6.6-19-34.8%).[119–121]

Studies that included patients seeking outpatient rehabilitation for methamphetamine use found similar proportions of people who had experienced suicidal thoughts. Among 83 methamphetamine users in outpatient methamphetamine treatment, Copeland & Sorenson[119] reported that 6% of methamphetamine users seeking treatment between 1995 and 1997 experienced suicidal ideation. Among a chart review of 500 methamphetamine users in an American outpatient rehabilitation clinic between 1989 and 1995, 6.9%

reported experiencing suicidal thoughts at the time of admission.[117] Similarly, 8.6% of methamphetamine users in outpatient rehabilitation in Hser et al.'s study[120] reported experiencing serious thoughts of suicide in the past 30 days. Christian et al.[121] also reported a similar proportion: 8% of 1,016 people entering outpatient rehabilitation for methamphetamine dependence between 1999 and 2001 reported experiencing suicidal thoughts in the past 30 days.

Women who use methamphetamine may experience significantly more MHA-related symptomatology. In their 2005 study, Hser et al.[120] reported that among 1,073 patients in outpatient or inpatient rehabilitation for methamphetamine abuse across California, women were significantly younger than men and significantly more women than men had experienced severe depression ($p=.002$), concentration or memory problems ($p=.0006$), or thoughts of suicide in the past 30 days. Significantly more women than men in this sample received mental health services ($p<.05$) over the course of the treatment. Franke et al.[61] also found key sex differences in MHA disorders among their sample of 108 inpatient methamphetamine users (22 female, 86 male): at both admission and discharge, significantly more women than men in their sample reported PTSD ($p<.001$), current/lifetime mental health disorder ($p<.001$), and non-addiction-related psychiatric comorbidities ($p<.001$). These results highlight a need to further investigate any sex differences in MHA symptoms among methamphetamine users.

Two studies focused on adolescent use of rehabilitation centres for methamphetamine dependence.[122,123] Although both sample sizes (90 vs 912 methamphetamine users) and sex (30% female vs 58% female) differed greatly between studies, both studies were set in outpatient centres and included methamphetamine users whose mean age was 16 years. In both these studies, females were more likely to use methamphetamine compared to males. Of the two studies, only Rawson et al.[122] collected information on psychiatric symptoms: depressive symptoms and auditory hallucinations were significantly more common in adolescent females compared to adolescent males (54% vs. 46%, $p =.000$ and 60% vs. 40%, $p =.010$, respectively). Reasons for these sex differences in symptoms are unclear; however, it is important to note that in their sample, Rawson et al. found that females were significantly more likely than men to report methamphetamine as their

preferred drug of use, while men preferred marijuana or alcohol.[122] This may contribute to symptoms such as increased hallucinations, which are associated with stimulant use rather than depressants like marijuana or alcohol.

2.6.2.5 Summary of Sex-Specific Trends

Overall, studies found that the average methamphetamine user was a male in their early 30s. Typically, males made up the majority (approximately 70%) of methamphetamine users in the samples of the included studies, although the percentage of males ranged from just under 50% to as high as 91%. However, females made up a larger portion of adolescent methamphetamine users, suggesting that younger females are more at risk of methamphetamine use.

Studies' findings conflicted on the relationship between sex and MHA symptoms and diagnoses. Some included studies in rehabilitation and inpatient settings reported that female methamphetamine users were more likely to have experienced MHA symptoms than males,[17,61,120] yet one other study in an ED department reported that males were more likely to have prior MHA diagnoses.[98] The role of MHA symptoms or diagnoses is not clear, this did not necessarily always translate to more admissions among women, with one study by Leamon et al.[107] reporting that women were more likely to be hospitalized than men, while McKetin et al.[87] did not find a difference in admission by sex. These findings could be due to differences in sample demographics, with females representing 39% of users in Leamon et al.'s study, but only 27% in McKetin et al.'s study. Most studies that reported the lengths of hospitalizations did not make comparisons by sex; however, based on one study described earlier by Iwanami et al.[116] of people with methamphetamine-induced psychosis, males may have longer hospital stays.

2.6.2.6 Limitations

There was a great degree of heterogeneity between the studies that met the inclusion criteria for this literature search. Cross-sectional studies, case-control studies, and longitudinal studies were included. Fewer than half of these studies used urine or serum

screens to identify methamphetamine users, and furthermore, some studies only had urine/serum screen results available for a portion of their sample. Other studies used self-reported information, medical records, national or regional databases, or a combination of these to identify methamphetamine users. Furthermore, due to differences in data sources of the studies (eg chart review versus provincial or national databases of health service use), sample sizes ranged from as small as 15 methamphetamine users in one study to over 2000 users in another.

While studies reported that psychiatric diagnoses were usually made through DSM-IV or DSM-5 criteria, other studies had a mixed methods design and included patient interviews and medical chart review to understand the symptoms experienced by methamphetamine users and their diagnoses. Importantly, most of the literature on MHA service use reported ED visits or hospital admissions – relatively few studies reported outpatient MHA service use. Furthermore, most studies only reported proportion of males and females in their sample, but few compared MHA service use by sex. Considering the heterogeneity in the study designs, samples sizes, psychiatric symptom diagnosis/reporting, and relative lack of information on outpatient MHA service use, this thesis will provide estimates of MHA service use in Ontario by 1) identifying methamphetamine users through use urine and serum drug screens and 2) using standardized health administrative databases to quantify their use of outpatient visits, ED visits, and MHA hospitalizations within 365 days of a positive test result.

Chapter 3

3 Methods

This chapter reviews the methods used in this thesis. Section 3.1 outlines the study population and data sources used. Section 3.2 describes the outcome measures, exposures, and covariates. Finally, Section 3.3 describes the statistical analysis techniques that were used to address the project objectives.

3.1 Data Sources and Record Linkage

The data used for this project were obtained from ICES, an Ontario-based non-profit research institute that houses clinical and administrative health databases, as well as population-based health surveys and patient records, to understand health service use, health outcomes, and inform health policy. Under section 45 of the Personal Health Information Protection Act (PHIPA), the use of personal health care data is authorized for research to inform health system evaluation and planning in Ontario without review by a Research Ethics Board. The ICES databases used in this project are described below:

1. The Registered Persons Database (RPDB) contains population sociodemographic information of Ontarians who have been registered under the Ontario Health Insurance Plan (OHIP) at any point in time and have been issued a unique health card number (HCN).[124] This database was used in this project to obtain each individual's age at index date, sex, postal code, and income quintile.
2. The Ontario Health Insurance Program (OHIP) database contains information on billings made by physicians for insured health services provided to Ontario residents.[125]
3. The Ontario Laboratories Information System (OLIS) is a provincial repository created by the Ministry of Health and Long-Term Care. It contains hospital, community, and public health lab test orders and results that are accessible to authorized health care providers and researchers.[125] Over 90% of community labs and nearly 60% of all provincial labs report to OLIS. As of December 31, 2017,

8.5 million Ontario residents lived in a geographic region in Ontario where laboratory results would likely be captured by hospitals reporting to OLIS.[126]

4. The Narcotics Monitoring System (NMS) captures information on all prescriptions for controlled medications dispensed by Ontario pharmacies[127]. Controlled medications listed by the federal Controlled Drugs and Substances Act include opiate analgesics such as morphine and codeine, and other controlled substances including amphetamines, barbiturates, and benzodiazepines.
5. The Ontario Mental Health Reporting System (OMHRS) reports information about adults assigned to a designated adult psychiatry inpatient bed in Ontario[128]. Information on admissions, discharges, and outcomes during an individual's inpatient stay is collected using a standardized tool called the Resident Assessment Instrument — Mental Health (RAI-MH©) version 2.0. This database also contains information on mental health service history, medications, and mental state indicators.
6. The Discharge Abstract Database (DAD) contains administrative, clinical, and demographic information on hospital discharges from acute inpatient institutions, day surgery, and chronic, rehabilitation, and psychiatric institutions[129]. One hundred sixty-six hospitals reported to DAD in 2016-2017 and 170 reported to DAD in 2017-2018[130]. Any psychiatric hospitalizations not included in OMHRS were captured by the DAD.
7. The National Ambulatory Care Reporting System (NACRS) records hospital- and community-based ambulatory care visits across Ontario, including care received in emergency departments and outpatient clinics.[131] From 2017 through 2019, 191 facilities in Ontario reported data to NACRS.[132]
8. The Community Health Centre (CHC) dataset contains information on visits made by patients to health care providers (including doctors and nurse practitioners) at community health centres. Patients are not enrolled at CHCs, and approximately 14% of people who visit CHCs are not insured by OHIP.

An individual's data (including full name, date of birth, postal code, and HCN) are collected by ICES and then assigned a unique ICES key number (IKN). The unique IKN can then be used to link an individual's health information across ICES datasets. Health

information is then de-identified for the purposes of project dataset creation, where personal identifiers such as their full name and complete date of birth and postal code are removed from the data. The datasets described above were linked for each Ontario resident at least 12 years or older who took a methamphetamine/amphetamine urine or serum test between January 1, 2017 and December 31, 2018 (inclusive). 2017 was chosen as the earliest year of inclusion of people with methamphetamine/amphetamine tests because in the years prior to 2017, fewer hospital and community laboratories reported test results to OLIS. December 31, 2018 was chosen as an end date for inclusion into the cohort to limit our follow-up window to the period prior to the imposition of COVID-19 lockdown restrictions that limited health service access.[133–135] The age restriction (12+) was chosen to align with the survey population of the American NSDUH, which surveys non-institutionalized Americans aged 12 years and older about their drug use.

The codes used to identify methamphetamine/amphetamine urine and serum drug screens are detailed in appendix A. The index date for those who tested positive was the date of their first positive urine or serum screen within the ascertainment window. For those who only had negative urine or serum screens, a random test date in the ascertainment window was chosen as their index date. Any records with invalid OHIP number, missing or invalid age (>105 years), missing or invalid sex, recorded death on or before index date, and non-Ontario residents were excluded from the study. Furthermore, individuals who had filled a prescription for Vyvanse, Adderall, Dexedrine, or other amphetamines within 120 prior to their first positive screen were identified through the NMS and excluded from the study due to the risk of a false positive methamphetamine screen while taking these drugs. A full list of these drugs can be found in Appendix B.

3.2 Measures

3.2.1 Outcome Measures

The outcome of interest for this project was mental health service use including outpatient visits, ED visits, and hospitalizations. More specifically, the primary objectives of this project were to determine:

1. The rate of outpatient MHA service use within 365 days following the first positive methamphetamine screen within the observation window.
2. The rate of MHA ED visits within 365 days following the first positive methamphetamine screen within the observation window.
3. The rate of MHA hospitalizations within 365 days following the first positive methamphetamine screen within the observation window.

Individual-level health records for those who had a urine/serum drug screen in the ascertainment window were linked to OMHRS, DAD, and NACRS to identify MHA-related service use. Mental health and addictions-related inpatient and ED discharges were identified in the DAD and NARCS databases, respectively, through MHA-related International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10 CA) codes. Similarly, inpatient admissions to psychiatric beds were identified in the OMHRS with DSM codes. Outpatient MHA-related visits were identified through OHIP diagnostic codes. Individuals in the cohort were followed for 365 days after index date. For individuals in the cohort who died within the 365-day follow-up period, the follow-up time was defined as the difference between index date and recorded death date.

The number of MHA outpatient visits, ED visits, hospitalizations, and total length of hospitalization within 365 days after index date were recorded for each person in the cohort. The total length of stay (LOS) was defined as the number of days between admission and discharge date. In cases of patients with multiple MHA hospitalizations within 365 of index date, the total LOS was the sum of the LOS of each individual hospitalization. In accordance with ICES definitions, the term ‘hospitalization’ in this thesis refers to an entire episode of care, defined as a “health problem from its first encounter with a health care provider through the completion of the last encounter”.[136] For example, if a patient were transferred from one hospital to another for the treatment of one illness, this patient would have one hospitalization recorded and the LOS would be the number of days between the date of admission to the first hospital and date of discharge from the second hospital. It is possible that some patients were admitted to hospital within 365 days after index date, but were not discharged before their follow-up

period ended: these patients were flagged as their total LOS was limited by the end of their follow-up period. If they were discharged prior to the end of the follow-up period, they were flagged as “discharged”.

MHA service use was also broken down into the following diagnostic groupings of psychiatric complications:

1. Schizophrenia spectrum and other psychotic disorders
2. Substance-induced psychotic disorders
3. Mood and anxiety disorders
4. Substance use disorders
5. Neurodevelopmental disorders
6. Deliberate self-harm
7. Other mental disorders

Percentages and rates of service use associated with each category listed above were reported. Importantly, deliberate-self harm is only recorded for ED visits and MHA hospitalizations, whereas the other categories include outpatient visits, ED, and hospitalizations. Schizophrenia spectrum and other psychotic disorders, mood and anxiety disorders, substance use disorders, and deliberate-self harm were defined as per the diagnostic grouping created by the Mental Health and Addictions group at ICES. Definitions for substance-induced psychotic disorders, neurodevelopmental disorders, and other mental health disorders were defined by the project team for this thesis specifically by compiling DSM, ICD, and OHIP DXCODES relevant to these conditions. Lists of codes used to define these categories can be found in Appendices C through E.

3.2.2 Exposure and Baseline Characteristics

The exposure of interest in this project was a positive drug screen for methamphetamine/amphetamine, which was obtained through OLIS. An individual who tested positive on a urine or serum drug screen anytime in 2017 or 2018 was a part of the methamphetamine-positive group and considered a methamphetamine user, while those

who nested negative throughout 2017 and 2018 were part of the methamphetamine-negative group and were considered a non-user.

The following baseline characteristics were recorded for each individual in the cohort:

1. Age in years at index date was obtained from the RPDB.
2. Sex was obtained from the RPDB.
3. Income quintile was obtained from the RPDB.
4. Rurality (rural or urban residence) was obtained from the RPDB.
5. Prevalent mental disorders (described below) within 5 years prior to index date was obtained through OHIP, OMHRS, DAD, NACRS, and CHC data.
    a. Schizophrenia spectrum and other psychotic disorders
    b. Substance-induced psychotic disorders
    c. Mood and anxiety disorders
    d. Substance use disorders
    e. Neurodevelopmental disorders
    f. Deliberate self-harm
    g. Other mental disorders
    h. Any prevalent mental disorder – defined as anyone with at least one of: 1) schizophrenia spectrum and other psychotic disorders OR 2) mood and anxiety disorders OR 3) neurodevelopmental disorders OR 4) deliberate self-harm OR 5) other mental disorders
6. Prior positive methamphetamine/amphetamine tests (within 3 years prior to index date) were obtained from OLIS.

3.3 Statistical Analysis

All analyses were conducted using SAS version 9.4.

3.3.1 Descriptive Statistics for Baseline Characteristics

Characteristics of the study sample were reported for each exposure group: mean (standard deviation) and median (interquartile range) for continuous variables, as well as

counts and proportions for categorical variables. Standardized mean differences were calculated by dividing the difference in means (for continuous variables) or proportions (for categorical variables) by the pooled standard deviation to identify any differences between groups. To understand the age distribution of the study sample, age was also categorized into 5-year groups as defined by Statistics Canada[137] and the percentage of people that fell within each age group was reported by exposure group. Noting the large sample size, standardized differences were used to identify meaningful between-group differences. Austin (2009) demonstrated that a standardized difference between two binary variables is related to the phi coefficient, which represents the correlation between two binary variables. A standardized difference of 0.1 (10%) is roughly equivalent to a phi coefficient of 0.05; a standardized difference of greater than 0.1 indicated a meaningful difference between groups.[138]

Importantly, upon obtaining the distribution of the ages of the study sample, a larger percentage of people with a negative test were older than 74 years of age compared to those with a positive test, raising the concern of a large number of false positives. Therefore, age was restricted to those who were at least 12 years old up to a maximum of 74 years of age at the date of entry into the cohort.

3.3.2 Objective 1: Determining the Rate of MHA Outpatient Visits, ED Visits, and Hospitalizations

To obtain the rates of MHA service use in methamphetamine/amphetamine-positive individuals and methamphetamine/amphetamine-negative individuals, regression models were constructed. The outcome variables were the number of MHA outpatient visits, ED visits, and hospitalizations, and the exposure variable was methamphetamine test result.

The number of MHA outpatient visits, ED visits, and hospitalizations were count outcomes; therefore, the Poisson and negative binomial regression models were considered to model the data. First, summary statistics were calculated for the number of visits within 365 days of index date for each health care setting to understand the spread of the data and inform model choice. Within each health care setting, the variance of the

number of visits was greater than the mean, indicating overdispersion of the data and violating the assumption of equal mean and variance of the outcome that is required for the Poisson model.[139] Noting this, the data were fit to the Poisson regression model as an initial starting point, and goodness-of-fit measures were examined to assess model fit. Model fit was first assessed based on the dispersion parameter, which is expressed as either the ratio of the 1) Pearson Chi-Square statistic or 2) the deviance to the degrees of freedom (DF). A dispersion parameter close to 1 suggests good model fit, while a ratio greater than 1 indicates overdispersion.[140] Generally, the Pearson Chi-Square statistic is preferred over the deviance.[141] In addition to the dispersion parameter, model fit was compared by the Akaike Information Criterion (AIC). Although the AIC value itself is uninterpretable, it can be used to select the best-fitting maximum likelihood based-models for a given dataset – the model that produces the smallest AIC value provides the best fit.[142]

The Poisson regression model for each outcome variable yielded a dispersion parameter greater than 1; therefore, a negative binomial regression was used to model the data. A negative binomial model assumes a conditional variance larger than the conditional mean, making it a suitable choice to model overdispersed data.[140] The negative binomial model produced dispersion parameters close to 1 for the number of visits within each health care setting. The negative binomial model also yielded smaller AICs than the Poisson model, indicating that it was an optimal fit for the data.

In cases of excessive zero counts in data, the Poisson and negative binomial models described above may lead to biased parameter estimates and incorrect inferences of results. These excessive zeros arise due to a mixture of two subgroups: one where individuals in the sample are at risk of the outcome, and one where they are not. In these cases, zero-inflated Poisson (ZIP) and zero-inflated negative binomial models (ZINB) can be used to model the data. Due to the large number of zeros in the dataset for ED visits and MHA hospitalizations, ZIP and ZINB models were also constructed and examined for optimal model fit based on the dispersion parameter and AIC. As described above with the Poisson regression model, the ZIP yielded a dispersion parameter greater than 1, whereas the ZINB yielded a dispersion parameter closer to 1 and a comparatively

smaller AIC value. Therefore, both the negative binomial and ZINB provided better model fit than the Poisson and ZIP models, respectively.

Both the negative binomial and ZINB had similar dispersion parameters and AIC values. An important consideration in the choice between these two models lay in the nature of the data and the research question: the outcome of interest was rates of MHA service use, and even healthy people may be at risk of MHA symptoms and require health care. In cases where both models produce similar goodness-of-fit values, the negative binomial may be favoured for ease of interpretability.[143] However, the goodness-of-fit statistics were more favourable for the ZINB model compared to the negative binomial model for ED visits, so the ZINB model was chosen to obtain rates of ED visits. Over 90% of MHA ED hospitalizations were zero; therefore, a ZINB model was chosen to obtain the rates of MHA hospitalization.

A similar process was followed when determining the rates of MHA encounters for the different diagnostic categories. The Poisson regression was used as an initial starting point to model the relationship between the number of visits associated with diagnostic category and methamphetamine/amphetamine test result. Due to overdispersion, a negative binomial regression model provided relatively better fit for the data. Importantly, zeros represented 80-98% of counts for health service use for schizophrenia spectrum and other psychotic disorders, substance-induced psychotic disorders, neurodevelopmental disorders, deliberate self-harm, and other mental disorders; therefore, these outcomes were zero-inflated, and a ZIP model was fit. However, the variance was greater than the mean and ZINB models yielded much more favourable dispersion parameters and AIC values for compared to the ZIP model; therefore, a ZINB model was used to obtain the rates and rate ratios (RRs) of service use associated with these categories, while a negative binomial model was used to obtain rates and RRs for substance use disorders and mood and anxiety disorders.

Although each person in the cohort was followed for 365 days, there were individuals who had shorter follow-up times due to death before the end of the follow-up period. Therefore, an offset term was included in the regression models to account for varying

exposure times within the cohort. The offset term was obtained by dividing the follow-up time by 365 and taking the log of the quotient to obtain a rate denominator of 365 person-days (reported as 1 person-year).

Rates, RRs, and 95% confidence intervals were calculated for each outcome variable and for each diagnostic category of mental disorders. As part of objective 1, age-adjusted rates and RRs were obtained by including age as a covariate in the regression models. The rates presented in this thesis are for individuals who are 30 years old. Rates of MHA service use were obtained with the NLEST macro available on SAS 9.4. This macro obtained confidence intervals that were symmetric about the predicted rates, resulting in negative lower confidence limits for some rates – these were presented as 0 in the results.

3.3.3 Objective 2: Identifying Sex Differences in MHA Service Use

To identify sex differences in the rate of MHA service use, sex-stratified rates of MHA visits were calculated by constructing a negative binomial model (or ZINB as described above) and including an interaction term for sex and methamphetamine/amphetamine test result. As with objective 1, crude and age-adjusted rates (at age=30 years) were obtained for females and males in each exposure group. To understand the effect of sex on the relationship between methamphetamine use and rates of MHA service use, RRs for females were calculated by dividing the rates of females with a positive test by the rates of females with a negative test. An identical process was performed for obtaining a comparable RR for males. A significant interaction term between sex and test result indicated statistically significant effect modification by sex.

3.3.4 Objective 3: Identifying Factors Associated with MHA Service Use and Total Length of Hospitalization

This project aimed to identify factors associated with 1) MHA outpatient visits, ED visits, hospitalizations, and 2) total length of hospitalization, namely: methamphetamine/amphetamine-use (positive or negative test result), sex, age, income quintile, rurality, and prevalent mental disorder other than substance use disorder and substance-induced psychotic disorder.

The factors of interest were coded as follows:

1) Methamphetamine/amphetamine test result: positive=1, negative=0
2) Sex: female=1, male=0
3) Age: Continuous variable
4) Income quintile: represented by 4 levels of dummy variables
5) Rurality: rural=1, urban=0
6) Prevalent mental disorder: yes=1, no=0

Factors Associated with MHA Health Service Use

To identify factors associated with MHA outpatient visits, ED visits, and hospitalizations, modified Poisson regression analyses were conducted for each health care setting using the PROC GENMOD procedure on SAS. The outcome variables (each of MHA outpatient visits, ED visits, and hospitalizations) were represented as a binary variable (0=no service use within the 365-day follow-up period, 1=yes service use within the follow-up period). The modified Poisson regression model was chosen to account for binary outcomes of MHA service use, the prospective nature of the study, and variable follow-up times (due to death before the end of the 365-day follow-up period). As described previously, an offset term was included to account for variable follow-up times and was obtained by dividing the follow-up time by 365 and taking the log of the quotient to obtain a rate denominator of 365 person-days (reported as 1 person-year). Furthermore, the modified Poisson regression is not prone to convergence errors[144] that may arise with the log-binomial model, which is an alternative model that can also be used for binary outcomes and the estimation of rate ratios. Finally, unlike the log-binomial model, the modified Poisson regression model also produces unbiased estimates of rate ratios even in cases of model misspecification.[145] The “repeated” statement with the subject ID (IKN) was used within the PROC GENMOD procedure to obtain robust standard errors and an independent correlation structure was specified.

Factors Associated with Total LOS

The total length of stay was treated as a count variable and reported for each individual in the cohort as the sum of the length of stay of each psychiatric episode of care. To identify factors associated with total length of stay among individuals who were hospitalized, a negative binomial regression model was constructed.

The negative binomial regression model was chosen due to its flexibility to handle count data. The total length of stay for each person who provided a methamphetamine test is modelled as the sum of the number of days associated with each episode of care. Although the Poisson regression model can be used to model count data, it relies on the assumption that the conditional mean of the outcome is equal to the conditional variance. However, LOS data is typically right-skewed[146,147] with variance greater than the mean (i.e., data is overdispersed), making the Poisson model an unsuitable choice. Previous studies[148,149] have shown that the negative binomial regression model performs well when data is overdispersed, typically providing a better fit for data and providing less biased standard errors.

In addition to methamphetamine test result, sex, age, income quintile, rurality, and prevalent mental disorder, the number of hospitalizations was added to the model as a covariate to adjust for people with multiple hospitalizations contributing to their total LOS.

4 Results

4.1 Description of the Cohort

4.1.1 Sociodemographic Characteristics

A total of 204984 people were screened for methamphetamine/amphetamine during 2017 and 2018, and 25,702 (12.5%) had a positive test within this period. Women accounted for 41.1% (n=10554) of people with a positive test and men represented 58.9% (n=15148) of people with a positive test. Total follow-up time for the cohort was

73569607 days: 9232420 days for the methamphetamine/amphetamine-positive group and 64337187 for the methamphetamine/amphetamine -negative group.

Details on the sociodemographic characteristics of the study sample can be found in table 4.1. Those who tested positive had a mean (SD) age of 37.7 (12.9) years and median [IQR] age of 36.0 [19.0] years. This was younger compared to those who tested negative, who had a mean (SD) age of 41.8 (16.5) years and median [IQR] age of 42.0 [29.0] years.

Age group distributions can be found in Appendix F and G. A higher percentage of people who tested positive for methamphetamine/amphetamine fell within the ages of 20-39 years of age compared to those who tested negative. Conversely, a higher percentage of those who tested negative were between the ages of 55 and 74 years compared to the methamphetamine-positive group. The percentages of people between the ages of 40 and 54 were comparable between both exposure groups.

People who were tested for methamphetamine/amphetamine were also most commonly in the lowest income quintile. However, a larger percentage (40.9%, standardized difference=0.194) of methamphetamine-positive individuals fell within the lowest income quintile compared to those who tested negative (31.4%). A larger percentage of the methamphetamine/amphetamine-negative individuals than methamphetamine/amphetamine-positive patients were in quintiles 4 (13.1% versus 9.9%) and 5 (15.0% versus 11.3%) (standardized difference=0.120 and 0.102, respectively). Data on income quintile was missing for 289 methamphetamine-positive individuals and 1,056 methamphetamine-negative individuals.

The majority of people in the sample also lived in urban areas: only 16.9% and 15.8% of methamphetamine-positive and methamphetamine-negative individuals, respectively, lived in a rural area at the time of index date. However, there was no meaningful difference between groups (standardized difference=0.025). Data on rurality was missing for 269 methamphetamine-positive individuals and 859 methamphetamine-negative individuals.

4.1.2 Prevalent Mental Disorders and Prior Positive Tests

All categories of mental disorders were significantly more prevalent in those who tested positive for methamphetamine compared to those who tested negative. The prevalence of any mental disorder (excluding substance use-related disorders) within the past 5 years was 76.1% among the methamphetamine-positive group and 65.7% among those who were methamphetamine-negative. Mood and anxiety disorders was the most common category of prevalent mental disorders in both exposure groups, noted in 71.7% with a positive methamphetamine result and in 63.6% of those with only negative tests. Notably, among methamphetamine-positive individuals, the percentage of people with prevalent neurodevelopmental disorders was twice as high (12.2%) when compared to the methamphetamine-negative group (6.1%) (standardized difference=0.211). The percentage of people who had a history of deliberate self-harm was also nearly twice as high in the methamphetamine-positive group at 13.8%, compared to 7.1% among those who tested negative (standardized difference=0.221).

Within the past two years, 21.3% of those with a positive test in 2017 or 2018 also had a prior positive methamphetamine or amphetamine screen, which was notably higher than the 3.3% of those who tested negative within this same period (standardized difference=0.571).

Table 4.1 Baseline sociodemographic, clinical characteristics, and standardized differences of the cohort by exposure group. Standardized differences > 0.10 indicated a meaningful difference between groups. Column percentages are reported for categorical factors.

	Methamphetamine/amphetamine-Positive	Methamphetamine/amphetamine -Negative	
	Total (N=25702)	**Total (N=179282)**	**Standardized Difference**
Demographics			
Age			
Mean (SD)	37.7 (12.9)	41.8 (16.5)	0.272
Median (IQR)	36.0 (19.0)	42.0 (29.0)	0.260
Income quintile, N (%)			
Quintile 1 (low)	10395 (40.9%)	55939 (31.4%)	0.194
Quintile 2	5704 (22.5%)	38585 (21.7%)	0.016
Quintile 3	3910 (15.4%)	32917 (18.5%)	0.084
Quintile 4	2883 (11.3%)	27406 (15.0%)	0.120
Quintile 5 (high)	2521 (9.9%)	23379 (13.1%)	0.102
Missing, N	289 (1.1%)	1056 (0.7%)	
Rural, Yes N(%)	4291 (16.9%)	28265 (15.8%)	0.025
Missing, N	269 (1.0%)	859 (0.5%)	
Prevalent mental disorders, Yes N (%)			
Schizophrenia Spectrum and other psychotic disorders	4191 (16.3%)	18561 (10.4%)	0.176
Substance-induced psychotic disorders	1916 (7.5%)	3836 (2.1%)	0.251
Deliberate self-harm	3543 (13.8%)	12695 (7.1%)	0.221
Mood and anxiety disorders	18273 (71.1%)	113560 (63.6%)	0.166
Substance use disorders	17373 (67.6%)	55632 (31.0%)	0.786
Neurodevelopmental disorders	3128 (12.2%)	10960 (6.1%)	0.211
Other mental disorders	7356 (28.6%)	40706 (22.7%)	0.136
Any prevalent mental disorder, excluding substance use and substance-induced psychotic disorders	11523 (76.1%)	81096 (65.7%)	0.188
Prior Positive Drug Screens			
Prior positive methamphetamine or amphetamine drug screen, Yes N (%)	5464 (21.3%)	5847 (3.3%)	0.571

4.1.2.1 Sex Differences in Sociodemographic Characteristics

Details of women and men who were tested for methamphetamine/amphetamine are shown in table 4.2. Females comprised 41.6% of the methamphetamine-positive group and 43.6% of the methamphetamine-negative group. Within each exposure group, there was no significant difference in mean/median age or distribution of age groups between females and males.

Income within each exposure group followed similar trends as described above, with both sexes most commonly falling within the lowest income quintile: 40.2% and 42.0% of methamphetamine-positive males and females, respectively, were within the lowest quintile. However, within each exposure group, there was no significant difference between sexes at each income quintile. There were significantly more methamphetamine-positive women and men than -negative women and men in income quintile 1. This trend was reversed in higher income quintiles – compared to the methamphetamine-positive group, there were significantly more methamphetamine-negative women and men in quintile 4, and significantly more men in quintile 5.

When comparing rural residence, a larger percentage of methamphetamine-positive females (18.4%) lived in rural areas compared to methamphetamine-positive males (15.8%). Similarly, among those who tested negative, 16.8% of females lived in rural areas compared to 15.1% of males. However, these differences by sex within each exposure group were not statistically significant (standardized difference=0.072 and 0.074, respectively).

4.1.2.2 Prevalent Mental Disorders and Prior Positive Tests in Females and Males

The prevalence of pre-existing mental disorders varied between sexes.

More females (75.7%) than males (67.9%) with a positive test had mood and anxiety disorders – this difference was significant (standardized difference=0.173). Significantly more methamphetamine-positive females than males (80.4% versus 67.3%) also had any prevalent mental disorder (standardized difference=0.160).

Schizophrenia spectrum and other psychotic disorders, substance use disorders, substance-induced psychotic disorders, and neurological disorders were all significantly more prevalent in males with a positive test than females with a positive test. Overall, 18.9% of males had a history of schizophrenia and other psychotic disorders compared to only 12.7% of females. The majority of males (69.9%) and females (64.3%) had a history of substance use disorder (standardized difference=0.121). 8.6% of males and 5.8% of females had a history of substance-induced psychotic disorder (standardized difference=0.110). The prevalence of neurological disorders was 13.7% in males and 10.0% in females (standardized difference=0.113). There were no significant differences in the prevalence of deliberate self-harm and other mental disorders between females and males (standardized difference of 0.059 and 0.004, respectively).

These trends differed slightly in those who had a negative methamphetamine test. In patients who were methamphetamine-negative, deliberate self-harm was significantly higher among females (9.4%) than males (5.3%) (standardized difference=0.160). As with the methamphetamine-positive group, there was a higher prevalence of mood and anxiety disorders in women than in men (71.6% and 57.0%, respectively, standardized difference=0.308). Finally, there was a significantly higher percentage of women with any prevalent mental disorder compared to men (76.2% versus 64.6%, respectively, standardized difference=0.256). 34.7% of men and 26.3% of women had substance use disorder, which was the only category of disorders that was more prevalent in men than in women (standardized difference=0.183). There were no significant differences in the prevalence of schizophrenia spectrum disorders, substance-induced psychotic disorders, neurological disorders, or other mental disorders by sex. In both exposure groups, a larger percentage of males than females had a prior positive test.

Table 4.2 Baseline sociodemographic, clinical characteristics, and standardized differences of females and males in the cohort

	Methamphetamine/amphetamine-Positive			Methamphetamine/amphetamine-Negative				
	Females (N=10554)	**Males (N=15148)**	**Standardized differences (Between sexes with positive result)**	**Females (N=78183)**	**Males (N=101099)**	**Standardized differences (Between sexes with negative result)**	**Standardized differences (Between females: positive vs negative)**	**Standardized differences (Between males: positive vs negative)**
Demographics								
Age								
Mean (SD)	37.2 (19.0)	38.1 (12.6)	0.067	41.3 (16.9)	42.1 (16.2)	0.050	0.268	0.278
Median (IQR)	35.0 (19.0)	36.0 (19.0)	0.084	41.0 (30.0)	42.0 (28.0)	0.050	0.249	0.269
Income quintile, N (%)								
Quintile 1	4395 (42.0%)	6000 (40.2%)	0.041	25548 (32.7%)	30391 (30.1%)	0.056	0.186	0.201
Quintile 2	2391 (22.8%)	3313 (22.2%)	0.019	16861 (21.7%)	21724 (21.6%)	0.002	0.026	0.009
Quintile 3	1510 (14.4%)	2400 (16.1%)	0.043	13977 (18.0%)	18940 (18.9%)	0.022	0.097	0.076
Quintile 4	1155 (11.0%)	1728 (11.6%)	0.015	11566 (14.9%)	15840 (15.8%)	0.024	0.115	0.125
Quintile 5	1022 (9.8%)	1499 (10.0%)	0.007	9819 (12.6%)	13560 (13.5%)	0.025	0.092	0.110
Missing, N	81 (0.8%)	208 (1.4%)	0.059	412 (0.5%)	644 (0.6%)	0.014		
Rural, Yes N(%)	1931 (18.4%)	2460 (15.8%)	0.072	13082 (16.8%)	15183 (15.1%)	0.074	0.041	0.016
Missing, N	76 (0.7%)	193(1.3%)	0.056	308 (0.4%)	551 (0.5%)			
Prevalent mental disorders, Yes N (%)								
Schizophrenia Spectrum and other psychotic disorders	1336 (12.7%)	2855 (18.9%)	0.170	6817 (8.7%)	11744 (11.6%)	0.096	0.128	0.202
Substance-induced psychotic disorders	610 (5.8%)	1306 (8.6%)	0.110	1117 (1.4%)	2719 (2.7%)	0.089	0.235	0.259
Deliberate self-harm	1581 (15.0%)	1962 (13.0%)	0.059	7370 (9.4%)	5325 (5.3%)	0.160	0.170	0.269
Mood and anxiety disorders	7987 (75.7%)	10286 (67.9%)	0.173	55949 (71.6%)	57611 (57.0%)	0.308	0.093	0.227
Substance use disorders	6782 (64.3%)	10591 (69.9%)	0.121	20566 (26.3%)	35066 (34.7%)	0.183	0.825	0.754
Neurodevelop-mental disorders	1058 (10.0%)	2070 (13.7%)	0.113	4465 (5.7%)	6495 (6.4%)	0.030	0.161	0.243
Other mental health disorders	3010 (28.5%)	4346 (28.7%)	0.004	19463 (24.9%)	21243 (21.0%)	0.092	0.082	0.178
Any prevalent mental disorder, excluding substance use and substance-induced psychotic disorders	8490 (80.4%)	3053 (67.3%)	0.160	59560 (76.2%)	65295 (64.6%)	0.256	0.104	0.253
Prior Positive Drug Screens								
Prior positive methamphetamine or amphetamine drug screen, Yes N (%)	2236 (21.2%)	3228 (21.3%)	0.124	2437 (3.1%)	3410 (3.4%)	0.256	0.575	0.567

4.1.3 Death Within the Cohort

There were 5338 deaths, 2.6% ofthe study sample died within the 365-day follow-up period (range=1-365 days), 34.6% (n=1,847) of whom were women and 65.4% (n=3,491) of whom were men. 2.7% (n=686) of people with a positive test died and 2.6% (n=4,652) of people with a negative test died within the follow-up period.

The percentages of people who died were different for women and men. 2.1% (n=223) of methamphetamine/amphetamine-positive women and 2.1% (n=1,624) of methamphetamine/amphetamine-negative women died. 3.1% (n=463) of methamphetamine/amphetamine-positive and 3.0% (n=3,028) of methamphetamine/amphetamine-negative men died.

4.2 Objective 1: Rates of MHA Service Use

The age-adjusted rates and rate ratios of MHA service use by outcome variable (outpatient use, ED use, and hospitalizations) are displayed in table 4.4. Crude rates and rate ratios can be found in the appendix.

4.2.1 Outpatient Service Use

Of the 204,984 people tested for methamphetamine, 58.3% used outpatient MHA services within 365 days of index date. Looking specifically within the 25702 people who tested positive for methamphetamine, 76.8% (n=19743) people used outpatient MHA services, compared to 55.7% (n=99865) in the methamphetamine-negative group.

The number of outpatient visits for everyone in the cohort ranged from 0 to 199, with a mean (SD) of 5.9 (11.2) visits in a year, or a median [IQR] of 1 [0, 6] visits.

For people 30 years of age, the rate of MHA outpatient use was estimated as 15.0 visits per person-year (95%CI 14.7, 15.4) for people who tested positive for methamphetamine and 5.7 (95%CI 5.6, 5.7) per person-year for those who tested negative. The rate of

outpatient use was 2.65 times greater in people who tested positive for methamphetamine compared to those who tested negative (95%CI 2.59, 2.71).

4.2.2 Emergency Department Use

Of the entire cohort, 17.2% of people (n=35187) who had a methamphetamine/amphetamine test used the ED for MHA services within the 365 days of follow-up. Within the methamphetamine-positive group, 29.3% (n=7541) people had an MHA-related ED visit, compared to only 15.4% (n=27646) of those who tested negative.

The number of ED visits ranged from 0 to 106. Among the entire study sample, the mean, SD number of visits was 0.5 (2.1), with a median [IQR] of 0 [0, 0]. Among those who had an ED visit, the mean, SD number of visits was 2.7 (4.4), with a median [IQR] of 1, [1, 3]. The rate of MHA ED visits was 1.16 (95%CI 0.65, 1.67) per person-year for people who tested positive for methamphetamine and 0.50 (95%CI 0.002, 1.00) per person-year for those who tested negative (at 30 years of age). The rate of ED use was 2.01 times greater in people who tested positive for methamphetamine compared to those who tested negative (95%CI 1.93, 2.10).

4.2.3 Hospitalizations

Overall, 9.3% (n=19,121) of the cohort had an MHA-related hospitalization. Similar to the trends seen in MHA outpatient and ED use, the percentage of people with MHA hospitalizations was greater among those who had a positive methamphetamine test (14.7%, n=3781) compared to those who had a negative test (8.6%, n=15340).

The number of MHA hospitalizations ranged from 0 to 44. Among the entire study sample, the mean, SD number of hospitalization was 0.2 (0.6), with a median [IQR] of 0, [0, 0]. Among those who were hospitalized, the mean SD number of hospitalizations was 1.6 (1.4), with a median [IQR] of 1, [1, 2]. For hypothesized individuals 30 years of age, the rate of hospitalizations was 0.33 (95%CI 0, 1.38) per person-year for people who tested positive for methamphetamine and 0.17 (95%CI 0, 1.89) per person-year for those

who tested negative. The rate of hospitalizations was 1.78 times greater in people who tested positive for methamphetamine compared to those who tested negative (95%CI 1.76, 1.89).

Table 4.3 Age-adjusted rates (per person-year) and rate ratios of MHA service use by methamphetamine/amphetamine test result

	Outpatient visits			ED visits			Hospitalizations		
Exposure group	**N (%)+**	**Rate (95%CI)**	**RR (95%CI)**	**N (%)+**	**Rate (95%CI)**	**RR* (95%CI)**	**N (%)+**	**Rate (95%CI)**	**RR* (95%CI)**
MA-positive	19,743 (76.8%)	15.0 (14.7, 15.4)	2.65 (2.59, 2.71)	7,541 (29.3%)	1.21 (1.17, 1.26)	2.01 (1.93, 2.10)	3,781 (14.7%)	0.33 (0, 1.38)	1.78 (1.67, 1.89)
MA-negative	99,865 (55.7%)	5.7 (5.6, 5.7)	ref	27,646 (15.4%)	0.48 (0.47, 0.48)	ref	15,340 (8.6%)	0.17 (0,0.89)	ref

MA: methamphetamine/amphetamine; RR: rate ratio; ED: emergency department; N: number; CI: confidence interval

+ Percentages represent the percentage of methamphetamine-positive/-negative patients who used MHA services by setting.

*RR presented are from the count part of the zero-inflated binomial model.

Table 4.4 Age-adjusted rates and rate ratios of health services use by diagnostic category within 365 days after index date

	Schizophrenia Spectrum and Other Psychotic Disorders			Substance Use Disorder			Substance-induced Psychotic Disorders			Deliberate Self-harm			Mood and Anxiety Disorders			Neurodevelopmental disorders			Other Mental Disorders		
	N (%)+	Rate (95% CI)	RR* (95% CI)	N (%)+	Rate (95% CI)	RR (95% CI)	N (%)+	Rate (95% CI)	RR* (95% CI)	N (%)+	Rate (95% CI)	RR* (95% CI)	N (%)+	Rate (95% CI)	RR (95% CI)	N (%)+	Rate (95% CI)	RR* (95% CI)	N (%)+	Rate (95% CI)	RR* (95% CI)
MA-Positive	3,022 (11.8 %)	0.73 (0, 14.1)	1.15 (1.07, 1.23)	15,365 (59.8 %)	13.0 (12.4, 13.5)	4.06 (3.89, 4.25)	1,566 (6.1%)	0.27 (0, 10.23)	1.79 (1.57, 2.03)	1,511 (5.9%)	0.13 (0, 2.39)	1.63 (1.45, 1.83)	10,975 (42.7 %)	2.14 (2.08, 2.20)	1.00 (0.97, 1.02)	1,314 (5.1%)	0.17 (0, 1.99)	1.05 (0.95, 1.17)	2,946 (11.5 %)	0.31 (0.30, 0.32)	1.05 (0.99, 1.12)
MA-Negative	12,944 (7.2%)	0.43 (0, 9.89)	ref	38,211 (21.3 %)	3.19 (3.12, 3.26)	ref	2,037 (1.1%)	0.04 (0, 3.65)	ref	3,993 (2.2%)	0.05 (0, 1.41)	ref	73,803 (41.2 %)	2.15 (2.12, 2.17)	ref	4,541 (2.5%)	0.08 (0, 0.99)	ref	18,284 (10.2 %)	0.29 (0, 23.0)	ref

MA: methamphetamine/amphetamine; RR: rate ratio; ED: emergency department; N: number; CI: confidence interval

+ Percentages represent the percentage of methamphetamine/amphetamine-positive/-negative patients who used health services for each diagnostic category of mental disorders.

*RR presented are from the count part of the zero-inflated binomial model.

4.2.4 Diagnostic Categories of MHA Visits

The diagnostic categories assigned to MHA visits are displayed in table 4.5. Generally, the percentage of people with visits for each type of mental disorder was higher in the methamphetamine/amphetamine-positive group compared to the methamphetamine/amphetamine -negative group across all diagnostic categories. The percentage of substance use disorder-related health service use in those with a positive methamphetamine/amphetamine test was nearly three times higher than those who did not have a positive test (59.8% versus 21.3%, respectively). Additionally, 6.1% of people who tested positive for methamphetamine used health services for substance-induced psychotic disorder, nearly 6 times the percentage among those who tested negative (1.1%). Notably, the percentages of people who used health services for neurodevelopmental disorders and deliberate self-harm were twice as high among those who had a positive methamphetamine test compared to those who did not (5.1% versus 2.5%, and 5.9% versus 2.2%, respectively). The differences in percentages of other psychiatric complications between methamphetamine/amphetamine -positive and -negative groups were not so pronounced; specifically, schizophrenia spectrum and other psychotic disorders (11.8% versus 7.2%), mood and anxiety disorders (42.7% versus 41.2%), and other mental disorders (11.5% versus 10.2%).

4.2.4.1 Rates of Health Service Use for Psychiatric Complications

Schizophrenia spectrum and other psychotic disorders

The rate of MHA service use associated with schizophrenia and spectrum disorder among methamphetamine-positive individuals was 0.73 (95%CI 0, 14.1) per person-year and 0.43 (95%CI 0, 9.89) per person-year among those who had a negative test. Those who were methamphetamine-positive had a 1.15 times greater rate (95%CI 1.07, 1.23) of MHA service use attributed to schizophrenia and spectrum disorders compared to those who only had a negative test.

Substance use disorders

The rate of substance use disorder-related health service use was 13.0 (95%CI 12.4, 13.5) visits/hospitalizations per person-year among people who were methamphetamine-positive and 3.19 (95%CI 3.12, 3.26) per person-year among people who were negative for methamphetamine. This difference in age-adjusted rates was significantly different, with methamphetamine-positive group having a 4.06 (95%CI 3.89, 4.25) times greater rate of service use associated with substance use disorders compared to those who did not have a positive test.

Substance-induced psychotic disorders

The percentages (6.1% and 1.1%) rates of service use attributable to substance-induced psychotic disorders were much higher in those who tested positive compared to those with a negative test, respectively. The rate of age-adjusted visits/hospitalizations was also 1.79 times (95%CI 1.57, 2.03) times greater among people with a positive test compared to a negative test.

Deliberate self-harm

In this study sample, 5.9% of people with a positive test and 2.2% with a negative test used health services for deliberate self-harm. The rate of MHA service use at 30 years old attributable to deliberate self-harm among the methamphetamine/amphetamine-positive group was 0.13 visits/hospitalizations (95%CI 0, 2.39) per person-year and 0.05 (95%CI 0, 1.41) per person-year among the methamphetamine/amphetamine-negative group. Adjusted for age, the rate of MHA service use associated with deliberate self-harm was 1.63 times greater (95%CI 1.45, 1.83) among people who tested positive for methamphetamine compared to those who only tested negative.

Mood and anxiety disorders

The rate of MHA service use attributable to mood and anxiety disorders was 2.14 visits/hospitalizations per person-year in people who tested positive and 2.15

visits/hospitalizations per person-year people who tested negative. There was no significant difference in the rates of mood and anxiety disorder-associated MHA service use between methamphetamine-positive individuals and methamphetamine-negative individuals (RR: 1.00, 95%CI 0.97, 1.02).

Neurodevelopmental disorders

The percentage of people with service use attributable to neurodevelopmental disorders was twice as high in the methamphetamine-positive group compared to the negative group (5.1% and 2.5%, respectively). However, there was no significant difference between their rates of service use (RR 1.05 95%CI 0.95, 1.17).

Other mental disorders

11.5% of people with a positive test and 10.2% of people with a negative test used MHA services to treat other mental disorders. There was no significant difference in the rates of service use associated with other mental disorders between methamphetamine/amphetamine-positive individuals and methamphetamine/amphetamine-negative individuals (RR=1.05, 95%CI 0.99, 1.12).

4.3 Objective 2: Identifying Sex Differences in MHA Service Use

The following section details the rates of MHA service use by sex, describing outpatient use, ED use, and hospitalizations. Rates and rate ratios of MHA service use by sex can be found in table 4.6, and rates by diagnostic group can be found in table 4.7.

4.3.1 Outpatient Use

Overall, 77.5% of women (n=8,176) who tested positive for methamphetamine used outpatient MHA services, compared to 76.4% (n=11,567) of men. This was much higher than the proportion of methamphetamine-negative women and men who used outpatient services (59.5% n=46,621 and 52.7% n=53,244, respectively). Overall, the rate of MHA

outpatient visits was lower in both men and women who tested negative for methamphetamine compared to those who had a positive test (see table 4.6).

After stratifying by sex and adjusting for age, the rate of MHA outpatient visits in methamphetamine/amphetamine-positive women who were 30 years old was 14.5 (95%CI 14.0, 15.0) visits per person-year compared to 5.7 (95%CI 5.6, 5.8) per person-year in women who tested negative. The rate of outpatient use in methamphetamine-positive women was 2.55 (95%CI 2.45, 2.64) times greater than in methamphetamine-negative women.

Similarly, methamphetamine/amphetamine-positive men 30 years of age had a rate of 15.4 (95%CI 14.9, 15.8) outpatient visits per person-year compared to 5.7 (95%CI 5.6, 5.7) in men who had a negative test. The rate of visits was 2.72 times greater in men with a positive test (95%CI 2.64, 2.81). There was a significant difference by sex, where the effect of methamphetamine use on MHA service use was greater in men than in women ($p<0.01$).

4.3.2 Emergency Department Use

The proportion of methamphetamine/amphetamine-positive women and men (28.6% and 29.9%, respectively) who visited the ED for MHA services was approximately double the proportion of ED visits by methamphetamine/amphetamine-negative women and men (16.1% and 14.9%).

The rate of ED visits in methamphetamine/amphetamine-positive women 1.89 times (95%CI 1.77, 2.02) greater than in methamphetamine/amphetamine -negative women (see table 4.6). Similarly, the rate of ED visits was 2.08 (95%CI 1.97, 2.20) times greater in methamphetamine/amphetamine -positive men compared to methamphetamine/amphetamine-negative men. There was no significant effect of sex on MHA ED use after methamphetamine/amphetamine exposure.

4.3.3 Hospitalizations

Overall, 45.1% of people with a positive test who were hospitalized were women, 54.9% were men, which was comparable to the respective proportions in the methamphetamine/amphetamine-negative group (43.1% and 56.9%, respectively). Among methamphetamine/amphetamine-positive women, 14.5% (n=1,525) had an MHA hospitalization within 365 days following index date, compared to 8.2% (n=8,246) of methamphetamine-negative women. Women who tested positive were hospitalized at a rate of 0.35 hospitalizations per person-year (95%CI 0.00, 0.74), which was 1.91 (95%CI 1.73, 2.10) times higher than the rate in women with a negative test.

Similarly, 14.9% of methamphetamine/amphetamine-positive men (n=2,256) had an MHA hospitalization in the 365-day follow-up period compared to 8.2% of men (n=8,246) with a negative test. The rate of hospitalization among men was 1.71 times greater among men with a positive test compared to a negative test (95%CI 1.57, 1.85). There was no significant effect of sex in the rate of MHA hospitalizations.

Table 4.5 Age-adjusted rates per person-year and rate ratios of MHA service use for women and men by methamphetamine test result

	Outpatient visits			ED visits			Hospitalizations		
Exposure group	**N (%)+**	**Rate (95%CI)**	**RR (95%CI)**	**N (%)+**	**Rate (95%CI)**	**RR* (95%CI)**	**N (%)+**	**Rate (95%CI)**	**RR* (95%CI)**
Female									
MA-positive	8,176 (77.5%)	14.5 (14.0, 15.0)	2.55 (2.45, 2.64)	3,018 (28.6%)	1.05 (0.81, 1.28)	1.89 (1.77, 2.02)	1,525 (14.5%)	0.35 (0.00, 0.74)	1.91 (1.73, 2.10)
MA-negative	46,621 (59.6%)	5.7 (5.6, 5.8)	ref	12,596 (16.1%)	0.49 (0.27, 071)	ref	7,094 (9.1%)	0.18 (0.00, 0.38)	ref
Male									
MA-positive	11,567 (76.4%)	15.4 (14.9, 15.8)	2.72 (2.64, 2.81)	4,523 (29.9%)	1.23 (0.97, 1.49)	2.08 (1.97, 2.20)	2,256 (14.9%)	0.32 (0.07, 0.56)	1.70 (1.57, 1.85)
MA-negative	53,244 (52.7%)	5.7 (5.6, 5.7)	ref	15,050 (14.9%)	0.51 (0.25, 0.77)	ref	8,246 (8.2%)	0.16 (0.00, 0.36)	ref

MA: methamphetamine/amphetamine; RR: rate ratio; ED: emergency department; N: number; CI: confidence interval

+ Percentages represent the percentage of methamphetamine-positive and -negative patients who used MHA services by setting.

*RR presented are from the count part of the zero-inflated binomial model.

4.3.4 Diagnostic Categories of MHA Visits

Schizophrenia spectrum disorders

Among the methamphetamine/amphetamine-positive patients, 9.3% of women (n=978) and 13.5% of men (n=2,044) used MHA services for schizophrenia and spectrum disorders within 365 days after their positive test.

The rate of service use for schizophrenia and spectrum disorders was 0.54 (95%CI 0, 1.20) per person-year among methamphetamine/amphetamine-positive women and 0.30 (95%CI 0, 0.65) per person-year among methamphetamine/amphetamine -negative women. Methamphetamine/amphetamine-positive women had a significantly higher rate of service use for schizophrenia spectrum disorders: their use of services was 29% higher than women with a negative test (RR 1.29, 95%CI 1.15, 1.46).

For men, the rate of service use for schizophrenia and spectrum disorders was 0.84 (95%CI 0.04, 1.64) per person-year among men with a positive test and 0.53 (95%CI 0, 1.14) per person-year among men with a negative test. Overall, this difference was not statistically significant (RR: 1.07 95%CI 0.99, 1.17).

There was a greater effect of methamphetamine use on the rates of service use for schizophrenia spectrum disorders in women than in men.

Substance use disorder

The effect of methamphetamine on substance use disorder-related health service use was significantly greater in women than in men. Overall, 56.6% of women with a positive test used health services for substance use disorders compared to only 18.0% of women with a negative test. Similarly in men, 62.0% of men with a positive test and 23.9% with a negative test sought health services for substance use disorders within the 365-day follow-up period.

Women who had a positive test for methamphetamine had a rate of 12.1 visits/hospitalizations associated with substance use disorder per person-year (95%CI 11.4, 13.0), compared to 2.69 visits/hospitalizations per person-year for women with a negative test (95%CI 2.61, 2.76). Overall, the rate of health service use for substance use disorder was 4.52 (95%CI 4.22, 4.85) times greater in women who tested positive compared to women who tested negative.

Men who had a positive test for methamphetamine had a rate of 13.7 visits/hospitalizations associated with substance use disorders per person-year (95%CI 13.0, 14.5), compared to 3.66 visits/hospitalizations per person-year for men with a negative test (95%CI 3.56, 3.76). The rate of health service use for substance use disorder was 3.76 (95%CI 3.54, 3.98) times greater in men who tested positive compared to men who tested negative.

Substance-induced psychotic disorder

Overall, 5.2% (n=546) of women with a positive test and 0.8% (n=603) of women with a negative test had a visit or hospitalization for substance-induced psychotic disorder, compared to 6.7% (n=1,020) of men with a positive test and 1.4% (n=1,434) of men with a negative test.

The rate of health service use for women with a positive test for methamphetamine/amphetamine was 0.26 (95%CI 0, 1.05) per person-year and 0.03 (95%CI 0, 0.14) per person-year for women who had a negative test. Women who tested positive had a 2.10 (95%CI 1.67, 2.65) times greater rate of health service use for substance-induced psychotic disorder compared to women who tested positive.

Men who tested positive for methamphetamine/amphetamine had a rate of 0.29 visits/hospitalizations (95%CI 0, 0.72) for substance-induced psychotic disorder per person-year, which was significantly greater than the rate among men with a negative test who had 0.05 visits/hospitalizations (95%CI 0, 0.26) per person-year (RR=1.60 95%CI 1.37, 1.87).

There was no effect modification by sex on the rate of health services for substance-induced psychotic disorder.

Deliberate self-harm

The percentage of people with deliberate self-harm was higher among men and women who tested positive for methamphetamine/amphetamine compared to those who tested negative. Six point two percent (n=654) of methamphetamine/amphetamine-positive women and 5.7% (n=857) of methamphetamine/amphetamine-positive men received treatment for deliberate self-harm in the 365 days following their positive test, compared to only 3.0% (n=2,366) and 1.6% (n=1,627) of methamphetamine/amphetamine-negative women and men, respectively.

For women who tested positive for methamphetamine/amphetamine, the rate of visits/hospitalizations for deliberate-self harm was 0.15 per person-year (95%CI 0, 0.64). In women with a negative test, the rate of health service use for deliberate self-harm was 0.07 (95%CI 0, 0.33) per person-year.

The rate of service use for deliberate self-harm among men with a positive test was 0.12 (95%CI 0, 0.39) visits/hospitalizations per person-year and 0.03 visits/hospitalizations per person-year (95%CI 0, 0.16) among men with a negative test. Methamphetamine/amphetamine-positive men had a 2.28 times greater rate of health service use associated with deliberate self-harm compared to those with a negative test (95%CI 1.90, 2.73).

Comparing the two RRs shows a significant difference, with a greater effect of methamphetamine on MHA service use for deliberate-self harm in men than in women.

Mood and anxiety disorders

Overall, 46.5% (n=4,809) of methamphetamine/amphetamine-positive women and 48.2% (n=37,681) of methamphetamine/amphetamine-negative women used health services for mood and anxiety disorders. The rate of MHA service use among methamphetamine/amphetamine-positive women was 2.46 (95%CI 2.36, 2.56), compared

to 2.65 (95%CI 2.65, 2.69) per person-year among women with a negative test. The rate of health service was significantly lower in methamphetamine/amphetamine-positive women compared to women who tested negative (RR=0.93, 95%CI 0.89, 0.97).

Conversely, a larger percentage of men with a positive test (48.2%, n=37681) than negative test (35.7%, n=36122) used health services for mood and anxiety disorders. The rate of mood and anxiety disorder-related service use in these men was 1.91 visits/hospitalizations (95%CI 1.85, 1.98) per person-year, compared to 1.75 (95%CI 1.73, 1.78) in men who only had a negative test (RR=1.09 95%CI 1.05, 1.13). There was a significantly greater effect of methamphetamine use on mood and anxiety-related health service use in men compared to women.

Neurodevelopmental disorder

Overall, health service use for neurodevelopmental disorders was more common in men than in women irrespective of test result.

Of the women who tested positive, 3.8% (n=399) of women also used mental health services for neurodevelopmental disorders, compared to 2.3% of women (n=1281) with a negative test. The rate of health service use among methamphetamine/amphetamine-positive women was 0.12 (95%CI 0, 0.38) visits/hospitalizations per person-year compared to 0.06 (95%CI 0, 0.20) among methamphetamine/amphetamine-negative women. This difference was not statistically significant (RR=1.14 95%CI 0.94, 1.36).

Among men who tested negative, 6.0% (n=915) who tested positive used health services for neurodevelopmental disorders compared to 2.7% of men (n=2720) with a negative test. Methamphetamine/amphetamine-positive men used health services at a rate of 0.21 (95%CI 0, 0.63) visits/hospitalizations per person-year, compared to 0.09 (95%CI 0, 0.30) among those who were negative. This difference was not statistically significant (RR=1.01 95%CI 0.89, 1.14)

There was no effect modification by sex on the rate of health service use for neurodevelopmental disorders.

Other mental disorders

Similar percentages of women and men with a positive test reported use of MHA services for other mental disorders: 11.4% of women (n=1198) with a positive test and 12.0% of women (n=9340) with a negative test used health services for other mental disorders. Overall, the rate of MHA service use for other mental disorders was higher among women than in men. The rate of other mental disorders was 0.39 (95%CI 0.28, 0.49) visits/hospitalizations per person-year in women with a positive methamphetamine/amphetamine test and 0.37 (95%CI 0.28, 0.47) per person-year in women with a negative test. Women who were methamphetamine/amphetamine-positive used health services for other mental health disorders at a 1.04 times higher rate than women with a negative test; however, this difference was not statistically significant (95%CI 0.95, 1.12).

Among men, 11.5% of those (n=1748) with a positive test and 8.9% of those (n=8944) with a negative test had documented health service use for other mental disorders. Methamphetamine/amphetamine-positive men used health services for treatment for other mental disorders at a rate of 0.26 (95%CI 0.19, 0.33) per person-year while the rate among methamphetamine/amphetamine-negative men was smaller at 0.22 (95%CI 0.17, 0.28) per person-year (RR=1.17 95%CI 1.08, 1.25).

There was effect modification by sex, where the effect of methamphetamine on MHA use for other mental disorders was greater in men than in women.

Table 4.6 Age-adjusted rates (per person-year) and rate ratios of psychiatric complications in women and men by methamphetamine test result

	Schizophrenia Spectrum and Other Psychotic Disorders			Substance Use Disorder			Substance-induced Psychotic Disorders			Deliberate Self-harm			Mood and Anxiety Disorders			Neurodevelopmental disorders			Other Mental Disorders		
Exposure group	**N (%)⁺**	**Rate (95%CI)**	**RR* (95% CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR (95%CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR* (95%CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR* (95%CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR (95%CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR* (95%CI)**	**N (%)⁺**	**Rate (95%CI)**	**RR* (95% CI)**
Female																					
MA-positive	978 (9.3%)	0.54 (0, 1.20)	1.29 (1.15, 1.46)	5968 (56.6%)	12.1 (11.4, 13.0)	4.52 (4.22, 4.85)	546 (5.2%)	0.26 (0, 1.05)	2.10 (1.67, 2.65)	654 (6.2%)	0.15 (0, 0.64)	1.53 (1.30, 1.80)	4809 (45.6%)	2.46 (2.36, 2.56)	0.93 (0.89, 0.97)	399 (3.8%)	0.12 (0, 0.38)	1.14 (0.95, 1.36)	1198 (11.4%)	0.39 (0.28, 0.49)	1.04 (0.95, 1.12)
MA-negative	4444 (5.7%)	0.30 (0, 0.65)	ref	14033 (18.0%)	2.69 (2.61, 2.76)	ref	603 (0.8%)	0.03 (0, 0.14)	ref	2366 (3.0%)	0.07 (0, 0.33)	ref	37,681 (48.2%)	2.65 (2.61, 2.69)	ref	1,281 (2.3%)	0.06 (0, 0.20)	ref	9340 (12.0%)	0.37 (0.28, 0.47)	ref
Male																					
MA-positive	2044 (13.5%)	0.84 (0.04, 1.64)	1.07 (0.99, 1.17)	9397 (62.0%)	13.7 (13.0, 14.5)	3.76 (3.54, 3.98)	1020 (6.7%)	0.29 (0, 0.72)	1.60 (1.37, 1.87)	857 (5.7%)	0.12 (0, 0.39)	2.28 (1.90, 2.73)	6166 (40.7%)	1.91 (1.85, 1.98)	1.09 (1.05, 1.13)	915 (6.0%)	0.21 (0, 0.63)	1.01 (0.89, 1.14)	1748 (11.5%)	0.26 (0.19, 0.33)	1.17 (1.08, 1.25)
MA-negative	8,00 (8.4%)	0.53 (0.00, 1.14)	ref	24178 (23.9%)	3.66 (3.56, 3.76)	ref	1434 (1.4%)	0.05 (0, 0.26)	ref	1627 (1.6%)	0.03 (0, 0.16)	ref	36122 (35.7%)	1.75 (1.73, 1.78)	ref	2,720 (2.7%)	0.09 (0, 0.30)	ref	8944 (8.9%)	0.22 (0.17, 0.28)	ref

MA: methamphetamine/amphetamine; RR: rate ratio; ED: emergency department; N: number; CI: confidence interval

+ Percentages represent the percentage of methamphetamine-positive/-negative patients who used MHA services by setting: for example, 9.3% of women (n=978) with a positive test used health services for schizophrenia spectrum and other psychotic disorders.

*RR presented are from the count part of the zero-inflated binomial model.

4.4 Objective 3: Identifying Factors Associated with MHA Service Use and Total LOS

4.4.1 Factors Associated with MHA Service Use

Factors associated with MHA service use among people with a positive test are presented in table 4.8.

MHA outpatient use

Sex was not associated with outpatient service use (RR 1.00, 95%CI 0.98, 1.00). Age was significantly associated with outpatient service use, with the risk of outpatient service use decreasing by 1% with every 1-year increase in age (RR: 0.99, 95%CI 0.99, 0.99, p<.0001). The risk of outpatient MHA visits also decreased by 3% to 5% as income quintile increased from the quintile 1 to quintile 5. Rural residence was associated with an 11% lower risk of outpatient MHA service use compared to urban residence (RR 0.89 95%CI 0.87, 0.91). The presence of a prevalent mental health disorder significantly increased the risk of outpatient MHA service use by 30% compared to people who did not have a prevalent mental disorder (RR 1.30 95%CI 1.28, 1.33).

MHA ED use

Women had a 9% lower risk of MHA ED use compared to men who had a positive test (RR 0.99 95%CI 0.88, 0.95). The risk of ED use also decreased by 2% with every 1-year increase in age (RR: 0.98 95%CI 0.98, 0.98). Although the risk of ED use was approximately 4-5% lower in quintiles 2 to 5 compared to the lowest income quintile, this difference was not statistically significant, and income was not associated with ED use. Similarly, although rural residents had a 4% lower risk of ED use compared to urban residents, this difference was not statistically significant. Having a prevalent mental disorder, however, significantly increased the risk of an MHA ED visit by 2.11 times (95%CI 1.98, 2.26) compared to those with a positive test who had no mental disorders.

MHA hospitalizations

Compared to men, women with a positive methamphetamine/amphetamine test had an 8% lower risk of an MHA hospitalization. Similar to the results seen in outpatient and ED use, the risk of hospitalization decreased by 1% with every 1-year increase in age (RR= 0.99 95% CI 0.99, 0.99). Income quintile was not associated with hospitalization. The risk of hospitalization was 8% lower for rural residents compared to urban residents; however, this was not statistically significant. Finally, as with outpatient and ED settings, having a prevalent mental disorder led to a 3.18 time increase in the risk of hospitalization.

Table 4.7 Relative risks of MHA outpatient visits, ED visits, and hospitalizations for people with a positive methamphetamine/amphetamine test

Variable	Outpatient Visits	ED Visits	Hospitalizations
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Sex (ref=M)	1.00 (0.98,1.01)	0.91 (0.88, 0.95)	0.92 (0.87, 0.98)
Age	0.99 (0.99, 0.99)	0.98 (0.98, 0.98)	0.99 (0.98, 0.99)
Income 2 vs 1	0.97 (0.95, 0.98)	0.96 (0.91, 1.00)	0.97 (0.89, 1.05)
Income 3 vs 1	0.96 (0.95, 0.98)	0.95 (0.90, 1.00)	0.98 (0.90, 1.07)
Income 4 vs 1	0.97 (0.95, 0.99)	0.95 (0.90, 1.02)	0.93 (0.84, 1.03)
Income 5 vs 1	0.95 (0.93, 0.97)	0.95 (0.89, 1.02)	1.05 (0.95, 1.16)
Rurality (ref=N)	0.89 (0.87, 0.91)	0.96 (0.91, 1.01)	0.92 (0.85, 1.00)
Prevalent mental disorder (ref=0)	1.30 (1.28, 1.33)	2.11 (1.98, 2.26)	3.18 (2.84, 3.56)

M: male; N: no; RR: relative risk; ED: emergency department; CI: confidence interval

4.4.2 Factors Associated with Total LOS

Overall, 19121 people in the entire cohort were hospitalized. Among those who had an MHA hospitalization, the total LOS varied from 0 to 364 days, with a mean (SD) of 24.7 (42.1) days and a median [IQR] of 10 [3, 27] days. Of everyone who was hospitalized, 18012 people were hospitalized and discharged before the end of the 365-day follow-up period. A total of 1109 people were hospitalized and were not discharged by the end of the follow-up period, and their LOS was truncated to the end of the 365-day follow-up period.

Focusing specifically on people with a positive test, the mean (SD) of the total LOS was 24.6 (42.7) days, and the median [IQR] was 9 [3, 27] days. Among people who had a positive methamphetamine/amphetamine test, sex and income were not significantly associated with total LOS. Age was significantly associated with total LOS: for every 1-year increase in age, the LOS increased by 1%, this difference was statistically significant (95%CI 1.01, 1.01). Rurality was associated with a significantly shorter total LOS compared to urban residents: the total LOS of rural residents was 74% of that of urban residents (RR 0.74, 95%CI 0.66, 0.83). Patients with a prevalent mental disorder also had a 46% longer total LOS by 47% compared to patients who did not have a prevalent mental disorder (RR 1.47, 95%CI 1.26, 1.70).

Table 4.8 Relative risks of factors associated with total length of MHA hospitalization among people with a positive methamphetamine/amphetamine test

Variable	RR (95%CI)
Sex (ref=M)	1.05 (0.97, 1.14)
Age	1.01 (1.01, 1.01)
Income 2 vs 1	1.02 (0.91, 1.13)
Income 3 vs 1	1.05 (0.93, 1.18)
Income 4 vs 1	0.97 (0.84, 1.11)
Income 5 vs 1	1.01 (0.88, 1.16)
Rurality (ref=N)	0.74 (0.66, 0.83)
Prevalent mental disorder (ref=0)	1.47 (1.26, 1.70)
Number of hospitalizations	1.30 (1.27, 1.34)

M: male; N: no; RR: relative risk; CI: confidence interval

5 Discussion

This chapter summarizes the findings of this project and their interpretation. Section 5.1 describes the results and compares them to findings in the existing literature. Section 5.2 outlines the study's strengths, 5.3 outlines its limitations, 5.4 describes implications and future directions, and section 5.5 provides an overall conclusion of this project.

5.1 Summary and Interpretation of Findings

This project aimed to answer the following research questions:

3) What was the rate of mental health service use – including outpatient visits, ED visits, hospitalizations, and diagnostic categories – within 12 months following a positive methamphetamine screen?

2 Was there effect modification by sex on the rate of mental health service use following a positive methamphetamine screen?

3) What were the sociodemographic and clinical factors associated with outpatient visits, ED visits, inpatient admissions, and total length of inpatient stay following a positive methamphetamine screen?

The following sections summarize the findings to these questions and compare it with the evidence in the literature.

5.1.1 Sociodemographic Characteristics

Sex

Men made up the majority (58.4%) of the study sample with a positive test, while women made up 41.6%. Other studies investigating drug use also found similar trends, with males representing the majority of methamphetamine users.[18,25,27,33,34,83] However, this project estimated that 41.6% of methamphetamine users were women, which was higher than in other studies. For example, women made up an estimated 11% of Canadian methamphetamine users according to the 2019 Canadian Centre on Substance use and Addiction telephone survey, and 35% of users according to Canadian surveys and trials recruiting from Canadian harm reduction centres.[34,150] Similarly, American survey data

from 2021 NSDUH reported that women represented 36.5% of people with past-year methamphetamine use.[27] Therefore, women may be underrepresented in survey data on regarding drug use in the population, and further research can be done to understand the prevalence of use among women compared to men.

Age

On average, people with a methamphetamine/amphetamine positive test were younger than those with a negative test, with mean age of 37.7 years and 41.8 years, respectively. The mean age of those with a positive test was slightly higher than what is commonly reported in the literature (mean/median age of 30-40 years).[81–85] In our sample, most people with a positive test fell within the ages of 20 to 39.

Although authors of other research studies[81,82,151] report that female methamphetamine users are often significantly younger than their male counterparts, there was no notable difference in age between females and males of either exposure group in this study sample. The reasons for this difference are unclear; however, it may be due to the nature of the way the study sample was created. Other studies of methamphetamine users are typically 1) surveys of convenience samples or 2) retrospective/prospective chart review or health administrative study of people presenting to health care settings and include patients of similar age ranges as in our study (i.e. include individuals from the pediatric and adult populations). However, our study identified people with probable methamphetamine use through urine and serum drug screens rather than through self-report or through health care visits with an ICD-10 code indicating a methamphetamine-related visit. Although we do not have the indications for testing in this study, one possible reason for this difference in findings is that the indication for drug testing is the same across age groups regardless of sex, and therefore, no difference was seen between ages in this sample. Another reason may be due to differences in geographic regions of studies: to our knowledge, this was the first provincial, population-level study in Ontario. Women and men in Ontario who use methamphetamine/amphetamine may be of similar ages compared to those in other regions.

Income quintile

The majority of people (40.9%) with a positive methamphetamine/amphetamine test in the study sample fell within the lowest income quintile, which was greater than the percentage of people in the methamphetamine/amphetamine-negative group (31.4%). This finding was consistent with the literature, where studies have found that users are more often in a low versus higher socioeconomic status group.[3,152,153]

Rurality

The majority of people (82.1%) of people with a positive test in this study lived in urban areas, which reflects the fact that about 86.2% of the Ontario population lived in urban areas (based on 2016 estimates from census data).[154] This suggests that our study has a larger percentage of users living in rural areas than would be expected as per the population distribution. Few studies reported rurality among methamphetamine users; however, Nickel et al.[3] reported comparable findings in their study, with 79% of methamphetamine users in Manitoba residing in urban areas.

Other studies[155–158] in the United States and one in Canada report higher rates of methamphetamine use among rural communities compared to urban metropolitan areas. Additionally, a study[159] of rural and urban drug users in the United States reported that rural deaths from methamphetamine increased between 1999 and 2019, and that people in rural areas who use methamphetamine are at higher risk of death compared to methamphetamine users from urban areas. Therefore, more research can be done to understand the relationship between methamphetamine use in rural and urban areas to understand their health service needs.

Prevalent mental disorders

Prevalent mental disorders were more common among people with a positive methamphetamine/amphetamine test than in those with a negative test across all diagnostic categories, which supports findings in the literature of higher prevalence of psychiatric comorbidities in methamphetamine users (and substance users, overall).[59,160,161]

When comparing prevalent mental disorders by sex, schizophrenia spectrum and other psychotic disorders, substance-induced psychotic disorder, substance use disorders, and neurodevelopmental disorders were all more common in methamphetamine/amphetamine-positive men than women.

Few studies look at sex differences in schizophrenia among drug users and the symptoms of drug use can mimic schizophrenia, which makes our findings difficult to compare to the literature. Generally, the prevalence of schizophrenia is similar among men and women but incidence is higher among men.[162] In a 2018 review by Hunt et al.[163], 42% of people with schizophrenia had substance use disorder and the prevalence of substance use was 26% higher in men with schizophrenia than in women.

Prevalent neurodevelopmental disorders in this study sample were higher in methamphetamine/amphetamine-positive men than women. The category in this study included conditions such as conduct disorder and attachment disorders. Studies of the relationship between methamphetamine use and adolescent behaviour (typically including conduct disorder, ADHD, and oppositional personality disorder) supported the findings in this project and reported that youth who use methamphetamine or have methamphetamine use disorder were more likely to have conduct disorder, hostile/anti-social behaviour (but not disorder diagnosis), and ADHD compared to youth who use other drugs.[164–167]

Mood and anxiety disorders were more common in women with a positive test than in men, which is also supported by other studies reporting psychiatric comorbidities among methamphetamine users.[19,168,169] There were no sex differences in the prevalence of deliberate self-harm or other mental disorders between men and women who had a positive test. Studies[60,170] of deliberate self-harm and components of the “other” mental disorder category (eg PTSD, eating disorders) are typically reported to be higher among women than men methamphetamine users.

5.1.2 Objective 1: Rate of MHA Service Use

5.1.2.1 Outpatient Use

Over 75% of people with a positive test used outpatient MHA services compared to 55.7% among those with a negative test only. The rate of outpatient MHA service use was 2.65 times greater among people with a methamphetamine/amphetamine-positive test compared to those with a negative test.

Some studies[85,87,88] reported use of and referrals to outpatient counselling, community health, and psychologist services in methamphetamine users as varying between 23-36% - much smaller than the ~75% estimate in our study. This difference could be due to MHA care access: these studies were based in Australia which has both private and public MHA psychiatrists and primary care providers,[171,172] whereas Ontario MHA psychiatrists and primary care clinics are largely publicly funded.

There is limited information in the literature focusing on the rates of MHA outpatient service use by methamphetamine users for comparison to our findings. Nickel et al.[3] reported that the rate of physician visits (not limited to MHA visits) among methamphetamine users in Manitoba was 8.7-10.4 visits/person-year, which was about 1.5-2 times higher than their estimate for non-users (5 visits per person-year), comparable but slightly smaller estimates than estimated in our study sample (15.0 vs 5.7 visits/person-year, respectively).

The high prevalence of MHA outpatient service use by people with a positive test in the current study highlights the need for further research into understanding the needs of methamphetamine users who use outpatient clinics. Dunn et al.[173] conducted a qualitative study of primary care physicians to understand common practices and concerns in treating people with methamphetamine addictions. Authors of this study reported difficulties in screening patients for methamphetamine use, in sending referrals to physicians in addiction medicine, in identifying ways to get in and maintain contact with patients who were housing insecure, and a lack of knowledge of effective treatments for methamphetamine addiction and related health problems. Therefore, more research can

be done to understand the outpatient healthcare needs of people who use methamphetamine and ways to support physicians who may encounter this patient population frequently.

5.1.2.2 ED Use

The percentage of people with a positive test who had a MHA ED visit was nearly twice as high compared to those who only had a negative test (29.3% vs 15.4%, respectively). The rate of ED use among people with a positive methamphetamine/amphetamine test was 2.01 times greater than those with a negative test.

Overall, studies have reported that ED use due by methamphetamine users has increased in recent years.[83,2,12,90,86,91] For example, an Ontario study by Crispo et al.[2] reported that there was a 15-times increase in amphetamine-related ED visits from 2003 to 2020, with 75% of patients reporting an ED revisit within 6 months of their first visit. Similarly, in their retrospective chart review of amphetamine-related ED visits to a Toronto hospital, Tardelli et al.[11] found that 30-40% of visits between 2017 and 2019 had a co-occurring mental disorder. Another health administrative study by Nickel et al.[3] reported that rates of ED use (not limited to MHA services) in Manitoba within one year after their first documented methamphetamine-related visit was 5.8-6.4 visits/person-year and 0.35 visits/person-year among the general population (an approximately 15 times greater rate among those with a popular test). This difference in rates compared to the findings of our project could be due a difference in reference populations: this project consisted of people who were screened for methamphetamine/amphetamine, whereas Nickel et al.[3] compared rates to a general population of Manitoba. The mental state of those screened for methamphetamine/amphetamine may not be reflective of the general population, leading to a smaller ratio of ED use in this study.

5.1.2.3 MHA Hospitalizations

In our study, 14.7% of people who had a positive test for methamphetamine/amphetamine had an MHA hospitalization within 365 days after index

date. The rate of MHA hospitalizations was 1.78 times greater among those who had a positive test compared to those who had a negative test.

Recent studies[11,12,14–16] have reported an overall increase in the rates of psychiatric admissions by methamphetamine users. However, compared to the findings in this project, some studies reported a greater percentage of methamphetamine users who had a psychiatric admission. Tardelli et al.[11] conducted a chart review and reported that in a Toronto hospital, the percentage of amphetamine-related inpatient admissions with a co-occurring mental disorder ranged from nearly 63% of all amphetamine-related admissions to about 70% between 2017 and 2019. For example, Richards et al.[12] reported that at a publicly funded academic hospital in Davis, California, 35% of methamphetamine users (identified through positive urine screens) in the ED had a psychiatric hold/transfer between May and August 2016. However, this estimate did not involve voluntary admissions.

However, two American studies[94,97] reported that there was no difference in the rates of MHA hospitalizations for psychiatric disorders between methamphetamine users and non-users. Both of these studies were American and looked solely at psychiatric admissions from the ED. Additionally, both studies had a similar demographic of methamphetamine users and non-users as in this project: the average person in the studies was 31-36 years of age and significantly more users presented with mental health problems. However, the different results seen in hospitalization trends could be because both studies looked at health service use approximately 20 years ago (2004-2006). Additionally, both studies were only based out of urban centres, whereas the study sample in the current project included health centres from across Ontario, including rural areas. Both studies identified non-users differently: one of the studies identified non-users through patients with a negative urine screen who visited the ED on the same day as someone with a positive screen, and the other identified non-users through physicians' notes in medical records indicating that a visit was not methamphetamine related. These differences in setting, time period, and participant selection may have contributed to the differences in results seen in this project. More research is needed to understand the impact of methamphetamine use on MHA hospitalizations.

5.1.2.4 Health Care Use by Diagnostic Category

Overall, the results of this project suggest that the rates of schizophrenia spectrum and other psychotic disorders, substance use disorders, substance-induced psychotic disorders, and deliberate self-harm were significantly higher in people with a positive methamphetamine/amphetamine test compared to people with a negative test.

However, there were no significant differences between the two groups in the rates of MHA service use associated with mood and anxiety disorders, neurodevelopmental disorders, or other mental disorders.

Schizophrenia Spectrum and Other Psychotic Disorders

In our study sample, 11.8% of people with a positive methamphetamine/amphetamine test used health services for schizophrenia spectrum and other psychotic disorders. This estimate is within the range cited by other studies, which suggest that primary psychotic disorders may affect 4.9% to 15.0%[3,57,58] of methamphetamine users. However, estimating the proportion of people with primary psychotic disorders in methamphetamine users is difficult due to challenges in differentiating symptoms from methamphetamine-induced psychosis. For example, other studies[174–176] of people with methamphetamine/amphetamine-induced psychosis have reported that anywhere from 5.0% to 38% of people had been diagnosed with primary schizophrenia in the 5 years after follow-up.

Few studies report the rate of schizophrenia or psychotic disorder diagnoses or health service use. Nickel et al.[3] reported that the rate of psychotic disorders in their cohort of methamphetamine users was 44 times that of non-users, which was much greater than in this project, where we found a 1.15 times greater rate of use. The comparator group in their study was the general population of Manitoba without a methamphetamine-related health care visit, whereas in our project, the comparator was anyone with a negative methamphetamine/amphetamine test – the mental state and drug use history of these two comparators is likely different, which would have led to the difference in results between studies. Another study by Zito et al.[104] found that people who had methamphetamine use

disorder with schizophrenia used acute inpatient and ED services at 4 times the rate of people who did not have methamphetamine use disorder with schizophrenia.

Substance Use Disorders

In the current study sample, nearly 60% of people with a positive test used health services for substance use disorders, which was greater than in Nickel et al.[3] comparable study, which reported that 45% of methamphetamine users used health services for substance use disorder within the first year of contact with the health system. The rate of MHA service use in our study for substance use disorders was over 4 times higher in people with a positive test than those with a negative test. Nickel et al.[3] reported that the rate of substance use disorder diagnosis in Manitoba within one-year after first contact was 18 times greater in methamphetamine users compared to non-users. The definition of substance use in their study was comparable to ours:

> "At least one hospitalization with a diagnosis for alcohol or drug-induced psychosis, alcohol or drug dependence, or nondependent abuse of drugs; or At least one physician visit with a diagnosis for alcohol or drug-induced psychosis, alcohol or drug dependence, or nondependent abuse of drugs."

Therefore, the reason for this difference may be due to a difference in comparator populations: the entire general population of Manitoba without a methamphetamine-related health contact was used as a comparator in the study by Nickel et al., whereas our study compared the MHA service use of people who had a methamphetamine/amphetamine drug screen. Therefore, the probable differences in mental state and drug use history between these comparator groups likely led to differences in the results of substance-use disorder related service use between these two studies.

Substance-Induced Psychotic Disorders

In the current study sample, 6.1% of people with a positive methamphetamine/amphetamine test used health services for substance-induced psychotic disorders within 365 days of their first positive test within the ascertainment

window compared to 1.1% of people with a negative test. The rate of associated visits/hospitalizations was 1.79 times greater among people with a positive test compared to those with a negative test.

The definition of substance-induced psychotic disorder in this project was not limited to methamphetamine, but included cocaine, opioids, and cannabis, among other substances. Generally, an estimated 26-46% of methamphetamine users experience methamphetamine-induced psychotic disorder or psychosis.[52] Psychosis is also a leading symptom among methamphetamine users upon presentation to the ED and hospitalization,[71,74,78,79] however, as described previously, differentiating between primary psychotic and substance-induced psychotic disorders remains difficult.

Deliberate Self-Harm

Overall, 5.9% of people with a positive test in the study sample used health services for deliberate self-harm. The rate of health service use for deliberate self-harm was significantly higher among people with a positive test compared to a negative test (RR 1.63). One meta-analysis found that methamphetamine use is associated with 4 times higher odds of suicidality.[177] A study by Marshall et al.[178] reported that of 149 injection drug users who used methamphetamine in Vancouver, 8.0% reported a suicide attempt (2.51 attempts per 100 person-years) which was higher than reported in this project. Studies[48,169] also generally support that deliberate self-harm is higher among methamphetamine users compared to people who do not use methamphetamine. Another study by Darke et al.[179] reported that between 2009 and 2015, 18.2% of all deaths among methamphetamine users in Australia were due to suicide, highlighting the risk of death by deliberate self-harm among methamphetamine users.

Mood and Anxiety Disorders

In our study cohort, 42.7% of people with a positive methamphetamine/amphetamine test used health services for mood or anxiety disorders. Although this proportion was difficult to compare to findings in the literature (which typically report the prevalence of mood

and anxiety disorders as separate categories and are defined differently across studies), other studies typically reported smaller percentages of methamphetamine users with mood and anxiety disorders. For example, Akindipe et al.[57] conducted an interview of 100 methamphetamine users and found that 16% had a mood disorder and 7% had an anxiety disorder. Lisa et al.[59] reported comparable figures from their interviews: 14% of methamphetamine users had depression and 11.8% had anxiety. Similarly, Glasner-Edwards[52] reported that 15% of methamphetamine users interviewed their study had depression and 23% had anxiety (which included diagnoses of generalized anxiety disorder, PTSD, and OCD). A health administrative study in Manitoba by Nickel et al.[3] that was similar in design to this thesis project found that 35% of people with methamphetamine-related health service use also had a mood and anxiety disorder-related health care visit.

Although there was no significant difference between the rates of mood and anxiety disorders between people with a positive and negative methamphetamine/amphetamine test in this study, this was not supported by other studies in the literature. For example, a Nickel et al.[3] reported that found that methamphetamine users in Manitoba had twice the rate of mood and anxiety disorders compared to people in the province who did not use methamphetamine. This difference is likely due to a difference in the population the authors used as a comparator: the entire population of Manitoba without a methamphetamine-related contact was used as a comparator and reference population. However, in this thesis project, methamphetamine non-users were defined as people who only had a negative methamphetamine test within the ascertainment window. The indication for drug testing was unknown, but it could be due to a history of or ongoing substance use. Therefore, people with a negative test are likely not comparable to the general population.

Neurodevelopmental Disorders

Overall, 5.1% of people with a positive methamphetamine/amphetamine test used health services for neurodevelopmental disorders. There was no significant difference between

the rates of service use for neurodevelopmental disorders for people with a positive test and people with a negative test.

Neurodevelopmental disorders like ADHD are reported to be significantly more common among people who use methamphetamine than people who do not use methamphetamine.[180] Furthermore, prenatal methamphetamine exposure is associated with neurodevelopmental disorders.[181–183] To our knowledge, no other studies report health service use for neurodevelopmental disorders among methamphetamine users.

Other Mental Disorders

In the current study, 11.5% of people with a positive test had other mental disorders compared to 10.2% with a negative test (including but not limited to personality disorders, post-traumatic stress disorders, and eating disorders). There was no difference in the rates of other mental disorders between people with a positive methamphetamine/amphetamine test and people with a negative test.

The findings in our study were difficult to compare to findings in the literature because other studies report findings for these disorders separately as their own categories. However, Nickel et al.[3] reported that 8% of methamphetamine users in Manitoba in their cohort used health services for personality disorders at a rate 20 times higher than the general population. Once again, this difference in RR could be due to differences in the comparator in this project versus in the study by Nickel et al. (i.e, a comparison group where individuals may be using other substances versus a general population of health service users across Manitoba who did not have a methamphetamine-related health care visit).

5.1.3 Objective 2: Sex Differences in MHA Service Use

5.1.3.1 Outpatient Use

Overall, over three quarters of women and men with a positive test used outpatient MHA services. In contrast, slightly over half of women and men with a negative test used

outpatient MHA services. No other population-level studies, to our knowledge, compared the use of MHA outpatient services in males and females who use methamphetamine.

In this study sample, the effect of methamphetamine use on outpatient MHA service use was significantly greater in men than in women.

5.1.3.2 ED Use

In this study, 28.6% of women with a positive test and 29.9% of men with a positive test had an MHA ED visit. There was no effect modification by sex on the rate of ED visits among methamphetamine users.

5.1.3.3 MHA Hospitalizations

14.5% of methamphetamine/amphetamine-positive women and 14.9% of methamphetamine/amphetamine-positive men were hospitalized, compared to 9.1% and 8.2% of women and men with a negative test, respectively.

Sex was not an effect modifier on the rate of MHA hospitalizations following a positive methamphetamine test.

5.1.3.4 Health Care Use by Diagnostic Category

This study presented novel findings regarding effect modification by sex on the rates of MHA service use (in each diagnostic category) by methamphetamine users.

Sex was an effect modifier on the rate of MHA service use for certain diagnostic categories following a positive methamphetamine/amphetamine test. The effects of methamphetamine use on rates of MHA service use for substance use disorders and schizophrenia spectrum disorders were each significantly greater in women, and effect on service use for mood and anxiety disorders, deliberate self-harm, and neurodevelopmental disorders were each significantly greater in men.

Sex was not an effect modifier on the relationship between methamphetamine use and rate of health service use for substance-induced psychotic disorders or other mental disorders.

Because this is the first study to our knowledge that investigates sex as an effect modifier on the rates of health service use among methamphetamine users, the following paragraphs draw comparisons to the literature regarding only the percentage of people with visits within each diagnostic category.

Schizophrenia spectrum and other psychotic disorders

A larger percentage of men (13.5%) than women (9.3%) with positive methamphetamine/amphetamine tests used health services for schizophrenia spectrum and other psychotic disorders.

Substance use disorders

MHA service use for substance use disorders were more common in males (62.0%) with a positive test than in females (56.6%) with a positive test. Substance use disorders are typically more common among men than in women.[27,184–186]

Substance-induced psychotic disorders

As with substance use disorders and schizophrenia spectrum disorders, health service use for substance-induced psychotic disorders were more common in methamphetamine/amphetamine-positive men than in women (6.7% versus 5.2%, respectively).

Deliberate self-harm

A larger percentage of women (6.2%) than men (5.7%) with a positive test used health services for deliberate self-harm. This finding was supported in the literature, which

typically reports that more women than men who use methamphetamine experience thoughts of self-harm and suicidality, especially with younger age groups.[82,100,120,168,170] However, more male methamphetamine users die by suicide than females.[179]

Mood and Anxiety Disorders

In the study sample, 45.6% of women with a positive test had a documented visit for mood and anxiety disorders compared to 40.7% of men with a positive methamphetamine/amphetamine test. Similar findings are reported in other surveys and health administrative studies, where more women typically report mood and anxiety disorders compared to men.[48,187–189]

Neurodevelopmental disorders

Overall, 6.0% of methamphetamine/amphetamine-positive men used MHA services for neurodevelopmental disorders compared to only 3.8% of women with a positive test. There is limited literature on the health service use related to neurodevelopment disorders in women and men who use methamphetamine. One study[190] reported that among adult methamphetamine users, more women than men had ADHD.

Other mental disorders

Similar percentages of women (11.4%) and men (11.5%) with a positive test used MHA services for other mental disorders. These findings contradict what is reported in the literature: typically, studies report that more women who use methamphetamine have PTSD, OCD, and eating disorders such as bulimia compared to men who use methamphetamine.[61,191,192]

5.1.4 Objective 3: Factors Associated with MHA Service Use and Total LOS

5.1.4.1 Factors associated with MHA Service Use

Overall, having a prevalent mental disorder led to a significantly increased risk of each of MHA outpatient visits, ED visits, and hospitalizations. In contrast, each one-year increase in age led to a 1-2% reduced risk of MHA service use.

MHA Outpatient Use

There are no studies to our knowledge that report on factors associated with outpatient MHA use in methamphetamine users. Looking specifically at outpatient visits, sex was not associated with outpatient service use among people with a positive test. Being in income quintiles 2 to 5 were associated with a lower risk of outpatient use compared to individuals in income quintile 1. Living in a rural area was associated with a significantly lower risk of MHA outpatient use compared to residence in an urban area. This could be due to study design: in order to enter this cohort, each individual had to have an interaction with the health care system, and because health services are generally more prevalent and easily accessible in urban areas,[193,194] there may have been more methamphetamine users from urban areas more easily able to access health services compared to rural counterparts.

MHA ED Visits

Opposing trends were seen with respect to ED visits, where men had a significantly higher risk of an MHA ED visit compared to women, which was supported by the literature. For example, in their study of methamphetamine users in Toronto, Rahimi et al.[195] reported that men were more likely than women to have an ED visit. Males who used methamphetamine being more likely to use the ED was also supported by other studies in the literature.[84,85,94] However, these studies were not limited to only MHA visits to the ED, but included ED visits due to other complications as well.

Interestingly, the current study found no relationship between rurality and ED visits among methamphetamine users. To our knowledge, there are no other studies in the literature that describe ED use among rural methamphetamine users for comparison to our results. However, a 2021 study[196] of mental health service use in Ontario found that generally, rural residents were likely to have their first MHA point of care be at a psychiatric ED.

In this study, income quintile was not associated with MHA ED visits. No other studies to our knowledge reported the association of income as a factor of interest in MHA ED use among methamphetamine users, specifically. One Ottawa study of people who use drugs found that low income/income assistance was associated with ED use. [197] Additionally, frequent ED users for MHA services most often live in low-income areas.[198]

MHA Hospitalizations

Comparable trends to ED visits were seen with respect to MHA hospitalizations in our study: men had a significantly higher risk of an MHA hospitalization compared to women with a positive test, and there was no association between income quintile or rurality and MHA hospitalization.

When comparing these findings to the literature, the trends are less clear. For example, in their 2007 American case-control study of psychiatric service use, Pasic et al.[94] reported that being male was associated with higher risk of psychiatric admissions among methamphetamine users, whereas Leamon et al.[107] and Rahimi et al.[195] reported that women were more likely to be admitted. Conversely, in McKetin et al.'s[87] 2018 study of methamphetamine-related health care use in Australia, there was no association between sex and psychiatric admissions. Therefore, more research is needed to understand the association between sex and MHA hospitalization.

Similarly, there is limited literature on the association between income and psychiatric admission in methamphetamine users. In general, low household income is associated with higher rates of psychiatric admission.[199] McKetin et al.[87] reported that low income

was associated with psychiatric admission in methamphetamine users, and other population-level studies[200,201] focusing on any amphetamine-related hospitalizations have also identified that low income is associated with hospitalization.

Finally, few studies have examined the association between rural and urban methamphetamine users and psychiatric admissions specifically. However, other studies[193,194] note the barriers in accessing psychiatric health care in rural areas. One Ontario study[202] found substance use hospitalizations were higher in rural youth compared to urban youth. More research can be done to understand how rurality affects health service use in methamphetamine users.

5.1.4.2 Factors associated with total LOS

Living in a rural area was associated with a significantly shorter total LOS among those with a positive test who had an MHA hospitalization. However, having a prevalent mental disorder and increased age were associated with a longer total LOS. Income quintile had no significant effect on individuals' total LOS.

Notably, sex was not associated with total LOS among people with a positive test. Once again, there is limited literature that reports sex and LOS of a psychiatric hospitalization for comparison. However, Iwanami et al.[116] reported in their study that men were more at risk of an MHA hospitalization compared to women who used methamphetamine.

Limited information is available in the literature regarding the total LOS of psychiatric hospitalizations among methamphetamine users and factors associated with LOS. However, one 2019 American study[203] that compared any hospitalization of drug users to non-drug users found that drug users had a significantly longer LOS (5.5 days vs 4.5 days, $p<0.001$). Winkelman et al.[200] also found that people with an amphetamine-related hospitalization had a significantly longer stay compared to both who used opioids and nondrug users. However, more research is needed focusing specifically on methamphetamine users to clearly identify trends and factors associated with psychiatric LOS.

5.2 Study Strengths

One strength of this study is the use of ICES databases which 1) capture health information of all insured residents from across Ontario and 2) provide consistency in data used in this project. To our knowledge, this is the largest study in Ontario that reports MHA service use among methamphetamine users and is also the largest study that focuses specifically on identifying any sex differences in methamphetamine and MHA service use. Furthermore, ICES has standardized definitions for MHA-related visits, which provides consistency in identifying MHA diagnoses. The use of ICES databases provide consistency in collection and reporting of data from residents visiting or admitted to health centres from across Ontario.

Additionally, the use of the NMS enabled us to exclude people who use prescription amphetamines, greatly reducing the chance of false positive tests in the study cohort.

Another strength of this study is that we were able to access important sociodemographic and clinical information (age, sex, income quintile, rurality, prior positive clinical tests, and MHA clinical history) and ascertain any associations between these variables, methamphetamine use, and MHA service use.

Another strength of this study is the use of urine and serum drug screens to identify recent methamphetamine use. Although studies[204–207] have demonstrated the validity, reliability, and specificity of self-reported drug use, there are conflicting reports on the sensitivity of self-reported drug use. Self-reported drug use estimates are also susceptible to bias; the use of drug screens avoids recall bias that is present when relying on self-reported estimates of drug use. Furthermore, social desirability bias can also lead to under-reporting of self-reported drug use and underestimation of true drug use. Memory problems are another factor that could lead to over-reporting of self-reported drug use.[208] The use of urine screen results in the OLIS database helps avoid these biases and allows consistency in the way probable methamphetamine users within Ontario were identified for inclusion into the cohort. As of December 31, 2017, 61.7% of geographical regions in Ontario that covered 8.5 million residents included were captured by OLIS, which

represented over 60% of Ontario residents at the time, and included both rural and urban regions in the province.[209,210] Although not all Ontario residents were captured, this remains the largest cohort study to our knowledge that focuses solely on MHA service use among people who use methamphetamine.

5.3 Study Limitations

One limitation of this study is that it was impacted by ascertainment bias. The study sample consisted of people who were selected by health care providers for methamphetamine/amphetamine testing. People who were selected for testing may have had greater access to health care than those who were not selected for testing, ultimately leading could have led to greater rates of detection of MHA use among those who underwent a drug screen test compared to those who did not.

This study was also limited by its restriction of methamphetamine/amphetamine test results to only 2 years (2017-2018). In the years prior to 2017, the number of laboratories reporting test results to OLIS increased each year before stabilizing in 2017 and 2018. However, due to COVID-19 restrictions limiting health care access and use,[133–135] and exacerbating mental health issues[211,212], test results reported to OLIS from 2019 onwards were not used for this study. Future studies should include more years of data to understand trends in methamphetamine use over time.

Another limitation of this study is the possibility of false positive drug screens. For example, Pope et al. conducted a 6-year review of over 15,000 amphetamine urinalysis results and found that false positives made up 3.9-9.9% of positive amphetamine screens.[213] To reduce the possibility of false positive screens in this project, people with filled prescriptions for certain amphetamine derivatives were excluded from the cohort; however, a range of other medications (including over-the-counter drugs) can still lead to a positive drug screen, including pseudoephedrine (commonly found in cold medications), bupropion, metformin, and fluoxetine, and there is no way to identify or exclude individuals who may have been using these medications at the time of their positive test.

Additionally, a limitation of this study was that the methamphetamine/amphetamine-negative group included former methamphetamine users and people who have never used methamphetamine. There may be important differences between these individuals within the group with respect to their medical history, including history of/current illicit drug use and prevalent mental disorders that are not reflected in this study.

This study was also limited by the lack of test results for other illicit substances. Polysubstance use is common among methamphetamine users, including concomitant opiate, cocaine, or marijuana use.[152,214,215] The use of any one or a combination of these substances may lead to users seeking MHA services. Because we did not know if individuals with a positive test were also using other substances, we cannot attribute their MHA service use to solely methamphetamine.

Finally, this study was limited the lack of data available on gender. For example, only sex is collected by the RPDB; however, studies suggest that methamphetamine use is more prevalent among transgender individuals compared to cisgender individuals, and also more prevalent among transgender women compared to both cisgender individuals and transgender men.[216–218] In transgender women, findings from other studies suggest that mental health conditions (namely anxiety, depression, and PTSD) may be associated with methamphetamine use.[219,220] Therefore, to gain a more comprehensive understanding of factors that impact MHA service use by methamphetamine users, future studies should aim to look at the effect of gender on methamphetamine use and MHA health service use.

5.4 Implications and Future Directions

This project has used health administrative data to describe the sociodemographic characteristics, prevalent mental disorders, and rates of MHA service use among methamphetamine users in Ontario. To our knowledge, this is the first population-level study that uses health administrative data to identify effect modification by sex on the relationship between methamphetamine and rates of MHA service use.

The results of this project have shown that the rates of MHA service use are significantly higher in people who use methamphetamine compared to those who do not. This study

identified that outpatient MHA service by methamphetamine users may be much higher than estimates in other studies. Future studies can aim to examine the diagnostic categories that are most associated with outpatient visits at these clinics to inform MHA service planning for methamphetamine users. This study also identified that rural residents may be overrepresented among methamphetamine users and that rurality may be associated with reduced risk of MHA outpatient service use and shorter LOS when hospitalized. However, there may not be any difference in use of EDs and hospitalizations between rural and urban methamphetamine users. Noting other literature that report rising rural methamphetamine use (and general illicit drug use), future studies can aim to understand the health outcomes of rural versus urban methamphetamine users.

This project also highlighted sex as an effect modifier on the relationship between methamphetamine exposure and MHA outpatient use, schizophrenia spectrum and other psychotic disorders, substance use disorders, deliberate self-harm, mood and anxiety disorders, and other mental disorders. Women who use methamphetamine may be at reduced risk of MHA ED visits and hospitalizations compared to men, while there may be no difference between the risk of MHA outpatient visits in men and women. Future studies can aim to understand the MHA outcomes of women and men at EDs and psychiatric hospitals, respectively, to understand which conditions impact admission and LOS and guide health system planning.

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Appendices

Appendix A: Codes used to identify people with a methamphetamine/amphetamine test.

CODE TYPE	Category	Codes	Description	Type of Test
LOINC	Amphetamine	16369-1	16369-1 [Amphetamines:ACnc:Pt:Urine:Ord:Confirm]	Categorical
		19059-5	19059-5 [Amphetamines cutoff:MCnc:Pt:Urine:Qn]	Continuous
		19261-7	19261-7 [Amphetamines:ACnc:Pt:Urine:Ord:Screen]	Categorical
		19262-5	19262-5 [AMPHETAMINES TESTED FOR:PRID:PT:URINE:NOM:SCREEN]	Categorical
		19343-3	19343-3 [Amphetamine:PrThr:Pt:Urine:Ord:Screen]	Categorical
		19346-6	19346-6 [Amphetamine:MCnc:Pt:Urine:Qn]	Continuous
		19347-4	19347-4 [Amphetamine cutoff:MCnc:Pt:Urine:Qn:Screen]	Continuous
		3349-8	3349-8 [AMPHETAMINES:ACNC:PT:URINE:ORD]	Categorical
		43983-6	43983-6 [AMPHETAMINES:ACNC:PT:URINE:ORD:SCREEN>500 NG/ML]	Categorical
		8150-5	8150-5 [AMPHETAMINES:MCNC:PT:URINE:QN]	Continuous
	Amphetamine (serum)	3348-0	3348-0 [Amphetamines:PrThr:Pt:Ser/Plas:Ord]	Categorical
	Methamphetamine	19554-5	19554-5 [Methamphetamine:PrThr:Pt:Urine:Ord:Screen]	Categorical
		19555-2	19555-2 [Methamphetamine:ACnc:Pt:Urine:Ord:Confirm]	Categorical
		3779-6	3779-6 [Methamphetamine:PrThr:Pt:Urine:Ord]	Categorical
		3780-4	3780-4 [METHAMPHETAMINE:MCNC:PT:URINE:QN]	Continuous
		XON12906-4	XON12906-4 [Methamphetamines:ACnc:Pt:Urine:Ord:Screen>500 ng/mL]	Categorical
	Amphetamine / or + Methamphetamine	16367-5	16367-5 [Amphetamine/Methamphetamine:MCrto:Pt:Urine:Ord]	Categorical
		40419-4	40419-4 [Amphetamine+Methamphetamine:PrThr:Pt:Urine:Ord]	Categorical

Appendix B: Codes used to identify and exclude people with stimulant prescription medications.

CODE TYPE	DCLASS	Codes	Description	Effective Date
DIN	EXC_VYV	02322951	Vyvanse	16/04/2012
		02322978	Vyvanse	16/04/2012
		02347156	Vyvanse	16/04/2012
		02347164	Vyvanse	16/04/2012
		02347172	Vyvanse	16/04/2012
		02439603	Vyvanse	31/07/2015
		02458071	Vyvanse	21/06/2017
		02490226	Vyvanse	13/09/2019
		02490234	Vyvanse	13/09/2019
		02490242	Vyvanse	13/09/2019
		02490250	Vyvanse	13/09/2019
		02490269	Vyvanse	13/09/2019
		02490277	Vyvanse	13/09/2019
	EXC_ADD	02248808	Adderall XR	16/04/2012
		02248809	Adderall XR	16/04/2012
		02248810	Adderall XR	16/04/2012
		02248811	Adderall XR	16/04/2012
		02248812	Adderall XR	16/04/2012
		02248813	Adderall XR	16/04/2012
	EXC_DEX	01924516	Dexedrine	16/04/2012
		01924559	Dexedrine Spansules	16/04/2012
		01924567	Dexedrine Spansules	16/04/2012
	EXC_AMP	02439239	Act Amphetamine XR	29/10/2015
		02439247	Act Amphetamine XR	29/10/2015
		02439255	Act Amphetamine XR	29/10/2015
		02439263	Act Amphetamine XR	29/10/2015
		02439271	Act Amphetamine XR	29/10/2015
		02439298	Act Amphetamine XR	29/10/2015
		02440369	PMS-Amphetamines XR	28/03/2017
		02440377	PMS-Amphetamines XR	28/03/2017
		02440385	PMS-Amphetamines XR	28/03/2017
		02440393	PMS-Amphetamines XR	28/03/2017
		02440407	PMS-Amphetamines XR	28/03/2017

		02440415	PMS-Amphetamines XR	28/03/2017
		02443236	Apo-Dextroamphetamine	18/12/2015
		02445492	Apo-Amphetamine XR	31/07/2019
		02445506	Apo-Amphetamine XR	31/07/2019
		02445514	Apo-Amphetamine XR	31/07/2019
		02445522	Apo-Amphetamine XR	31/07/2019
		02445530	Apo-Amphetamine XR	31/07/2019
		02445549	Apo-Amphetamine XR	31/07/2019
		02448319	Act Dextroamphetamine SR	30/04/2018
		02448327	Act Dextroamphetamine SR	30/04/2018
		02457288	Sandoz Amphetamine XR	28/02/2017
		02457296	Sandoz Amphetamine XR	28/02/2017
		02457318	Sandoz Amphetamine XR	28/02/2017
		02457326	Sandoz Amphetamine XR	28/02/2017
		02457334	Sandoz Amphetamine XR	28/02/2017
		02457342	Sandoz Amphetamine XR	28/02/2017

Appendix C: ICD-10 and DSM codes used to define neurodevelopmental disorders.

CODE TYPE	Codes	Description
ICD10	F80	Specific developmental disorders of speech and language
	F81	Specific developmental disorders of scholastic skills
	F82	Specific developmental disorder of motor function
	F83	Mixed specific developmental disorders
	F84	Pervasive developmental disorders
	F88	Other disorders of psychological development
	F89	Unspecified disorder of psychological development
	F90	Hyperkinetic disorders
	F91	Conduct disorders
	F92	Mixed disorders of conduct and emotions
	F933	Sibling rivalry disorder
	F938	Other childhood emotional disorders
	F939	Childhood emotional disorder NOS
DSM-IV	299	Pervasive developmental disorders
	3072	Tic disorders
	3073	Stereotypic movement disorder
	31381	Oppositional defiant disorder
	31389	Reactive attachment disorder of infancy or early childhood
	3139	Disorder of infancy, childhood, or adolescence NOS
	314	Attention-deficit hyperactivity disorder
	315	Learning and communication disorders
DSM-5	299	Pervasive developmental disorders
	3072	Tic disorders
	3073	Stereotypic movement disorder
	31381	Oppositional defiant disorder
	31389	Reactive attachment disorder of infancy or early childhood
	3139	Disorder of infancy, childhood, or adolescence NOS

	314	Attention-deficit hyperactivity disorder
	315	Learning and communication disorders
ICD-10-CM	F80	Specific developmental disorders of speech and language
	F81	Specific developmental disorders of scholastic skills
	F82	Specific developmental disorder of motor function
	F83	Mixed specific developmental disorders
	F84	Pervasive developmental disorders
	F88	Other disorders of psychological development
	F89	Unspecified disorder of psychological development
	F90	Attention-deficit hyperactivity disorder
	F91	Conduct disorders
	F933	Sibling rivalry disorder
	F938	Other childhood emotional disorders
	F939	Childhood emotional disorder NOS

Appendix D. ICD-10 and DCM codes used to define substance-induced psychotic disorder.

CODE TYPE	Codes	Description
ICD-10	F105	Mental and behavioural disorders due to use of alcohol, psychotic disorder
	F107	Mental and behavioural disorders due to use of alcohol, residual and late-onset psychotic disorder
	F115	Mental and behavioural disorders due to use of opioids, psychotic disorder
	F117	Mental and behavioural disorders due to use of opioids, residual and late-onset psychotic disorder
	F125	Mental and behavioural disorders due to use of cannabinoids, psychotic disorder
	F127	Mental and behavioural disorders due to use of cannabinoids, residual and late-onset psychotic disorder
	F135	Mental and behavioural disorders due to use of sedatives or hypnotics, psychotic disorder
	F137	Mental and behavioural disorders due to use of sedatives or hypnotics, residual and late-onset psychotic disorder
	F145	Mental and behavioural disorders due to use of cocaine, psychotic disorder
	F147	Mental and behavioural disorders due to use of cocaine, residual and late-onset psychotic disorder
	F155	Mental and behavioural disorders due to use of other stimulants including caffeine, psychotic disorder
	F157	Mental and behavioural disorders due to use of other stimulants including caffeine, residual and late-onset psychotic disorder
	F165	Mental and behavioural disorders due to use of hallucinogens, psychotic disorder
	F167	Mental and behavioural disorders due to use of hallucinogens, residual and late-onset psychotic disorder
	F175	Mental and behavioural disorders due to use of tobacco, psychotic disorder
	F177	Mental and behavioural disorders due to use of tobacco, residual and late-onset psychotic disorder
	F185	Mental and behavioural disorders due to use of volatile solvents, psychotic disorder
	F187	Mental and behavioural disorders due to use of volatile solvents, residual and late-onset psychotic disorder
	F195	Mental and behavioural disorders due to multiple drug use and use of psychoactive substances, psychotic disorder
	F197	Mental and behavioural disorders due to multiple drug use and use of psychoactive substances, residual and late-onset psychotic disorder
DSM-IV	2913	Alcohol-induced psychotic disorder, with hallucinations
	2915	Alcohol-induced psychotic disorder, with delusions
	2921	Substance-induced psychotic disorder

DSM-V	2919	Alcohol-induced psychotic disorder
	2929	Substance-induced psychotic disorder
OHIP DX	292	Drug psychosis
ICD-10-CM	F1015	Alcohol abuse with alcohol-induced psychotic disorder
	F1025	Alcohol dependence with alcohol-induced psychotic disorder
	F1095	Alcohol use, unspecified with alcohol-induced psychotic disorder
	F1115	Opioid abuse with opioid-induced psychotic disorder
	F1125	Opioid dependence with opioid-induced psychotic disorder
	F1195	Opioid use, unspecified with opioid-induced psychotic disorder
	F1215	Cannabis abuse with psychotic disorder
	F1225	Cannabis dependence with psychotic disorder
	F1295	Cannabis use, unspecified with psychotic disorder
	F1315	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced psychotic disorder
	F1325	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced psychotic disorder
	F1395	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced psychotic disorder
	F1415	Cocaine abuse with cocaine-induced psychotic disorder
	F1425	Cocaine dependence with cocaine-induced psychotic disorder
	F1495	Cocaine use, unspecified with cocaine-induced psychotic disorder
	F1515	Other stimulant abuse with stimulant-induced psychotic disorder
	F1525	Other stimulant dependence with stimulant-induced psychotic disorder
	F1595	Other stimulant use, unspecified with stimulant-induced psychotic disorder
	F1615	Hallucinogen abuse with hallucinogen-induced psychotic disorder
	F1625	Hallucinogen dependence with hallucinogen-induced psychotic disorder
	F1695	Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder
	F1815	Inhalant abuse with inhalant-induced psychotic disorder
	F1825	Inhalant dependence with inhalant-induced psychotic disorder
	F1895	Inhalant use, unspecified with inhalant-induced psychotic disorder
	F1915	Other psychoactive substance abuse with psychoactive substance-induced psychotic disorder
	F1925	Other psychoactive substance dependence with psychoactive substance-induced psychotic disorder
	F1995	Other psychoactive substance use, unspecified with psychoactive substance-induced psychotic disorder

Appendix E: ICD-10 and DSM codes used to define "other mental disorders" category.

CODE TYPE	Codes	Description
ICD-10	F07	Personality and behavioral disorders due to known physiological condition
	F21	Schizotypal disorder
	F50	Eating disorders
	F51	Nonorganic sleep disorders
	F60	Specific personality disorders
	F64	Gender identity disorders
	F65	Disorders of sexual preference
	F66	Other sexual disorders
	F68	Other disorders of adult personality and behaviour
	F69	Unspecified disorder of adult personality and behaviour
	F45	Somatoform disorders
	F43	Reaction to severe stress, and adjustment disorders
	F941	Reactive attachment disorder of childhood
	F942	Disinhibited attachment disorder of childhood
	F985	Stuttering [stammering]
	F986	Cluttering
	F950	Transient tic disorder
	F951	Chronic motor or vocal tic disorder
	F952	Combined vocal and multiple motor tic disorder [de la Tourette]
	F958	Other tic disorders
	F959	Tic disorder, unspecified
	F984	Stereotyped movement disorders
	F982	Feeding disorder of infancy and childhood
	F983	Pica of infancy and childhood
	F980	Nonorganic enuresis
	F981	Nonorganic encopresis
	F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence
	F989	Unspecified behavioural and emotional disorders with onset usually occurring in childhood and adolescence
DSM-5	301	Personality disorders

	3010	Paranoid personality disorder
	3012	Schizoid/schizotypal personality disorder
	3014	Obsessive-compulsive personality disorder
	3015	Histrionic personality disorder
	3016	Dependent personality disorder
	3017	Antisocial personality disorder
	30181	Narcissistic personality disorder
	30182	Avoidant personality disorder
	30183	Borderline personality disorder
	30189	Other personality disorders
	3019	Personality disorder not otherwise specified
	302	Sexual disorders
	307	Feeding & eating disorders of infancy/childhood, tic disorders, elimination disorders, stereotypic movement disorder, eating disorders, primary sleep disorders
	3101	Personality change due to general medical condition
	3083	Acute stress disorder
	309	Adjustment disorders
	3090	Adjustment disorder with depressed mood
	30924	Adjustment disorder with anxiety
	30928	Adjustment disorder with mixed anxiety and depressed mood
	3093	Adjustment disorder with disturbance of conduct
	3094	Adjustment disorder with mixed disturbance of emotions and conduct
	30981	Posttraumatic stress disorder
	30989	Other specified trauma- and stressor-related disorder
	3099	Adjustment disorder unspecified
	31389	Reactive attachment disorder
ICD-10-CM	F07	Personality and behavioral disorders due to known physiological condition
	F21	Schizotypal disorder
	F50	Eating disorders
	F51	Nonorganic sleep disorders
	F60	Specific personality disorders
	F64	Gender identity disorders
	F65	Disorders of sexual preference
	F66	Other sexual disorders
	F68	Other disorders of adult personality and behaviour
	F69	Unspecified disorder of adult personality and behaviour

	F45	Somatoform disorders
	F43	Reaction to severe stress, and adjustment disorders
	F941	Reactive attachment disorder of childhood
	F942	Disinhibited attachment disorder of childhood
	F985	Stuttering [stammering]
	F986	Cluttering
	F950	Transient tic disorder
	F951	Chronic motor or vocal tic disorder
	F952	Combined vocal and multiple motor tic disorder [de la Tourette]
	F958	Other tic disorders
	F959	Tic disorder, unspecified
	F984	Stereotyped movement disorders
	F982	Feeding disorder of infancy and childhood
	F983	Pica of infancy and childhood
	F980	Nonorganic enuresis
	F981	Nonorganic encopresis
	F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence
	F989	Unspecified behavioural and emotional disorders with onset usually occurring in childhood and adolescence
	301	Personality disorders
	3010	Paranoid personality disorder
	3012	Schizoid/schizotypal personality disorder
	3014	Obsessive-compulsive personality disorder
	3015	Histrionic personality disorder
	3016	Dependent personality disorder
	3017	Antisocial personality disorder
	30181	Narcissistic personality disorder
	30182	Avoidant personality disorder
	30183	Borderline personality disorder
	3019	Personality disorder not otherwise specified
	302	Sexual disorders
	3101	Personality change due to general medical condition
	307	Feeding & eating disorders of infancy/childhood, tic disorders, elimination disorders, stereotypic movement disorder, eating disorders, primary sleep disorders
	3083	Acute stress disorder
DSM-IV	309	Adjustment disorders

	3090	Adjustment disorder with depressed mood
	30924	Adjustment disorder with anxiety
	30928	Adjustment disorder with mixed anxiety and depressed mood
	3093	Adjustment disorder with disturbance of conduct
	3094	Adjustment disorder with mixed disturbance of emotions and conduct
	30981	Posttraumatic stress disorder
	3099	Adjustment disorder unspecified
	31389	Reactive attachment disorder

Appendix F Distribution of ages by methamphetamine/amphetamine test result

	Methamphetamine/ Amphetamine-Positive	Methamphetamine/ Amphetamine-Negative	
	Total (N=25,702)	**Total (N=179,282)**	**Standardized Difference**
Age group, N (%)			
12-14	77 (0.3%)	2,810 (1.6%)	0.132
15-19	1,198 (4.7%)	15,768 (8.8%)	0.166
20-24	2,609 (10.2%)	17,430 (9.7%)	0.014
25-29	3,886 (15.1%)	16,895 (9.4%)	0.174
30-34	4,246 (16.5%)	15,308 (8.2%)	0.243
35-39	3,605 (15.0%)	14,648 (8.2%)	0.187
40-44	987 (9.4%)	13,850 (7.7%)	0.084
45-49	2,234 (8.7%)	14,951 (8.3%)	0.013
50-54	2,063 (8.0%)	18,500 (10.3%)	0.079
55-59	1,521 (5.9%)	18,673 (10.4%)	0.165
60-64	898 (3.5%)	14,410 (8.0%)	0.196
65-69	480 (1.9%)	9,795 (5.5%)	0.192
70-74	283 (1.1%)	6,244 (3.5%)	0.160

Appendix G Distribution of ages by sex for each exposure group.

	Methamphetamine/Amphetamine-Positive			Methamphetamine/Amphetamine-Negative				
	Females (N=10,554)	**Males (N=15,148)**	**Standardized differences (Between sexes)**	**Females (N=78,183)**	**Males (N=101,099)**	**Standardized differences (Between sexes)**	**Standardized differences (Between females)**	**Standardized differences (Between males)**
Demographics								
Age group, N (%)								
12-14	40 (0.4%)	37 (0.2%)	0.024	1,652 (2.1%)	1,158 (1.2%)	0.076	0.157	0.109
15-19	568 (5.4%)	630 (4.2%)	0.057	7,959 (10.2%)	7,809 (7.7%)	0.086	0.180	0.151
20-24	1,198 (11.4%)	1,411 (9.3%)	0.067	7,723 (9.9%)	9,707 (9.6%)	0.009	0.048	0.010
25-29	1,666 (15.8%)	2,220 (14.7%)	0.031	7,153 (9.2%)	9,742 (9.6%)	0.017	0.202	0.154
30-34	1,713 (16.2%)	2,533 (16.7)	0.013	6,303 (7.7%)	9,005 (8.6%)	0.030	0.252	0.235
35-39	1,413 (13.4%)	2,192 (14.5%)	0.031	6,122 (7.8%)	8,526 (8.4%)	0.022	0.181	0.190
40-44	2,602 (10.1%)	1,615 (10.7%)	0.044	5,833 (7.5%)	8,017 (7.9%)	0.018	0.068	0.094
45-49	868 (8.2%)	1,366 (9.0%)	0.028	6,400 (8.2%)	8,551 (8.5%)	0.010	0.001	0.020
50-54	792 (7.5%)	1,271 (8.3%)	0.033	7,823 (10.0%)	10,677 (10.6%)	0.018	0.089	0.074
55-59	596 (5.7%)	925 (6.1%)	0.020	7,777 (10.0%)	10,896 (10.8%)	0.027	0.161	0.169
60-64	355 (3.4%)	543 (3.6%)	0.012	6,177 (7.9%)	8,233 (8.1%)	0.009	0.198	0.195
65-69	224 (2.1%)	256 (1.7%)	0.032	4,334 (5.5%)	5,461 (5.4%)	0.006	0.179	0.202
70-74	134 (1.3%)	149 (1.0%)	0.027	2,927 (3.7%)	3,317 (3.3%)	0.025	0.159	0.160

Curriculum Vitae

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