THE EPIDEMIOLOGY OF METHAMPHETAMINE USE AMONG STREET YOUTH AND INJECTION DRUG USERS

by

BRANDON DAVID LEWIS MARSHALL

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B.Sc. (Hons), The University of British Columbia, 2006

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ABSTRACT

Background: Given the limited understanding of the epidemiology of methamphetamine (MA) use among street-involved youth and injection drug users (IDU), this thesis sought to: systematically characterise the evidence base demonstrating associations between MA use and adverse health outcomes among young people; examine the incidence and predictors of MA injection initiation among a cohort of IDU in Vancouver; describe the prevalence and correlates of MA use among sexual minority drug users; determine whether frequent MA injection predicts emergency department (ED) utilisation; and finally, explore the pathways through which MA use drives injection-related risk behaviour including syringe sharing.

Methods: Street-involved youth and IDU participating in three open prospective cohort studies were asked to complete semi-annual interviewer-administered questionnaires, provide blood samples for HIV testing, and consent to hospital database linkages. A variety of longitudinal techniques were used to investigate the association between self-reported MA-related outcomes (e.g., initiation, frequent use) and individual, social, and structural determinants of interest.

Results: A systematic review identified consistent associations between MA use and a number of health outcomes, including depression, suicidal ideation, and

psychosis. Scientific evidence to suggest an association between MA use and a number of previously suggested harms (e.g., infectious disease transmission, dental problems) is equivocal. Some subpopulations, including sexual minority drug users, are more likely to use MA, which appears to exacerbate exposure to HIV-related risks and other vulnerabilities. Longitudinal analysis revealed that young people, non-injection stimulant users, homeless individuals, and those involved in the city's open drug scene are most likely to initiate MA injection. The injection of MA, particularly frequently, was associated with a number of health and behavioural outcomes, including an increased hazard of ED utilisation and syringe sharing. Barriers to accessing harm reduction and HIV prevention services likely account for many of these relationships.

Conclusions: Methamphetamine use is increasingly common among street youth and IDU in Vancouver. Its use and resultant harms appear to be driven by intersecting individual, social, and structural factors. Comprehensive interventions that are based upon sound scientific evidence and that address existing health and social inequities among marginalised populations are required.

PREFACE

This statement is to certify that the work presented in this thesis was conceived, conducted, written, and disseminated by Brandon DL Marshall (BDLM). All research described in this dissertation was approved by the University of British Columbia/Providence Health Care Research Ethics Board (certificate number H08-03072). The co-authors of the manuscripts, including Dr. Thomas Kerr (TK), Dr. Jean A Shoveller (JAS), Dr. Jane A Buxton (JAB), Dr. Evan Wood (EW), Dr. Thomas L Patterson (TLP), Dr. Eric Grafstein (EG), Ms. Jiezhi Qi (JQ), Mr. Daniel Werb (DW), and Dr. Julio SG Montaner (JSGM) made contributions only as is commensurate with committee, collegial or co-author duties. The principal investigators of the larger research program from which the studies in this dissertation were derived (TK and EW) had access to all of the data and as corresponding authors take full responsibility for the integrity of the results and accuracy of the statistical analyses. With substantive input from co-supervisors TK and JAS, BDLM designed the studies and wrote the research protocols. With guidance and input from TK, JAS, JAB, TLP, and JQ, BDLM performed the research and conducted the statistical analyses described in Chapters 3 through 6. BDLM led the systematic review described in Chapter 2, and, in collaboration with DW, conducted the search strategy and selection of studies for inclusion. DW reviewed the material presented in Chapter 2 and approved the final version of the manuscript for submission. EW, JAS, JAB,

JSGM, and TK contributed intellectual content to the material in Chapter 3 and approved the final version of the manuscript for submission. JAS, EW, TLP, JSGM, and TK provided significant scientific input and approved the final version of material presented in Chapter 4. JQ assisted with the statistical analysis described in Chapter 5, while EG assisted with the acquisition of the data and EG, JAB, EW, JAS, and TK provided input with regard to the interpretation of the results. JAB, EW, TLP, and TK contributed important intellectual content to the preparation of the material presented in Chapter 6. All manuscripts contained in this thesis were prepared and written by BDLM. Final drafts of the manuscripts were prepared following the inclusion of material based on comments from the co-authors, the journal editors, and external peer reviewers. The following publications arose from work presented in Chapters 2 and 3 of this dissertation, respectively:

1. Marshall BDL, Werb D. Health outcomes associated with methamphetamine use among youth people: A systematic review. *Addiction* 2010:**105**(6):991-1002.
2. Marshall BDL, Wood E, Shoveller JA, Buxton JA, Montaner JSG, Kerr T. Individual, social, and environmental factors associated with initiating methamphetamine injection: Implications for drug use and HIV prevention strategies. *Prevention Science* (in press).

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DEDICATION

To Michael

CHAPTER 1

BACKGROUND, RATIONALE, AND OBJECTIVES

1.1 THE GLOBAL EPIDEMIOLOGY OF METHAMPHETAMINE USE

Methamphetamine (MA), first synthesised in 1919, is a central nervous stimulant that gained significant popularity in the latter half of the twentieth century [1]. MA stimulates the release of dopamine, noradrenalin, adrenaline, and serotonin, thus resulting in increased alertness, concentration, energy, decreased appetite, and feelings of euphoria [2]. At higher doses and with increasing frequency of use, MA has high potential for abuse and dependence, with chronic administration potentially leading to long-lasting neurotoxic effects [3]. MA and related amphetamines are also used for therapeutic purposes, with low doses of MA (trademarked under the name Desoxyn®) approved in the United States for the treatment of hyperactivity disorder in children and for the short-term treatment of obesity [4]. In this dissertation, MA is used as a general term to include amphetamine, methamphetamine, and d-methamphetamine hydrochloride (i.e., "crystal meth") in order to be consistent with epidemiologic literature and since the research findings are generally applicable to all forms of the drug.

The use of amphetamine-type substances (ATS) in general and methamphetamine (MA) in particular are increasingly recognized as major global

health problems [5]. The use of MA has been reported in over 100 countries, with a majority reporting MA injection as well [6]. The 2010 World Drug Report suggests that the global prevalence of ATS use is second only to cannabis, with estimates suggesting that up to 53 million individuals (1.2% of the global population aged 15-64) have used ATS at least once in the past 12 months [7]. Although a global phenomenon, the prevalence of use varies widely, with countries in North America, Europe, and Southeast Asia reporting the highest levels of consumption [7]. Globally, MA consumption has remained relatively constant since 2002, although regions such as South and Central America and the Middle East have experienced significant increases, particularly among young people [8].

In the United States, data from the 2007 National Survey on Drug Use and Health (NSDUH) indicate that 0.1% of 12 to 17 year olds and 0.4% of 18 to 25 year olds reported using MA in the past month, representing over 150,000 young users in the US [9]. Although overall MA use in the United States is stable and in many regions declining, the United Nations Office on Drugs and Crime (UNODC) 2010 *World Drug Report* noted significant increases in purity, concomitant with a 50% decrease in the average street price since 2007 [7]. In Canada, provincial student surveys suggest that past year use of MA among adolescents is approximately 3% [10, 11]. Prevalence is highest in the western regions of both countries [12].

The contexts, motivations, and risk factors for MA use vary widely, depending largely on the geographic setting and population under study. The occupational use of MA (i.e., to stay alert for longer hours and to increase energy and productivity) has been documented in a number of work environments [13, 14]. Within the MSM community, MA has long been recognised as a drug to increase energy, improve body appearance, and enhance sexual experiences [15-17]. However, some have argued that many of these studies present excessively individualised motivations for MA use, and thus overlook the role that cultural and structural contexts play in mitigating or promoting drug use and subsequent risk behaviour [18]. Furthermore, a growing literature has demonstrated how factors exogenous to the individual (e.g., homelessness, community deprivation and poverty) are important drivers of MA use, particularly among young vulnerable populations [19, 20]. Other commonly identified risk factors for MA use include underlying psychiatric disorders, positive peer norms towards MA use, exposure to incarceration, and parental involvement in crime or familial drug use [21-23].

1.2 METHAMPHETAMINE USE AMONG STREET YOUTH AND IDU

Given the growing contribution of injection drug use to the global HIV epidemic (injection drug users [IDU] account for 30% of HIV infections outside of Africa [24]), MA injection is an increasingly important area of epidemiologic study.

Compared to non-injection modes of consumption (e.g., smoking, snorting) injecting MA has been associated with higher levels of dependence and an increased frequency of use [25, 26]. Among individuals who first consume MA through non-injection routes, transitions to injecting are common and are generally associated with poorer social functioning and increased dependence [27]. MA injection has been associated with increased HIV incidence and prevalence among IDU in several settings [28-32], although further research is required to elucidate the relative contributions of injecting and sexual behaviour to overall transmission risk [6]. Evidence does suggest that both co-occur; for example, IDU who primarily use MA are more likely to report syringe sharing [33-35], and MA injection (compared to non-injection MA use) has been associated with increased rates of sexual risk behaviour and STI diagnoses [26, 36]. Of further concern is the fact that injection drug use is the principal route of hepatitis C (HCV) infection in North America, accounting for approximately 70% of acute cases [37]. Preliminary studies have demonstrated an increased risk of HCV acquisition among injecting and non-injecting MA users [38]. For these reasons, the increasing prevalence of MA use among both established injectors and those at risk for initiating injection drug use is of significant public health concern [33, 39].

Research involving populations at high risk for initiating injection drug use provides critical information regarding the relationships between MA consumption

and other modes, typologies, and transitions in drug use. Street-involved youth represent one such population [40], and thus constitute a major focus of this thesis. The term "street-involved youth" is used here to denote a young person who spends a substantial amount of time on the street or is heavily engaged in the street economy [41]; therefore, street youth in this context may be absolutely, periodically, or at imminent risk of homelessness [42]. MA use among street youth is a growing problem: data from the Public Health Agency of Canada (PHAC) Enhanced Street Youth Surveillance (E-SYS) program suggests that MA use among street-involved youth increased fourfold between 1999 and 2005 [43]. Although many aspects regarding the contexts of and motivations for MA use among street youth has yet to be elucidated, there is evidence to indicate that this population experiences a unique set of health risks and harms. For example, two recent studies identified an association between MA use and hepatitis C seropositivity among street youth, indicating increased exposure to parenteral risks [44, 45]. These findings exemplify the pressing public health challenges posed by MA use among street youth, and indicate that rigorous epidemiologic research is required to inform the development of effective prevention strategies.

1.3 STUDY SETTING

Problematic substance use continues to represent a significant public health problem in British Columbia, with rates of illegal drug use and drug-related mortality greater than any other province in Canada [46]. Additionally, recent studies have demonstrated an increasing prevalence of MA use among some populations, including: street-involved youth [45]; the lesbian, gay, bisexual, and transgendered (LGBT) community [47]; and among individuals who inject drugs (IDU) [33, 48]. Several indicators suggest that MA use is most common in Western Canada, with use heavily concentrated among vulnerable populations in the urban centres of Vancouver and Victoria. For example, in a 2006 nationwide survey of youth residential substance abuse treatment facilities, the vast majority of MA-related admissions occurred in British Columbia [49]. Data from E-SYS suggests that street-involved youth in Vancouver are at least 20 times more likely to report MA use compared to youth residing in Toronto, Ottawa, and Halifax [43]. Increases in MA-related morbidity and mortality have also been recorded; for example, MA-attributable fatal overdoses in BC rose from two in 2001 to 16 in 2005 [50].

Considerable local and provincial media attention has been given to the detrimental impacts of MA use on users and their communities [51, 52]. In response to these concerns, new legislative initiatives have been implemented, including the 2004 British Columbia Integrated Methamphetamine Strategy [53]. Although the

amount of funding dedicated to community-based prevention and treatment programs for youth with substance dependence has increased substantially under this strategy [54], the dominant policy response to MA, particularly at a federal level, continues to focus on supply reduction interventions and other enforcement-based approaches [55, 56]. The vast majority of these interventions remain unevaluated, and their long-term effectiveness has been questioned by several authors [57-59]. Furthermore, approaches that aim to reduce the population-level use of MA through enforcement and precursor control strategies may in fact exacerbate inequities in health and access to care experienced by marginalised populations most affected by MA-related harms. This "inequality paradox" is an increasingly well-recognized phenomenon and has been demonstrated in many areas of health [60, 61]. For these reasons, novel research is required to inform the development of evidence-based public health policy and practice that effectively reduces the health and social harms related to MA use, particularly among vulnerable populations and young people.

1.4 CONCEPTUAL FRAMEWORK

The risk environment framework is utilised as the theoretical foundation from which to examine how a variety of factors exogenous to the individual interact to (re)-produce HIV- and drug-related harms [62]. In contrast to epidemiologic

paradigms which privilege individual–level factors in mitigating harmful behaviour and achieving health, the risk environment approach seeks to articulate how social, physical, and political-economic factors intersect to produce differential exposures to infectious disease risk and drug-related harms [63]. The model postulates that social, physical, and structural environments impose constraints on individual behaviour that shape risk factors for disease, as well as access to services [62, 64]. The model thus describes the "risk environment" of drug users as a product of interplay between individual, social, environmental, and structural factors. Therefore, a primary objective of this research was to apply the risk environment framework to examine how social, physical, and structural factors augment and modify individuals' exposure to MA initiation, use, and related harms.

A burgeoning literature also supports the adoption of an "ecological approach" within epidemiology and public health [65-67], which emphasizes how individuals and communities interact with and in some cases resist exogenous factors which (re)-produce harms. Interventions informed by these approaches often seek to build not only individual but community capacity to address health inequities, and are hypothesized to result in better sustainability and longer-term effectiveness than programs that rely on individual behaviour change alone [67]. Accordingly, analyses presented herein were informed by ecological models to

identify potential casual pathways and mechanisms that may be amenable to policy and programme intervention.

1.5 STUDY DESIGN

The empirical analyses presented in this dissertation (i.e., Chapters 3 through 6) rely on data derived from three open prospective cohort studies of street-involved youth and IDU in Vancouver. These studies comprise a larger program of research focused on the study of the initiation and natural history of injection drug use, and are administered by one research centre (i.e., the British Columbia Centre for Excellence in HIV/AIDS).

To avoid replication in subsequent chapters, the cohort studies used in the analyses are summarised here. Where appropriate, specific eligibility criteria and other procedures are explained in the methods sections of each chapter. The At Risk Youth Study (ARYS) is a prospective cohort of drug-using street-involved youth. To be eligible, participants must have been between the age of 14 and 26 and used illicit drugs other than or in addition to marijuana in the past 30 days from the date of enrolment. To be consistent with previous studies and to capture as much as possible the spectrum of youth homelessness [40, 68], housing status is not included as an eligibility criterion. The Vancouver Injection Drug Users Study (VIDUS) is a study of HIV negative IDU in which all participants must have injected an illicit

drug in the past 6 months to be eligible for inclusion. The AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) is a cohort of HIV positive individuals, who, similar to those in ARYS, must have recently used an illicit drug other than or in addition to marijuana. HIV infection is detected using third-generation ELISA, and all positive test results are confirmed using Western blot. To be eligible, participants of all studies must have resided in the Metro Vancouver region, been greater than 14 years of age at enrolment, and provided informed consent.

Recruitment procedures for the three studies are similar, with the primary modes of enrolment being self-referral, word of mouth, and street outreach. In order to maximise representativeness, outreach is conducted in a range of neighbourhoods in which street youth and drug users are known to congregate. Outreach teams consisting of street nurses and study staff also work in close collaboration with local service organisations and agencies to ensure that specific hidden subpopulations (e.g., ethnic minorities, survival sex workers) are represented. Organisations are encouraged to refer eligible participants to the study offices. Detailed sampling and recruitment procedures for these three cohorts have been described elsewhere [69-71].

At baseline and semi-annually, participants complete a detailed interviewer-administered questionnaire. Sociodemographic data, as well as information

pertaining to drug use patterns, sexual- and injection-related risk behaviours, and health care utilisation are collected. The survey for each study consists of a uniform set of questions, which permits the aggregation and analysis of data from all enroled participants. Nurses collect blood samples for HIV and hepatitis C serology and also provide basic medical care and referrals to appropriate health care services. Participants receive $20 for each study visit. All studies have been approved by the University of British Columbia/Providence Health Care Research Ethics Board. Ethics documentation and approval for the analyses described in this dissertation are provided in **Error! Reference source not found.**.

Given that the use of MA continues to persist in many settings despite decades of public health intervention, effective prevention efforts are increasingly recognized as a key component in comprehensive, evidence-based MA strategies [72, 73]. Therefore, epidemiologic investigations involving young people who use MA and those at risk for initiation are critical to inform the development and implementation of preventive interventions. It is for this reason that adolescent and youth populations are predominately (but not exclusively) the focus of the material presented in this dissertation. For the analyses that focused on youth, we have adopted the World Health Organization (WHO) definition of "young person" as any individual between the age of 10 and 24 [74]. In instances where other age cut-offs were used to define the analytic sample, a detailed rationale for doing so is

provided. For example, since some studies and youth organisations include in their definition of "young person" any individual less than 30 years of age [75-77], expanding the eligible criteria to include older participants in those cases increased the comparability and utility of the study results.

1.6 OUTSTANDING QUESTIONS AND STUDY JUSTIFICATION

Although the prevalence of, motivations for, and correlates associated with MA use have been well described in some populations [12, 15, 78-81], there are several important gaps in knowledge that hinder the implementation of effective MA-related policy and public health responses, particularly for street-involved young people. The majority of studies utilise cross-sectional data; thus, factors associated with MA initiation and trajectories of use have not been thoroughly investigated. Although several recent qualitative studies of young people have provided important insight into some of the individual and social reasons for initiating and using MA [20, 82-84], these studies have yet to be corroborated with quantitative longitudinal analyses. The environmental and structural factors (e.g., housing conditions, interactions with law enforcement) that influence MA initiation, use, and harms have also been largely unexplored.

The majority of MA-related research to date has been generated as a result of studies involving men who have sex with men (MSM). Its use within gay social

environments and contexts has informed a large body of research that provides a number of important insights into the common patterns of MA use and its relation to the sexual transmission of HIV, as well as the underlying psychological, sociological, and behavioural motivations associated with MA use and dependence [15, 78, 79, 85, 86]. Elucidating whether the context and risks associated with MA use are similar for street youth and IDU populations is critical to determine whether comprehensive and well-studied interventions for MSM [87-89] may be equally effective for younger and more street-entrenched populations.

Finally, although early studies demonstrated a greatly increased risk of HIV infection and other health and behavioural outcomes among MA users [90-93], more recent research has demonstrated that many observed associations are a result of selection bias or incomplete adjustment for confounding [94-96]. The evidence to suggest a strong relationship between MA use and a number of harms (e.g., violent behaviour [97], parenterally-transmitted HIV infection [96], mortality [94] etc.) is equivocal. Given the level of scientific uncertainty upon which public health responses to MA use are often founded, it is crucial to more rigorously evaluate the direct and indirect impacts of MA consumption on a broad set of health and behavioural outcomes.

1.7 STUDY OBJECTIVES

This project addresses the abovementioned gaps in knowledge by examining a number of social, environmental, and structural predictors of MA initiation, use, and harms among street-involved youth and IDU in Vancouver. This research also seeks to characterise specific negative health outcomes associated with frequent and prolonged use of MA. Finally, the work described in this dissertation incorporates aspects of psychological and behavioural models often used in studies involving MSM with those of a "risk environment" approach, more commonly invoked in research involving IDU. Specifically, the following five objectives are explored:

1. **To characterise the scientific evidence examining associations between MA use and adverse health outcomes among young people**. Chapter 2 provides the results of a systematic review examining known health outcomes associated with MA use among youth. In addition to informing evidence-based policy and public health responses that seek to reduce MA-related harms, this work identifies gaps in knowledge where research investigating the impact of MA use on specific health outcomes is equivocal. The findings of this paper were also used to generate hypotheses and construct research questions for subsequent epidemiological analyses described in Chapters 3 through 6.

2. **To examine the incidence and predictors of MA injection initiation among a cohort of injection drug users.** Motivated by the lack of effective MA-related preventive interventions [72], this longitudinal analysis sought to uncover the primary predictors of MA injection initiation among established injectors. In accordance with the risk environment framework, it was hypothesized that MA injection initiation is driven by a combination of individual, social, environmental, and structural factors.
3. **To describe the prevalence and correlates of MA use among sexual minority street youth and IDU**. Sexual minority young people are known to be at a high risk of substance use disorders and a variety of other adverse health outcomes [98-100]. Therefore, the primary hypotheses were that the prevalence of MA use would be higher among sexual minority participants compared to heterosexual individuals, and that MA use among this population exacerbates HIV-related vulnerabilities and other health inequities.
4. **To determine whether frequent MA injection is a risk factor for emergency department (ED) utilisation among street-involved youth**. The use of MA has been associated with health problems that commonly present in the ED; therefore, the hypothesis of this study was that youth who frequently inject MA are at an increased hazard of ED utilisation. The ED diagnoses and

reasons for discharge were also characterised in order to gain a better understanding of the spectrum of acute health care problems experienced by frequent MA users. It is argued that the integration of MA-specific, youth-driven harm reduction programs with emergency and addiction treatment services would reduce reliance on emergency services and better address the health care needs of this marginalised population.

5. **To examine whether the relationship between MA injection and engagement in injection-related risk behaviour is mediated by service access barriers**. MA injectors experience a number of social and structural barriers to accessing HIV prevention programs [101]. In this cohort study of young IDU, a mediation analysis was conducted to formally test the hypothesis that having difficulty accessing safer injecting equipment mediates the association between MA injection and syringe sharing.

1.8 SUMMARY

This thesis is delineated into seven chapters. In Chapter 1, I have provided a summary of global MA epidemiology and a review of research to date examining its use among street-involved youth and IDU. The objectives of the research, the study setting and the study design have also been described. The second chapter provides a systematic review of literature examining the relationship between MA use and

increased levels of morbidity and mortality among young people. This chapter also serves as a call for further research of higher methodologic quality to investigate the relationship between MA use and suspected harms. Informed by the risk environment framework, the epidemiological analyses in Chapters 3 through 6 aim to provide the reader with an in depth examination of the trajectories, typologies, correlates, and harms of MA use. Beginning with MA injection initiation in Chapter 3, I then explore the individual, social, and structural pathways through which MA use exacerbates exposure to risks and harms in Chapters 4, 5, and 6. The results of these studies can thus inform both the timing and targets of MA-related preventive, treatment, and other population-level interventions. Finally, Chapter 7 provides a summary of the key findings, practical implications, limitations, recommendations, and directions for future research.

CHAPTER 2[1]

A SYSTEMATIC REVIEW OF HEALTH OUTCOMES ASSOCIATED WITH METHAMPHETAMINE USE AMONG YOUNG PEOPLE

2.1 INTRODUCTION

In many countries, responses to MA consumption among youth have focused primarily on supply reduction through precursor chemical regulation, drug seizures, and the dismantling of clandestine MA laboratories [102]. Although these methods appear to be successful in some instances at reducing MA-related hospital and treatment admissions [58, 103], recent analyses have demonstrated that their overall impact appears to be transitory [59]. Given the limited effectiveness of these interventions, several drug policy organizations including the United Nations Office on Drugs and Crime (UNODC) have called for a more balanced approach aimed at reducing both the supply and demand of MA [8, 104].

Prevention and treatment programs that work to decrease the number of new users, limit harm among novice users, and reduce morbidity among chronic users are the central tenets of MA demand reduction strategies for adolescents and youth [102]. However, if effective public health responses to MA use are to be

[1] A version of this chapter has been published previously and is re-printed here with permission. Marshall BDL, Werb D. Health outcomes associated with methamphetamine use among young people: a systematic review. *Addiction*. 2010;105(6):991-1002.

implemented, a clear and comprehensive understanding of the specific harms associated with MA use among youth is necessary. Although several reviews examining the harms associated with MA use have been published [105-107], few are systematic and none have focused on the use of MA and associated harms among young people. Since many MA-related health outcomes may present only after chronic use [108], the health implications for novice and young users may be significantly different and thus require further investigation. Because MA use may affect individuals differently depending on their physical and psychological developmental stage, more evidence is also required to inform the development and implementation of treatment models for MA dependence among young people [109]. Finally, a systematic review of MA-related health harms among youth is of particular relevance to clinical settings, where physicians may wish to screen young patients for morbidities associated with the use of MA and counsel current users to reduce future harms. Therefore, we conducted a systematic review to evaluate the scientific evidence regarding health outcomes associated with MA use among individuals 10 to 24 years of age. Given the high level of public concern regarding the harms of MA use [110], we sought to adhere to the most rigorous methodological standards for conducting systematic reviews to provide a solid evidence base for future MA-related research and knowledge translation activities.

2.2 METHODS

We followed the guidelines developed and recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group [111].

2.2.1. Search Strategy

We conducted a comprehensive review of 30 electronic databases to identify potentially relevant studies, dissertations, and conference proceedings, including: MEDLINE®; Ovid MEDLINE® In-Process & Other Non-Indexed Citations; EBM Reviews, including the Cochrane Database of Systematic Reviews; EMBASE; International Pharmaceutical Abstracts; Journals@Ovid; CINAHL; PsychINFO; Science Citation Index Expanded & Social Sciences Citation Index (via Web of Science®); CAB Direct; ERIC; Sociological Abstracts; SocINDEX; Academic Search Complete; LGBT Life; ProQuest Dissertations and Theses; Conference Papers Index; Native Health Research Database; BioMed Central; and the NLM Gateway Meeting Abstracts database. Search terms included methamphetamine and common variants, youth, adolescent, juvenile, and young people. Methodological filters were used to exclude case reports and case series where possible. Hand searching of relevant conference proceedings, reference lists of published reviews and included studies was also conducted. We restricted our search to English-language publications but did not restrict with respect to year of publication. All searches

were conducted between January 2, 2009 and January 31, 2009. The detailed search strategy may be found in Appendix 1.

2.2.2. Inclusion Criteria

Studies were eligible for inclusion if they were published in a peer-reviewed journal, dissertation database, or academic conference proceedings. Grey literature, case reports, and case series were excluded. Consistent with the WHO definition of young people [74], studies were excluded if the mean or median age of the sample was greater than 24 or less than 10 years of age. Where necessary, we contacted study authors for additional data. Reviews and editorials were excluded. In cases where conference abstracts and peer-reviewed publications presented identical data, we opted to include the most recent publication.

To be eligible for inclusion, studies must have examined a specific and well-defined group of MA users. Studies assessing use of a broad class of drugs (e.g., stimulants) were excluded. However, to be consistent with previous reviews [21, 105], studies that examined the effects of amphetamine, methamphetamine, or crystal methamphetamine were included. Due to the incomplete and inconsistent measurement of injection or non-injection consumption, the results were not stratified by primary route of administration. In order to maximise the clinical relevance of our findings, health outcomes were categorised according to the WHO International Classification of Diseases (ICD)-10 [112]. Studies that did not report an

outcome with an analogous ICD-10 code (e.g., drug dealing, syringe sharing) were excluded. Disorders designated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as being diagnosed in infancy, childhood, or adolescence (e.g., attention deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder) were also excluded [113]. Given that these disorders usually first present during childhood or early adolescence, it is probable that they are antecedents as opposed to consequences of MA use. Foetal or infant outcomes related to the prenatal use of MA during pregnancy were also excluded, although complications during pregnancy or childbirth were eligible for inclusion. Although cross-sectional analyses are unable to determine temporality between exposure and outcome and thus inferences regarding causality are limited, for the sake of completeness, studies using a cross-sectional design were included. Readers are reminded that health outcomes in these instances may have preceded MA consumption; thus, caution whilst making inferences from these studies is warranted.

The primary author (BDLM) screened the titles and abstracts of each record. Studies that did not meet our eligibility criteria were excluded, while full-text articles were retrieved for all studies for which eligibility was unclear. These articles were then screened independently by both authors (BDLM and DW). Based on the inclusion criteria, studies were categorised as "potentially relevant" or "irrelevant"

by each author. Classifications were compared for each record and any discrepancies were discussed until a consensus was reached.

2.2.3. Data Extraction, Analysis, & Quality Assessment

A standardised form was created to manage data extraction for each eligible record. Information regarding the size, scope, sample, methods, and results of each study were entered by one author (BDLM) and independently checked for accuracy and completeness by the other (DW). Eligible studies were assessed for methodological quality using a modified version of the Downs and Black checklist for the reporting of health care studies [114]. This checklist has been shown to be a valid and reliable tool for the assessment of the methodological quality of observational studies [114]. Higher scores out of a total score of 18 represent higher overall methodological quality. Each study was scored by the primary author (BM) and verified independently by a co-author (DW). Detailed information regarding the checklist items and scoring criteria are available in Appendix 2.

2.3 RESULTS

2.3.1 Literature Search

Database and hand searching yielded a total of 2,097 potentially eligible studies published between 1970 and 2009. An initial screening led to the exclusion

of 1,866 records; a further 181 were removed following an assessment of the full-text articles. Initial agreement between the authors was good ($\kappa = 0.70$); consensus-based reasons for exclusion are provided in Figure 2.1. We were unable to determine the age distribution of the samples presented in two studies despite attempting to contact study authors for further information; thus, 47 publications that met our inclusion criteria were included in the final qualitative synthesis.

2.3.2 Methodological Quality Assessment

The modified Downs and Black scores ranged from 6 to 17 with a median score of 13 (interquartile range [IQR]: 10 - 16). We observed a statistically significant trend of improving methodological quality over time ($R^2 = 0.26$, $p < 0.001$). An analysis of the checklist sub-domains revealed that "external validity" received the poorest score across all studies, with only 13 (28%) containing samples representative of the entire population from which they were recruited (i.e., comprising the entire population, an unselected sample of consecutive patients, or a random sample).

2.3.3 Summary of Included Studies

Of the 47 studies included in the review (see Table 2.1), the majority were conducted in Canada and the United States ($n = 26$, 55%), with the remaining studies conducted in Thailand ($n = 9$, 19%), Australia ($n = 3$, 6%), Taiwan ($n = 3$, 6%), Japan

(*n* = 2, 4%), and one study (2%) conducted in South Africa, China, Argentina, and the United Kingdom, respectively. The median sample size was 478 (IQR: 172 – 1795). Most studies employed cross sectional designs (*n* = 34, 72%), while few used case control designs (*n* = 6, 13%), prospective cohorts (*n* = 5, 11%), or retrospective reviews (*n* = 2, 4%). The majority relied on self-reported MA use (*n* = 36, 77%), with recall periods varying between lifetime use and use in the past week. Five (11%) studies used a combination of self-report and urine tests to define MA use [22, 91, 115-117], four (9%) studies relied on a diagnosis of MA dependence [118-121], and two (4%) studies relied on MA positive toxicology tests from coroner's reports [122, 123]. Potentially confounding factors were inconsistently assessed across studies, and only 18 (38%) studies presented an adjusted or stratified analysis.

The studies included in this review examined a variety of health outcomes, although over half (*n* = 27, 57%) assessed diseases and conditions classified as mental and behavioural disorders. Outcomes involving infectious diseases (e.g., HIV, sexually transmitted infections [STIs]) were also common (*n* = 13, 28%). Eight (17%) studies examined outcomes classified as "external causes of morbidity and mortality", an ICD-10 category that includes experiencing violence, suicide, and self-harm. Two (4%) studies examined health outcomes related to injuries and poisonings (i.e., overdose) and two (4%) assessed the association between MA use and dental diseases. Diseases during pregnancy and childbirth were identified in

one study. One article examining emergency room use and one describing overall mortality were also included.

2.3.4 Mental & Behavioural Disorders

Studies examining mental and behavioural disorders spanned the entire time period (i.e., 1970 – 2009) and were of variable methodological quality. Analyses of data from the nationally representative Youth Risk Behavior Survey (YRBS) in the United States have suggested that suicidal ideation and eating disorders are more common among youth who have ever used MA [124-126]. The NSDUH has also been used to examine mental health outcomes associated with MA use among youth in the United States. Using responses from the K6 Scale (a validated screening tool used to screen individuals for severe mental illness [127]), Herman-Stahl *et al*. demonstrated that elevated scores were more common among youth who reported recently using MA; however, this association did not persist in a multivariate model [23]. MA users in this large nationally representative sample were also more likely to have been the recipient of mental health treatment, and were at increased risk for having a past year DSM-IV diagnosis for alcohol or drug use disorders [128, 129].

Symptoms of MA-induced psychosis among young MA users were well described within eligible studies. One of the earliest studies included in our review demonstrated that young MA injectors reported higher rates of paranoia compared to those who consumed MA orally [117]. Another early study observed an increased

risk of hallucinations and paranoia among daily MA users compared to those who used MA less frequently [130]. Hallucinations have been found to be one of the most common health problems reported by MA users [45, 131, 132]. Frequent use of MA has also been associated with elevated scores on the hypochondriasis and schizophrenia subscales of the Minnesota Multiphasic Personality Inventory [118, 133].

The link between MA use and depression has been examined in a number of different settings. For example, treatment samples in Taiwan and the United States have shown that individuals seeking treatment for MA dependence are more likely to be diagnosed with major depressive disorder upon entry [115, 134, 135]. In Chiang Rai, Thailand, depressive symptoms were shown to be elevated among students who tested positive for MA in urinalysis, although this association failed to remain significant in multivariate analyses [22]. In Chiang Mai, Celentano *et al.* observed that frequent MA use (defined as ≥4 days per week) was associated with depressive symptoms, though only among males [136]. A recent prospective cohort study of young Thai MA users found that depressive symptoms decreased significantly among those who stopped using MA over the 12 month study period [137]. In Australia, analyses of a prospective cohort of high school students found evidence to suggest that MA initiation during adolescence was associated with

adulthood depression, whereas early depression was not predictive of future MA use [138, 139].

2.3.5 Infectious Diseases

All studies examining infectious disease outcomes were conducted in North America or Thailand, except for one South African study demonstrating that recent and lifetime users of MA were more likely to have been told by a health care worker that they had an STI [140]. In Thailand, STI outcomes (i.e., self-reported symptoms and laboratory-confirmed diagnoses) and their relationship with MA use have been well described. The majority of studies have reported nonsignificant findings. For example, in a large prospective cohort study of sexually active MA users in Chiang Mai province, frequent MA use was not associated with either prevalence [141] or incidence [142] of laboratory confirmed STIs. A separate Thai study examining self-reported STI symptoms among a treatment sample of drug users observed that symptoms were *less* common among those seeking treatment for MA abuse, compared to those with opioid dependence [143]. One school-based study has shown an increased risk of *Chlamydia trachomatis* infection among MA-using women, although this association did not persist in a multivariate model [144].

Four studies examined the association between MA use and HIV prevalence. Two were conducted among young MSM populations in the US and both reported null results. In an analysis of data from the multi-site Young Men's Survey, MA use

during sex was not associated with HIV infection, and in a smaller community-based study in Chicago, recent MA use failed to reach significance in a multivariate model. Evidence to suggest an increased risk of infectious diseases (i.e., HIV and hepatitis C) among young MA injectors is also equivocal [45, 75, 145, 146].

2.3.6 External Causes of Morbidity & Mortality

Several studies have assessed the relationship between MA use and intentional self-harm and suicide. For example, in a cross-sectional analysis of Nevada students who completed the 2005 YRBS, participants who reported ever using MA were also more likely to report attempting suicide [126]. In a Japanese treatment sample, suicide attempts were more common among those diagnosed with MA-induced psychosis [120]. A population-based five year review of suicide cases in Utah observed a high prevalence of MA (9%) in toxicological samples [122]. In contrast, two community-based studies failed to show an association between MA use and intentional self-harm [147, 148].

2.3.7 Injuries & Poisonings

Two studies examined non-fatal overdose among young drug users [149, 150]. These studies report significantly elevated risks of overdose among non-injection MA users [149], as well as among those who inject MA either on its own or in combination with other illicit drugs such as heroin [149, 150].

2.3.8 Diseases of the Oral Cavity, Salivary Glands, & Jaws

Evidence to suggest a strong association between MA use and dental diseases among young people is scant. One case control study conducted in Argentina observed a greater number of decayed, missing, or extracted teeth among MA users compared to controls [151]. One other cross sectional study of detained Chinese youth reported that teeth grinding and jaw pain were more common among a group of primarily amphetamine users [152]. However, both studies scored 9 on the modified Downs and Black checklist and contained significant misclassification, confounding and generalisability problems.

2.3.9 Diseases during Pregnancy, Childbirth, & the Puerperium

One hospital-based case control study of pregnant women observed that women who reported MA use were no more likely to experience complications during pregnancy compared to non-MA using controls [121].

2.3.10 Other Outcomes

In one recent study conducted in Canada, street youth who ever used MA were more likely to report using the emergency room in the past six months [145]. The only study eligible for inclusion in our review that addressed mortality was a retrospective review of 26 deaths involving MA in Ontario, Canada between 1972

and 1973. The authors calculated the mortality rate among MA users to be four times that of the general population [123].

2.4 DISCUSSION

Consistent, scientifically sound evidence demonstrating associations between MA use and a number of health outcomes (e.g., depression, psychosis, behavioural problems) were identified. Furthermore, the results of our review suggest that suicide and overdose likely contribute to increased morbidity and mortality among young MA users. However, we failed to observe a strong evidence base for several previously cited MA-related harms, including an increased risk of HIV/STI infection and onset of dental diseases such as tooth decay. Many studies did not meet the methodological standards proposed by Downs and Black for the reporting of health care studies [114]. Due largely to the high proportion of cross-sectional studies based on convenience or treatment samples, less than a third of eligible studies met the criteria for external validity. Future research of higher methodological quality is therefore required before conclusions can be reached regarding many of the harms frequently perceived to be associated with MA use among youth.

Few studies have reported data relevant to the development of effective prevention and treatment interventions targeted towards MA using young people [109]. One randomised controlled trial to examine the effectiveness of a preventive

intervention for MA use has been conducted [72]. Other interventions, including the Montana Meth Project (MMP), have approached MA consumption among youth as a "consumer product marketing problem", relying on saturation-level advertising to graphically depict perceived negative health and social consequences of MA use through social marketing [153]. Empirical evidence to support the campaign is, however, weak; in fact, the graphic depiction of MA users as unhygienic and dangerous appears to have coincided with increases in the acceptability of MA use among target populations [154]. Given the disputed effectiveness of social marketing campaigns rooted in the perception and exaggeration of MA-related harms [154], evidence-based interventions that rely on scientifically rigorous evidence are recommended.

The paucity of sound evidence regarding the association between MA use and dental diseases warrants special consideration. Given that extensive media and public health attention has focused on the oral health effects of MA use (i.e., "meth mouth") [155, 156], it is surprising that we identified only two studies examining dental outcomes among youth. While it is possible that extensive tooth decay and MA-induced caries may only present after several years of chronic MA use (and thus studies demonstrating these associations may have been excluded on account of the older median age of study samples), some authors have noted the lack of valid evidence supporting a specific risk of dental diseases associated exclusively with

MA use [157]. Several mechanisms have been proposed (e.g., MA-induced xerostomia, increased consumption of soft drinks, reduced hygienic behaviours [158]), though it is noteworthy that all causal pathways remain hypothetical [157]. Further epidemiological research in this area is therefore required.

In many eligible studies [22, 78, 115, 141, 144], the strength of bivariate associations between MA use and health outcomes greatly diminished after controlling for potential confounders, and the observed confounded relationships indicate that MA use may often act as a marker of other causal risk factors. Given these findings, future studies should carefully assess potential confounders and adjust for them using stratified or multivariate analyses. Furthermore, cross-sectional designs (such as those employed by a majority of the included studies) fail to disentangle the temporal relationship between MA use and hypothesised harms. It is likely that several conditions examined in this review are in fact risk factors or antecedents for MA use as opposed to outcomes. Prospective cohort studies that follow individuals' MA use trajectories and health outcomes over time are therefore crucial to the creation of evidence-based policies and interventions for MA prevention and treatment. For example, although many cross-sectional studies have identified a link between MA use and depression, only with the publication of more recent studies using prospective cohort designs [137-139] have researchers begun to delineate the temporal relationship between MA use and depression. Evidence from

these studies suggests that MA use (particularly in early adolescence) precedes the onset of depressive symptoms in adulthood. This information is critical for intervention; thus, research able to identify temporal relationships between MA use and health outcomes should be prioritised.

The lack of a consistent association between MA use and some health outcomes (e.g., STI symptoms) may be due to measurement bias in the ascertainment of exposures or outcomes. The vast majority of studies utilised self-reported measures of drug use and other risk behaviours (e.g., condom use); however, these measures have been shown to have reasonable validity in a number of settings [159-161]. Furthermore, self-reported MA use has been shown to have substantial agreement with urinalysis among youth seeking treatment for substance abuse [162]. Nonetheless, it is possible that observed null associations do not represent evidence of no effect but are instead indicative of systematic or random misclassification diluting true relationships between MA use and harms. In contrast, positive associations may be due to a variety of biases or uncontrolled confounding. For example, detection bias, that is, the preferential screening for health conditions (e.g., psychiatric disorders) among MA users compared to controls, likely accounts for some of the observed significant associations, particularly in case control studies or those based on treatment samples.

Our review is limited by the fact that we excluded some potential sources of data such as grey literature and case series. However, we argue that drug policy and public health responses are best informed by high quality peer-reviewed evidence, and thus we opted to restrict our search to peer-reviewed sources. As in all systematic reviews, it is possible that we missed some eligible studies in our search strategy. We sought to mitigate this bias by duplicating our search and by contacting authors to obtain necessary information. We also recognise that the selection and qualitative synthesis of eligible studies is ultimately a subjective process. However, having two reviewers independently conduct the screening procedure, using a standardised form to extract the data, and assessing methodological quality using a validated checklist helped to ensure a level of objectivity in our search strategy.

We conclude that despite widespread government and public alarm concerning MA use among young people, there remains limited rigorous scientific evidence for many of the perceived harms related to MA use. Despite the limitations of the available evidence, however, it is clear that MA use is associated with certain acute health outcomes. Until further research of sufficient methodological quality is conducted, current preventive and treatment interventions should concentrate on harms for which strong and consistent associations with MA use have been established.

Figure 2.1: Flowchart of systematic review screening and selection process

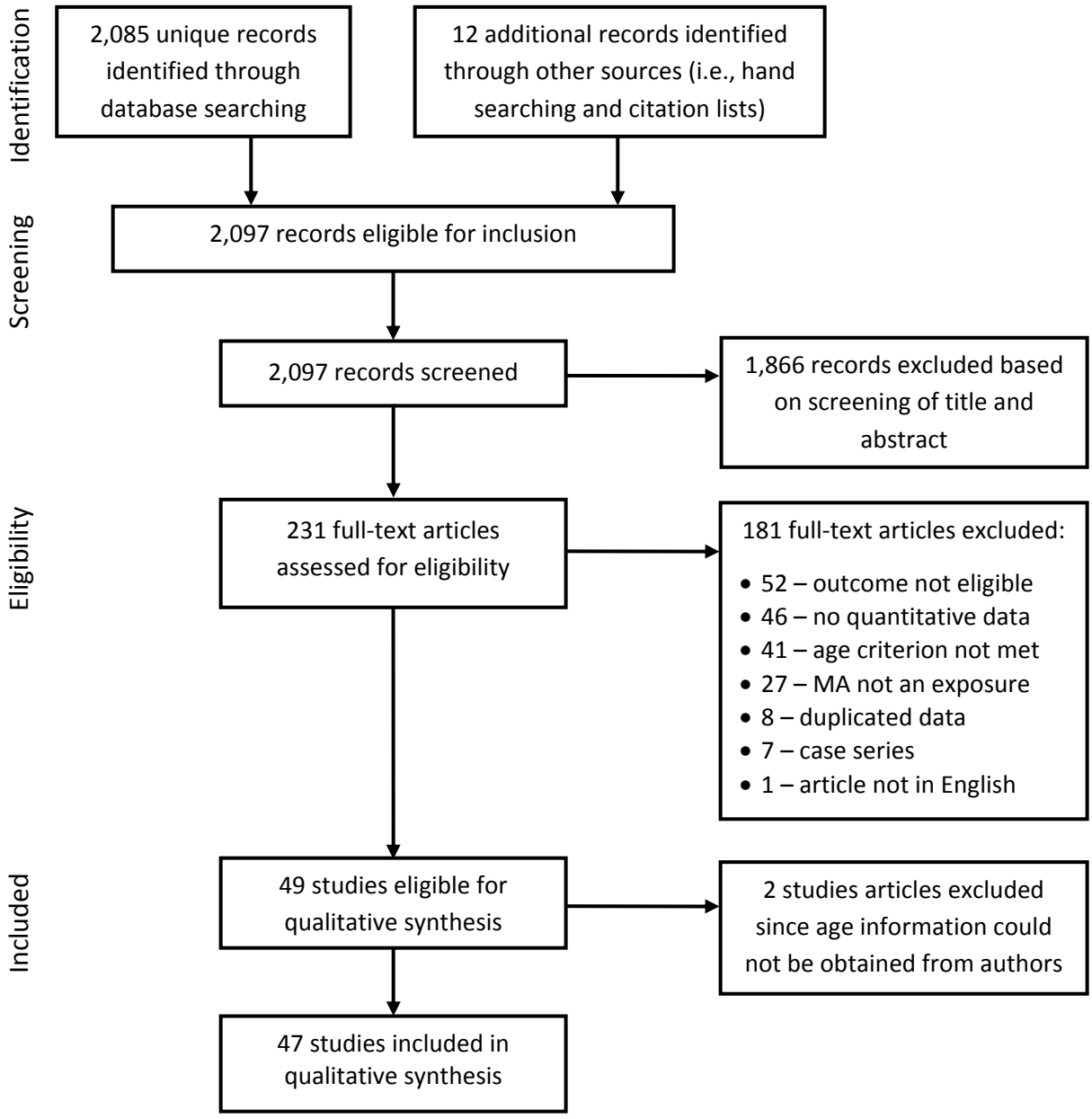

Table 2.1: Summary of studies included in systematic review (*n* = 47)

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
Sutcliffe 2009a, Thailand [137]	Prospective cohort	863 sexually active MA users recruited through street outreach. Age: 18-25	16	Self-reported MA use	Depression symptoms at last visit (CES-D cut-off ≥22)	Depression less likely among early (AOR = 0.44 [0.26 – 0.74]) and late (AOR = 0.66 [0.43 – 1.00]) cessation group
Sutcliffe 2009b, Thailand [142]	Prospective cohort	519 sexually active MA users recruited through street outreach. Age: 18-25	12	Self-reported frequency of MA use in the past 3 months	Incidence of lab-confirmed STI	Frequency of MA use not associated with STI incidence for women (RR = 1.63 [0.62 – 4.29]) or men (RR = 1.55 [0.74 – 3.26])
Martin 2009, Canada [163]	Cross-sectional (ARYS)	478 street youth recruited through street outreach. Median age = 22	15	Self-reported MA use in the past 6 months	Self-reported victim of assault in the past 6 months	MA use not associated with experiencing assault (AOR = 1.20 [0.70 – 2.07])
Wood 2008, Canada [145]	Cross-sectional (ARYS)	478 street youth recruited through street outreach. Median age = 22	16	Self-reported lifetime history of MA use	Lab-confirmed HCV, self-reported mental illness and ER use	MA use not associated with HCV but was associated with mental illness (OR = 1.79 (1.18 – 2.73) and ER use (AOR = 1.66 [1.04 – 2.66])
Werb 2008, Canada [149]	Cross-sectional (ARYS)	478 street youth recruited through street outreach. Median age = 22	16	Self-reported MA use in the past 6 months	Self-reported non-fatal overdose in the past 6 months	Overdose associated with MA injection (AOR = 2.33 [1.25 – 4.32]) and non-injection (AOR = 2.00 [1.06 – 3.77])
Walls 2008, US [147]	Cross-sectional venue-based sample	142 LGBT youth. Age: 14-21	15	Self-reported lifetime history of MA use	Suicide attempt, suicidal ideation	MA use associated with suicidal ideation (AOR = 2.98, $p<0.05$) but not with suicide

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
						attempt
Plüddemann 2008, South Africa [140]	Cross-sectional school-based sample	4,605 grade 8 students in Cape Town	13	Self-reported MA use	Ever had an STI (told by health care worker)	STIs more common among MA users
Pisetsky 2008, US [124]	Nationally representative sample (YRBS)	13,917 high school students in US	14	Self-reported lifetime history of MA use	Ever had an eating disorder (self-reported)	Eating disorders more common among MA-using females (OR = 3.3) and males (OR = 12.9)
Luncheon 2008, US [125]	Nationally representative sample (YRBS)	6,826 female high school students in US	16	Self-reported lifetime history of MA use	Suicidal ideation	MA use was independently associated with suicidal ideation (AOR = 2.2 [1.4–3.3])
Celentano 2008a, Thailand [141]	Cross-sectional	658 sexually active MA users. Age: 18-25	15	Self-reported frequency of MA use past 3 months	Prevalence of lab-confirmed STI	Frequent MA not associated with prevalent STI for women or men
Celentano 2008b [136]	Cross-sectional	1,189 sexually active MA users. Age: 18-25	15	Self-reported frequency of MA use past 3 months	Depression symptoms (CES-D cut-off ≥22)	Frequent MA use associated with depression among males (AOR = 1.3 [1.0 – 1.6])
Wu 2007, US [129]	Nationally representative household survey (NSDUH)	24,409 individuals aged 16 through 23	17	Self-reported lifetime history of MA use	Mental health treatment, DSM-IV diagnosis of alcohol or drug use disorders	All outcomes more common among MA users.
Poulin 2007, Canada [164]	Cross-sectional school-based sample	12,990 high school students in Atlantic provinces.	16	Self-reported MA use in the past 12 months	Depressive symptoms (CES-D scale)	MA users more likely to report elevated depression symptoms
Noffsinger 2007, US [126]	Nationally representative	Nevada high school students	10	Self-reported lifetime history of	Suicide attempt, suicidal ideation	MA users more likely to report suicide attempt and

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
	sample (YRBS)			MA use		ideation (both $p < 0.001$)
Herman-Stahl 2007, US [23]	Nationally representative survey (NSDUH)	23,645 individuals aged 18 to 25	17	Self-reported MA use in the past 12 months	High K6 Scale score - screening tool for severe mental illness	High K6 scale scores more common among MA users (OR = 2.8 [2.1 – 3.7]), but not significant in multivariate model
Garofalo 2007, US [78]	Cross-sectional	310 young MSM recruited through street outreach. Age range: 16 -24	15	Self-reported MA use in the past 12 months	HIV prevalence, psychological distress (GSI)	MA use not independently associated with HIV positivity or psychological distress
Degenhardt 2007a, Australia [138]	Prospective cohort (VAHCS)	1,943 high school students. Mean age: 15	16	Self-reported MA use in the past 12 months	Depression and anxiety (CIS-R & GHQ>2)	Current MA use associated with CIS-R and early MA associated with GHQ>2 in adulthood
Degenhardt 2007b, Australia [139]	Prospective cohort (VAHCS)	1,936 high school students in grades 9 and 10. Mean age: 15	16	Self-reported MA use in the past 12 months	Depression and anxiety (CIS-R & GHQ>2)	Early depression and anxiety not predictive of future MA use in adulthood (AOR – 1.1 [0.7 = 1.8])
Yen 2006a, Taiwan [115]	Case control treatment sample	200 MA users and 400 community controls. Mean age: 17	11	Positive urine test for MA upon admission and self-report	Psychiatric disorders	MA use associated with depressive symptoms, adjustment disorder, any disorder, and >1 comorbid disorders (vs. 0)
Yen 2006b, Taiwan [135]	Cross-sectional treatment sample	299 MA users. Mean age: 17	10	Self-reported early MA use (≤15 years of age)	Psychiatric disorders	Early-onset females more likely to have depressive disorder (p=0.002).
Wu 2006, US	Nationally	19,084 individuals	16	Self-reported MA	DSM-IV	MA use associated with

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
[128]	representative survey (NSDUH)	aged 16 through 23		use in the past 12 months	diagnosis of alcohol abuse past 12 months	alcohol dependence (AOR = 32 [15 – 69]) and abuse (AOR = 17 [9 – 35])
Sommers 2006, US [131]	Cross-sectional	106 youth with median age: 22	8	Self-reported frequency of MA use	Psychological problem index	More frequent MA use associated with a greater number of self-reported psychological problems
Miura 2006, Japan [165]	Case control study	Youth in juvenile detention	13	Self-reported history of MA use	Any psychiatric treatment	MA users more likely to report treatment (AOR = 8.7 [4.0 – 19])
Martin 2006, Canada [45]	Cross-sectional	180 street youth and LGBT youth. Mean age: 21	11	Self-reported MA use in the past week	Self-reported health problems & lab-confirmed HIV or HCV	MA users more likely to report hallucinations (p = 0.024) and test positive for HCV (p = 0.014)
Baskin-Sommers 2006, US [148]	Cross-sectional	243 youth recruited through outreach. Mean age: 21	10	Self-reported history of MA	Self harm	Self-harm not associated with MA use
Yen 2005, Taiwan [116]	Cross-sectional treatment sample	200 youth in a detox program. Mean age: 17	11	Self-reported frequency of MA use	Suicidal ideation	Frequency of MA use not associated with suicidal ideation
Rawson 2005, US [132]	Cross-sectional treatment sample	305 youth in an addiction program. Mean age: 16	8	Drug of choice upon entry	Self-reported depression and hallucination	Depression (p = 0.015) and hallucinations (p = 0.009) more common among MA group
Palmer 2005, US [118]	Case control study	60 youth in a treatment program. Mean	11	Drug of choice upon entry	MMPI	MA users scored higher on schizophrenia (p = 0.017) and hypochondriasis (p = 0.027)

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
		age: 16				scales
Ochoa 2005, US [150]	Cross-sectional (UFO Study)	617 young IDU. Median age: 22	16	Self-reported injection of MA with heroin	Self-reported overdose past 12 months	Injecting MA and heroin associated with overdose (AOR = 1.7 [1.2 – 2.7])
McGregor 2005, Thailand [119]	Cross-sectional treatment sample	30 individuals in treatment. Mean age: 21	11	Self-reported years of MA use	Amphetamine Withdrawal Questionnaire	Greater withdrawal severity associated with year of MA use ($p < 0.001$)
McGrath 2005, China [152]	Cross-sectional treatment sample	119 youth in a rehab program. Mean age: 20	9	Self-reported history of MA use	Oral health sensations (e.g., teeth grinding)	MA users more likely to report teeth grinding ($p < 0.001$) and jaw pain ($p < 0.001$)
Callor 2005, US [122]	Retrospective review	164 suicide cases in Utah. Age: <21	10	Toxicology positive for MA	Suicide completion	High prevalence of MA among suicide completers (9%)
Harawa 2004, US [166]	Cross-sectional (YMS)	3,316 young MSM. Age: 15-22	16	Used MA during sex past 6 months	HIV prevalence	MA use during sex not associated with HIV (AOR = 0.8 [0.5 – 1.5])
Beyrer 2004, Thailand [143]	Cross-sectional treatment sample	535 youth at a treatment centre. Age: <25	15	Seeking treatment for MA use	Self-reported STD symptoms	MA participants less likely to report STD symptoms (AOR = 0.5 [0.3 – 0.8])
Paz-Bailey 2003, Thailand [144]	Cross-sectional (PHRAYA)	Youth attending vocational schools. Mean age: 18	16	Self-reported lifetime history of MA use	Lab-confirmed *Chlamydia* infection	MA use associated with CT among women (OR = 2.6 [1.1 – 6.1]) but not significant in multivariate model
Shafer 2002, US [75]	Cross-sectional (UFO Study)	304 young IDU. Median age: 22	14	Injected MA most often past month	HIV prevalence	MA associated with HIV infection (OR = 2.5 [0.9 – 7.3])
Sattah 2002,	Cross-sectional	Youth attending	16	Positive urine test	Depression	Depression score higher for

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
Thailand [22]	(PHRAYA)	vocational schools Mean age: 18		and self-reported MA use	symptoms	MA users (p<0.001) but not significant in model
Vongsheree 2001, Thailand [91]	Cross-sectional treatment sample	1,725 youth in detox clinic. Mean age: 22	13	Positive urine test for MA upon entry	HIV prevalence	MA use not associated with HIV infection
Hawke 2000, Canada & US [134]	Prospective cohort	937 youth in treatment programs. Age: 15-18	14	Self-reported lifetime history of MA use	Self-reported STI & psychiatric disorders	MA users more likely to have: depression (p = 0.008), dysthymia (p = 0.001) and PTSD (p = 0.006)
Uchida 1995, Japan [120]	Cross-sectional treatment sample	94 incarcerated youth. Mean age: 18	8	Diagnosis of MA-induced hallucinations	Suicide attempt	Suicide attempters more likely diagnosed with MA-induced psychotic disorder (p < 0.05)
Hall 1994, Australia [130]	Cross-sectional	231 drug users. Median age: 24	12	Self-reported frequency of MA use	Self-reported paranoia and hallucinations	Daily MA users more likely to report hallucinations and paranoia
Little 1988, US [121]	Hospital-based case control study	104 pregnant women in hospital. Mean age: 23	10	Self-reported abuse of MA	Pregnancy complications	No association between MA use and pregnancy complications
Di Cugno 1981, Argentina [151]	Case control study	198 youth in a treatment program	9	Self-reported drug used most often in the past 12 months	DMF index	Mean DMF index significantly higher for MA users (p < 0.01) and MA/marijuana users (p < 0.001) compared to controls
Kalant 1975, Canada [123]	Retrospective review of deaths	26 deaths involving MA in Ontario. Median age: 24	13	Toxicology positive for MA	Mortality	MA users have a higher morality when compared to the general population (SMR > 4)
Gardner 1972,	Cross-sectional	104 patients with	10	Urine test at entry	Paranoia	Paranoia more common

Study	Study Design	Participant Characteristics	Score	Exposure Measurement	Outcome(s)	Main Findings
UK [117]	treatment sample	non-opioid drug abuse. Mean age: 23		and self-reported MA use		among MA injectors (p < 0.005)
Cox 1972, Canada [133]	Cross-sectional	75 drug users	8	Self-reported MA use	MMPI	High hypochondriasis and hypomania scores more common among heavy MA users (p<0.05)
Davis 1970, US [146]	Retrospective review	75 patients with hepatitis. Mean age: 21	6	Self-reported lifetime history of MA use	Lab-confirmed diagnosis of hepatitis	MA-associated hepatitis represented 2/3 of the total cases admitted to hospital

Abbreviations: AOR – adjusted odds ratio; ARR – adjusted rate ratio; ARYS – At Risk Youth Study; CES-D – Centre for Epidemiologic Studies depression scale; CIS-R – Clinical Interview Schedule; ER – emergency room; GHQ – General Health Questionnaire; GSI – Global Symptom Inventory; HCV – Hepatitis C; LGBT – lesbian, gay, bisexual, or transgender; MA – methamphetamine; MMPI – Minnesota Multiphasic Personality Inventory; NSDUH – National Survey on Drug Use and Health; PHRAYA - Prevalence of HIV, STD, Drug Use and Risk Behaviors in Adolescents and Young Adults; PTSD – posttraumatic stress disorder; VAHCS – Victoria Adolescent Health Cohort Study; YMS – Young Men's Survey; YRBS – youth risk behavior survey.

CHAPTER 3[2]

INDIVIDUAL, SOCIAL, AND ENVIRONMENTAL FACTORS ASSOCIATED WITH INITIATING METHAMPHETAMINE INJECTION: IMPLICATIONS FOR DRUG USE AND HIV PREVENTION STRATEGIES

3.1 INTRODUCTION

Chronic MA use has been associated with various physical and psychological harms [1, 105]. The literature demonstrating a link between MA use and high-risk sexual behaviour among MSM is substantial [15, 79, 86], with several studies showing associations between MA use and HIV seroconversion [90, 167]. A growing literature has demonstrated how injecting MA (versus non-injection modes of consumption) is associated with more severe symptoms of dependence and a greater number of health and social problems [25, 26]. Evidence suggests that among IDU, transitioning to MA use increases HIV risk and has other important negative health implications. For example, compared to persons who inject other drugs, MA injectors are more likely to report sexual risk behaviours including sex work and unprotected vaginal and anal intercourse [34, 35]. Furthermore, IDU who

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inject MA are more likely to engage in injection-related risk behaviour including syringe sharing [33], experience non-fatal overdose [168], and in some settings, test positive for HIV [30].

Given the adverse health outcomes associated with MA injection noted above, interventions to prevent transitions to injecting MA should be a public health priority. However, few studies have been conducted to examine MA initiation among IDU, and thus little evidence base exists to inform the development of prevention strategies. Limited evidence indicates that the majority of MA users consume other drugs prior to the initiation of use [169]. Qualitative work suggests that social factors play an important role in MA initiation; for example, several studies have found that sex partners and friends often offer MA to new users and prepare the drug for administration [82, 83]. Very little research has examined transitions to MA injection, although coping style and sensation seeking are often given as primary motivations for initiation among younger MA injectors, while substitution for other drugs is more commonly reported among older IDU [169, 170]. In response to the lack of evidence to inform effective prevention interventions, this study was conducted to determine the incidence of initiating MA injection and to examine the individual, social, environmental, and economic predictors of initiation among a prospective cohort of adult IDU.

3.2 METHODS

Data for this analysis were derived from the Vancouver Injection Drug Users Study (VIDUS). Detailed sampling and recruitment procedures are provided in Section 1.4. The analysis was restricted to individuals participating in the VIDUS cohort as it is the longest running and therefore provided enough follow-up time to ascertain MA initiation.

For this study, all VIDUS participants who completed a baseline survey and at least one interview during the study period (June 2001 to May 2008) were eligible for inclusion. We constructed a study sample of MA injection naïve individuals by excluding all participants who reported ever injecting MA at first study visit. The outcome of interest was ascertained by examining responses to the question, "In the last six months, which of the following drugs did you inject?"). We defined an event as the first instance of answering "amphetamine (e.g., speed)", "methamphetamine", or "crystal meth".

Rhodes' risk environment framework [62] was used to inform the selection of potential predictors of MA injection initiation. In accordance with this framework, we hypothesised that a broad set of individual, social, environmental, and economic factors act to increase the likelihood of transitions in drug use and subsequent risk behaviour. We also included as potential confounders sociodemographic and other individual characteristics that have been found in previous literature to be

associated with MA initiation and use [171-173]. We included variables such as age (per year older), sex (female versus male), sexual orientation (lesbian, gay, bisexual, transgendered/transsexual [LGBT] versus heterosexual), age at first injection (per year older), and childhood sexual abuse (CSA). Due to the small number of ethnic minority individuals in the sample, we dichotomised ethnicity as Caucasian (white) versus other. We also included drug use variables, including non-injection crack cocaine use, injection heroin use, injection cocaine use, and non-injection methamphetamine use. Social, economic, and environmental variables considered included: relationship status (married or common law versus single or casually dating); syringe sharing; injecting with a sex partner; buying or using drugs in the Downtown Eastside (DTES) area (i.e., the city's open drug scene epicentre), respectively; currently having an area restriction or outstanding warrant; and injecting drugs while incarcerated (e.g., in detention, prison, or jail). Unless otherwise indicated, all variables refer to the six month period preceding the date of the interview.

We compared the sociodemographic characteristics of those who initiated MA injection versus those who did not using Pearson's χ^2 test and the Wilcoxon rank sum test. We then used Kaplan-Meier methods to generate the survival function and cumulative incidence of MA injection initiation over the study period. Based on previous research from our setting demonstrating increased rates of MA

use among younger drug users [145], we stratified the survival function by age at baseline (i.e., <24 versus ≥24). The time to initiating MA injection was estimated by taking the midpoint between the date of the first interview during which MA injection was reported and the preceding interview in which the participant was MA injection naïve. To examine changes in the values of the explanatory variables over time, Cox proportional hazards models were used to calculate the unadjusted hazard ratio for each variable. We used a lagged method to estimate the association between each independent variable and the outcome of interest. Specifically, to avoid associations attributable to reverse causation, the information recorded at the last follow-up prior to the estimated date of MA injection initiation was used for these analyses.

Since the primary objective of this study was to determine the set of individual, social, environmental, and economic factors which best predicted MA injection initiation, we chose to construct an explanatory multivariate model. A modified backward stepwise regression was used to select covariates based on two criteria: the Akaike information criterion (AIC) and type III *p*-values [174]. Lower AIC values indicate a better overall fit and lower *p*-values indicate higher variable significance. Starting with a full model containing all candidate variables, covariates were removed sequentially in order of decreasing *p*-values. At each step, the *p*-values of each variable and the overall AIC were recorded, with the final model

having the lowest AIC. This model building procedure has been justified elsewhere [175]. Statistical analysis was conducted using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina) and all *p*-values are two-sided.

3.3 RESULTS

Between June 2001 and May 2008, 1,878 participants completed a baseline and at least one follow-up interview and were eligible for this analysis. We excluded 541 (28.8%) individuals who reported injecting MA prior to the beginning of the study period, as well as 20 (1.5%) for whom MA use data was not available; therefore, 1,317 MA injection naïve participants were included in the final study sample. Participants who had already initiated and were thus excluded did not differ with respect to age but were more likely to be male and of Caucasian ethnicity (both $p < 0.001$). The median age at first interview during the study period was 39.9 (IQR: 32.2 – 46.1), 522 (39.6%) were female, and the majority (54.5%) were of Caucasian ethnicity. Detailed sociodemographic information of the study sample is provided in Table 3.1. To investigate loss to follow-up, we compared the sociodemographic characteristics of the 177 (13.4%) participants who never returned for follow-up with those who remained in the study. Participants lost to follow-up did not vary with respect to age ($p = 0.809$), sex ($p = 0.493$), ethnicity ($p = 0.807$), sexual abuse ($p = 0.993$), baseline crack use ($p = 0.396$) or non-injection MA use ($p = 0.253$). However, those

lost to follow-up were more likely be homeless at baseline (26.7% versus 19.3%, p = 0.023).

During the seven year study period, eligible participants contributed 4,638 person-years of follow-up over 8,955 interviews. Thus, the average amount of time between follow-up interviews was 6.2 months. In total, 200 individuals reported initiating MA injection, resulting in an overall incidence density of 4.3 (95%CI: 3.7 – 4.9) per 100 person-years. The Kaplan-Meier curve and cumulative incidence of MA injection initiation stratified by age at study entry is shown in Figure 3.1. Among young injectors (i.e., less than 24 years of age), the cumulative incidence of MA injection reached almost 40% over the seven year study period.

The results of the Cox proportional hazards analyses are provided in Table 3.2. The results of the bivariate analyses are shown in the first two columns, and all variables retained in the final multivariate model are displayed in the last two columns of the table. Factors that remained significant in multivariate analysis and where positively associated with an increased hazard of MA injection initiation included: CSA (adjusted hazard ratio [aHR] = 1.63, 95%CI: 1.18 – 2.23, p = 0.004), using drugs in the DTES (aHR = 2.15, 95%CI: 1.49 – 3.10, $p < 0.001$), homelessness (aHR = 1.43, 95%CI: 1.01 – 2.04, p = 0.047), non-injection crack use (aHR = 2.06, 95%CI: 1.36 – 3.14, p = 0.001) and non-injection MA use (aHR = 3.69, 95%CI: 2.03 – 6.70, $p < 0.001$). Older age (aHR = 0.96 per year, 95%CI: 0.95 – 0.98, $p < 0.001$) and

female sex (AOR = 0.58, 95%CI: 0.41 – 0.82, p = 0.002) were protective for MA injection initiation. We note that while gender was not associated with initiation in bivariate analysis, the adjusted estimate was highly significant. Further investigation revealed that the protective effect of female gender not seen in bivariate analysis was due to the higher prevalence of CSA among women.

As a sub-analysis, we sought to determine whether a different model building protocol other than an AIC-based approach significantly altered the interpretation of our results. To do so, we fit a multivariate model consisting of all variables significant at $p < 0.05$ in bivariate analyses. The two modeling strategies produced the same set of predictors (data not shown), thus suggesting that the results are robust and not an artifact of predictor selection procedure.

3.4 DISCUSSION

The present study revealed a high incidence of MA injection initiation, particularly among young IDU, stimulant users, the homeless, and those involved in the city's open drug scene. These results indicate that a variety of individual, social, and environmental factors increase the likelihood of initiating MA use among established injectors, and suggest that a broad set of interventions based on a risk environment framework are required to prevent MA injection initiation and resultant harms.

This analysis demonstrates that several individual-level factors were independently associated with MA injection initiation among a cohort of adult IDU. For example, our results support previous research showing that young people are at high risk of MA injection initiation [145]; therefore, young IDU should be a major focus of interventions that seek to prevent MA injection initiation. However, given that many participants initiated MA injection relatively late in their drug use careers, prevention interventions should also include strategies for older IDU in addition to programs targeted to younger populations and new injectors. Our finding that childhood sexual abuse was independently associated with MA injection initiation is not surprising given previous research demonstrating a high prevalence of CSA among MA treatment samples [176] and the existence of a dose response relationship between frequency of CSA and likelihood of MA initiation in young adulthood [171]. Although more research is required to establish the causal relationship between CSA and MA use, one possible explanation is that individuals with psychopathology arising from traumatic childhood experiences gravitate towards MA use as a coping strategy and form of self-medication [177, 178]. CSA has also been shown to predict engagement in other adverse health behaviours, including injection drug use initiation and sex work [179, 180]. Tailored and targeted programs that provide support and services to drug users who have experienced CSA are recommended.

Transitions from non-injection to injection heroin use have been relatively well-described [181-183]; furthermore, extensive polydrug use (including the concurrent use of amphetamine-type substances) and transitions to MA injection have also been observed among heroin users [184]. We found that the non-injection use of MA was a strong and independent predictor of initiating MA injection, which supports previous studies demonstrating that transitions from non-injection to injection modes of MA consumption are common [27, 145]. Preliminary work also suggests that MA use is less persistent and has shorter periods of regular use over the life course as compared to heroin and cocaine [185]. Further research is required to fully elucidate the typologies and trajectories of MA use in this setting.

Consistent with the risk environment framework, social and environmental factors that facilitate exposure to broader drug use scenes were found to predict MA injection initiation. For example, a strong relationship between involvement in the city's open drug scene and an increased incidence of MA injection was observed. Further research is required to investigate the impact of these environments on drug use initiation and transitions; however, a recent network analysis of IDU living in Winnipeg, Canada identified a strong relationship between a higher connectedness to communal injection drug use settings and HIV risk behaviour and polydrug use [186]. It may be that an open drug scene represents one such setting in which individuals are more likely to be introduced to novel drugs and modes of use.

Future studies should investigate how interventions that alter or prevent exposure to open drug scenes mitigate the risk of initiating MA injection. For example, supervised injecting facilities have been shown to be effective micro-environmental interventions that modify the drug using environment and thus reduce risk behaviour and other drug-related harms [187]. Finally, our finding that homelessness was independently associated with MA injection initiation supports other studies demonstrating a strong link between unstable housing status and engagement in HIV risk behaviour among IDU [76, 188]. However, it should be noted that the large decrease in the point estimate for this variable (i.e., from HR = 2.34 to aHR = 1.43) after adjustment for other covariates suggests that this association may have been driven in part by confounding factors such as increased exposure to sexual abuse and heavier patterns of drug use among homeless individuals.

The results of this study have important implications for interventions which aim to prevent transitions to MA injection and avert MA-specific risks and harms. Given that factors both endogenous (e.g., age) and exogenous (e.g., involvement in open drug scenes) to the individual were independently associated with initiating MA injection, we argue that comprehensive programs which address a broad set of individual, social, structural, and environmental factors are required to prevent MA initiation among IDU. Since limited evidence exists to support the long-term

effectiveness of supply reduction strategies [56, 189], alternative interventions that address economic and social inequities are recommended. A growing literature has demonstrated that structural interventions effectively reduce HIV risk among marginalised populations [190, 191]. For example, the expansion of stable and low-threshold housing programs for active drug users has been shown to be a highly effective structural HIV prevention strategy [192]. These results suggest that low-threshold housing may also prevent transitions to other modes and types of drug use by way of reducing exposure to chronic homelessness and open drug scenes. Although research demonstrating efficacious treatment modalities for patients with MA dependence is scant [193, 194], some psychosocial approaches are effective and several substitution therapies are promising [195]. While further research in this area is needed, the immediate expansion of evidence-based treatment for MA dependence among IDU populations as a means of preventing the transition to MA injection should be a public health priority.

There are several limitations of this study that should be noted. The analyses are not derived from a random sample of injectors; therefore, the findings cannot necessarily be generalised to the entire IDU community or to other populations. However, the sociodemographic characteristics of our sample are similar to those of other studies conducted in British Columbia [196]. Furthermore, the geographic patterns of MA production and availability vary across North America [12]. In this

manner, the incidence and predictors of MA initiation observed in this study may not be representative of other urban centres in North America or elsewhere. The study is also susceptible to recall bias and socially desirable reporting, although there is no reason to believe that the magnitude of these biases would differ between MA initiates and non-initiates. Since a question ascertaining lifetime history of MA injecting was not added until the second round of baseline interviews, this information could not be obtained for 268 (14.3%) participants. However, since methamphetamines were uncommon in Vancouver prior to 2001 [48], few of these individuals would have initiated MA injecting prior to enrolment; thus, we expect the magnitude of this bias to be acceptably small. Finally, as in other survival analyses of observational data, noninformative censoring may have biased the results. However, there were few sociodemographic differences between those lost to follow-up and those who remained in the study.

In summary, this study demonstrates a high incidence of methamphetamine injection initiation among a cohort of established injectors. In this longitudinal analysis, several factors amenable to public health intervention preceded the initiation of MA injection. Given the risks and harms associated with MA use among IDU populations, the development, implementation and evaluation of these programs should be a public health priority.

Figure 3.1: Kaplan-Meier analysis of methamphetamine injection initiation among a cohort of injection drug users.

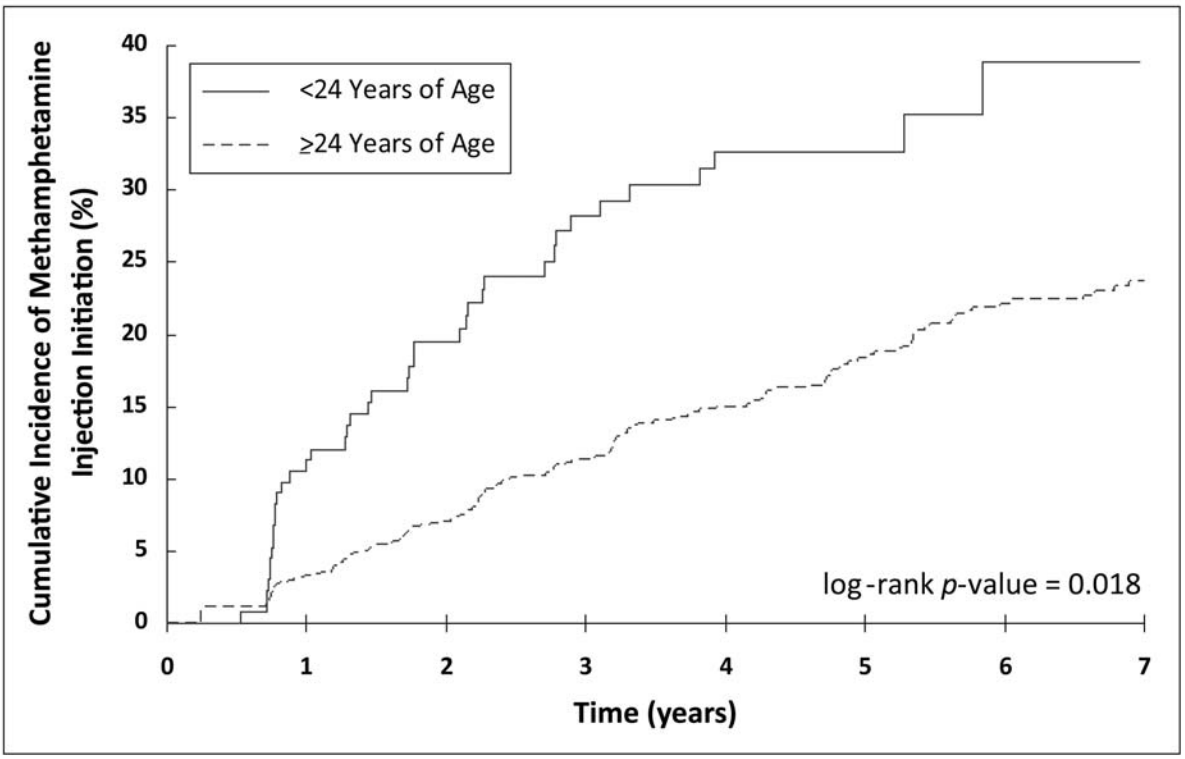


Table 3.1: Sociodemographic characteristics of injection drug users who did and who did not initiate methamphetamine injection over the study period.

Characteristic	Initiated MA Injection *n* = 200	Did Not Initiate MA Injection *n* = 1117	*p*-value
Age† (median, IQR)	36 (28 – 43)	40 (33 – 46)	<0.001
Age of First Injection (median, IQR)	18 (15 – 23)	19 (16 – 25)	0.002
Sex (*n*, %)			
Female	75 (37.5)	447 (40.0)	0.503
Male	125 (62.5)	670 (60.0)	
Ethnicity (*n*, %)			
Caucasian	114 (57.0)	602 (53.9)	0.308
Aboriginal*	74 (37.0)	394 (35.3)	
Asian	5 (2.5)	52 (4.7)	
Black	5 (2.5)	35 (3.1)	
Other	2 (1.0)	34 (3.0)	
Sexual Orientation (*n*, %)			
LGBT[a]	16 (9.2)	81 (10.2)	0.678
Heterosexual	158 (90.8)	710 (89.8)	

Note: † age at first interview during study period; * Aboriginal includes self-identified First Nation, Inuit, or Métis ancestry; a LGBT = lesbian, gay, bisexual, transgendered, or transsexual.

Table 3.2: Cox proportional hazards model of time to initiating methamphetamine injection among a cohort of injection drug users (*n* = 1317).

Characteristic	Unadjusted HR* (95% CI)	*p* - value	Adjusted HR* (95% CI)	*p* - value
Age (per year older)	0.96 (0.95 – 0.98)	<0.001	0.96 (0.95 – 0.98)	<0.001
Sex (female vs. male)	0.86 (0.64 – 1.14)	0.291	0.58 (0.41 – 0.82)	0.002
Ethnicity (Caucasian vs. other)	1.22 (0.92 – 1.61)	0.173		
Relationships Status (married vs. single/dating)	0.63 (0.42 – 0.93)	0.019		
Sexual Orientation (LGBT[a] vs. heterosexual)	0.86 (0.52 – 1.44)	0.576		
Sexual Abuse[‡] (yes vs. no)	1.44 (1.08 – 1.90)	0.012	1.63 (1.18 – 2.23)	0.004
Age of First Injection (per year older)	0.98 (0.96 – 0.99)	0.016		
Buy Drugs in DTES[c†] (yes vs. no)	2.40 (1.71 – 3.36)	<0.001		
Use Drugs in DTES[c†] (yes vs. no)	2.78 (1.97 – 3.92)	<0.001	2.15 (1.49 – 3.10)	<0.001
Homeless[†] (yes vs. no)	2.34 (1.68 – 3.25)	<0.001	1.43 (1.01 – 2.04)	0.047
Non-injection Crack Use[†] (yes vs. no)	3.14 (2.11 – 4.67)	<0.001	2.06 (1.36 – 3.14)	0.001
Non-injection MA[b] Use[†] (yes vs. no)	4.54 (2.52 – 8.16)	<0.001	3.69 (2.03 – 6.70)	<0.001
Injection Heroin Use[†] (yes vs. no)	2.15 (1.59 – 2.89)	<0.001		
Injection Cocaine Use[†] (yes vs. no)	1.71 (1.24 – 2.35)	0.001		
Inject with a Sex Partner[†] (yes vs. no)	1.17 (0.77 – 1.76)	0.463		
Syringe Sharing[†] (yes vs. no)	1.75 (1.07 – 2.85)	0.025		
Warrant or Area Restriction[¶] (yes vs. no)	2.02 (1.35 – 3.00)	0.001		
Inject while Incarcerated[†] (yes vs. no)	3.93 (0.97 – 15.91)	0.055		

* HR = Hazard Ratio; a LGBT = lesbian, gay, bisexual, transgendered, or transsexual; b MA = methamphetamine; c DTES = Downtown Eastside; † refers to activities in the past 6 months; ‡ refers to lifetime experiences; ¶ at the time of interview.

CHAPTER 4

PATHWAYS TO HIV RISK AND VULNERABILITY AMONG LESBIAN, GAY, BISEXUAL, AND TRANSGENDERED METHAMPHETAMINE USERS: A MULTI-COHORT GENDER-BASED ANALYSIS

4.1 INTRODUCTION

Like many other marginalised groups, lesbian, gay, bisexual, and transgendered (LGBT) populations experience a range of health inequities and vulnerabilities compared to the general population [197]. In addition to the multiple health conditions that disproportionately affect LGBT populations, sexual minorities also experience significant barriers to accessing appropriate care and prevention services [198, 199]. Due in part to the historical invisibility of LGBT persons and a reluctance among some communities to consider sexual minorities as a "legitimate" marginalised group, this population continues to be underrepresented in public health research and practice [200]. Furthermore, some public health discourses promote heteronormativity by portraying non-heterosexual sexuality and sexual behaviour as dangerous and "risky" [201]. In this manner, the marginalisation of sexual minority realities from dominant public health and societal discourse heightens this population's differential exposure to contexts of social, political, and

structural health risks [202]. Health research has only recently begun to demonstrate empirically how exposure to these modes of oppression impacts the health status of LGBT persons [203].

Increased vulnerability to substance use is recognised as yet another manifestation of inequitable social conditions and systems of marginalisation [204]. A large volume of studies have demonstrated a high prevalence of substance use and dependence among sexual minority groups [205, 206]. For example, methamphetamine (MA) use has been well-studied among gay, bisexual, and other men who have sex with men (MSM), particularly in relation to increased sexual risk behaviour and HIV transmission [79, 207, 208]. Although much less research has been conducted among sexual minority women, several cross-sectional studies have demonstrated that lesbian and bisexual-identified females report significantly higher rates of MA use [47, 209]. MA use among women who inject drugs (IDU) has also been associated with sexual- and injection-related HIV risk behaviour [35]. These studies and other research imply important gender differences in the typologies of and adverse health outcomes associated with MA use [210]. Gender-based analyses involving sexual minority populations are therefore needed to better inform effective public health approaches and practice.

The objective of this study was to determine the prevalence of MA use among sexual minority males and females. Furthermore, the relationships between MA use

and a range of individual, social, and structural HIV-related vulnerabilities were identified, with the aim of indentifying through which pathways MA use may exacerbate exposure to contexts of risk.

4.2 METHODS

4.2.1 Study Design

Data derived from the ARYS, VIDUS, and ACCESS studies were used for these analyses. Detailed sampling and recruitment procedures for these cohorts are described in Section 1.4. In this analysis, data from all three studies were combined to achieve a sample size with sufficient power to examine MA use among the sub-sample of participants who identified as a sexual minority. Doing so also permitted an examination of MA use patterns across a diverse spectrum of drug users (e.g., street-involved youth, older IDU) in this setting.

4.2.2 Study Sample

Data from each cohort used was collected during the same time frame; thus, all individuals were observed over the same follow-up period. All participants who completed a baseline survey between September 2005 and May 2008 were eligible for inclusion. At baseline, participants were asked to identify their biological sex at birth and their current sexual orientation. "Sexual minority status" was defined as

answering affirmatively to one of: gay, lesbian, bisexual, transgendered, transsexual, or other. Participants who refused to report their sex at birth or current sexual or gender identity were excluded from this analysis.

4.2.3 Study Hypotheses

The primary hypothesis guiding this analysis was based on the risk environment framework and a careful assessment of prior literature investigating the relationship between MA use and HIV risk behaviour. The primary hypothesis was that MA use among sexual minority drug users would be associated with differential exposure to individual, social, and structural HIV vulnerabilities. The secondary hypothesis was that the relationship between MA use and these factors would differ significantly between sexual minority males and females. In an effort to build on previous studies [78, 93, 167], this study sought to examine not only individual-level HIV risk behaviour but also contextual factors including homelessness, neighbourhood of residence, the consumption of drugs in public, and the regulation of these spaces by law enforcement personnel. The relationship between MA use and physical violence and depression was also considered, which have each been identified as independent risk factors for HIV infection [208, 211].

4.2.4 Variables of Interest

The primary outcome of interest was ascertained by examining responses to the questions, "In the last six months, did you use non-injection (crystal) methamphetamine?" and "In the last six months, did you inject (crystal) methamphetamine?" Participants who responded "yes" to either or both questions were defined as methamphetamine (MA) users in all subsequent analyses. The proportion of participants reporting daily or greater use of injection or non-injection MA use in the past 6 months was also determined. All variables examined in this study, including the outcomes and independent variables of interest, were assessed consistently and equivalently across all three studies.

Based on prior literature examining MA use among marginalised populations [26, 32, 35, 145, 212], a broad set of sociodemographic characteristics, drug use patterns, sexual activities, markers of violence and depression, and other contextual factors were assessed as explanatory variables. These variables were also chosen to represent both "micro" (i.e., the immediate social environment of drug use) and "macro" (i.e., the societal, economic, and legal context that structure drug use and harm) levels articulated by the risk environment framework [62]. Sociodemographic characteristics examined included age (per year older), Aboriginal ancestry (yes versus no), current relationship status (single/dating versus married/regular partner), and baseline HIV status (positive versus negative). All other variables

(unless otherwise indicated) referred to behaviours or activities in the past six months since the date of the interview. Drug use variables assessed included other stimulant use (i.e., non-injection cocaine use and crack use, respectively), any injection drug use, and experiencing a non-fatal overdose. The following sexual activities were examined: number of casual or regular partners excluding those in the context of sex work (>1 versus ≤1); any vaginal or anal unprotected intercourse with casual or regular partners (yes versus no); and sex trade work, defined as a categorical variable with "no" as the reference level and consistent condom use with all clients and any unprotected intercourse with clients as the second and third levels, respectively. Exposure to (i.e., experiencing) physical violence was also ascertained (yes versus no), and the Center for Epidemiologic Studies Depression Scale (CES-D) was used to measure the level of depressive symptomatology among participants [213]. Finally, contextual factors examined included: residency in the Downtown South (DTS), an area known as a mixed business and entertainment district that is also inhabited by a large street youth population [214]; homelessness (yes versus no); having a warrant or area restriction (i.e., "no go zone") influence where drugs are consumed or purchased (yes versus no); and using drugs in public spaces (≥ most often versus < most often). Warrants and area restrictions are legal orders to restrict access to certain areas of the city, and are commonly issued by law

enforcement personnel in an attempt to disrupt crime and reduce street level disorder [215].

4.2.5 Statistical Analysis

As a preliminary analysis, the baseline sociodemographic characteristics and MA use patterns between heterosexual and sexual minority participants were compared, stratified by biological sex at birth. Pearson's χ^2 test was used to compare categorical variables and the Wilcoxon rank sum test was used for continuous variables. The longitudinal predictors of MA use were then identified by using generalised estimating equations (GEE) with a logit link for binary outcomes. GEE were appropriate for this analysis since the factors associated with recent MA use over the baseline and four follow-up periods were serial (i.e., time-dependent) variables. GEE account for the correlation between repeated measures for each subject; thus, valid estimates of association and standard errors are obtained [216]. GEE models incorporate periods during which participants report engaging and not engaging in the outcome, and as such data from all baseline and follow-up interviews were used in this analysis.

Since a primary objective of this study was to determine whether the predictors of MA use differed between males and females, all analyses were stratified by biological sex at birth. A modified backward stepwise procedure was applied to select covariates based on two criteria: the Akaike information criterion

(AIC) and type-III *p*-values [174]. Lower AIC values indicate a better overall fit and lower *p*-values indicate higher variable statistical significance. Starting with a full model containing all variables that were significant in bivariate analyses at $p < 0.10$, covariates were removed sequentially in order of decreasing *p*-values. At each step, the *p*-values of each variable and the overall AIC were recorded, with the final model having the lowest AIC. To compensate for potential variations in recruitment and selection procedures between studies, each model was also adjusted for cohort of enrolment. Statistical analysis was conducted using SAS version 9.1.3 and all *p*-values are two-sided.

4.3 RESULTS

4.3.1 Sample Characteristics

Between September 2005 and May 2008, 2,109 unique individuals were enrolled into the ARYS, VIDUS or ACCESS cohorts. A total of 14 (0.7%) refused to report their sex at birth or current sexual/gender identity and were thus excluded for the analysis. Of the 2,095 eligible participants, 1,389 (66.3%) were male and 706 (33.7%) were female. Among all participants, the median age at baseline was 37.0 (IQR: 24.7 – 45.4) and 641 (30.6%) were of Aboriginal ancestry. The majority identified their sexual or gender identity as heterosexual (*n* = 1,847, 88.2%), followed by bisexual (*n* = 168, 8.0%), gay (*n* = 43, 2.1%), lesbian (*n* = 9, 0.4%), and

transgendered, transsexual, or other (n = 28, 1.3%). Among those who reported their biological sex at birth as female, 144 (20.4%) identified as a sexual minority compared to only 7.5% (n = 104) of biological males.

4.3.2 Baseline Methamphetamine Use

Sociodemographic characteristics and methamphetamine use patterns for males and females stratified by sexual orientation are displayed in Table 4.1. At baseline, sexual minority males were more likely to be younger (median = 33 versus 39, p = 0.001), HIV positive (40.4% versus 21.2%, p < 0.001), and of Aboriginal ancestry (40.4% versus 23.7%, p < 0.001). Sexual minority males were also significantly more likely to have been recruited into the ARYS (i.e., street youth) and ACCESS (i.e., HIV positive IDU) cohorts. In contrast, sexual minority females were less likely to be of Aboriginal ancestry (33.3% versus 43.9%, p = 0.023). Among both males and females, sexual minority participants were significantly more likely to report injection and non-injection MA use in the past 6 months (Table 4.1). Notably, over half (62.1%) of sexual minority males reported recently using MA, and a significant proportion (16.7%) reported injecting MA at least daily. Among all sexual minority individuals, MA use was most common among ARYS participants (69.3%), followed by participants enroled in VIDUS (36.1%), and ACCESS (21.3%). Approximately half (n =142, 57.3%) of sexual minority participants reported having used MA for at least a year since the date of the baseline interview.

4.3.3 Longitudinal Predictors of Methamphetamine Use

The results of the longitudinal analysis examining the factors associated with MA use among sexual minority males are presented in Table 4.2. Bivariate analyses indicated that male MA users were more likely to experience a variety of sexual HIV risks and vulnerabilities, including for example multiple recent sex partners (odds ratio [OR] = 1.91, p = 0.002), unprotected intercourse (OR = 1.86, p = 0.004), and unprotected intercourse in the context of sex work (OR = 3.25, p = 0.005). MA using men were also more likely to report injection drug use (OR = 2.31, p = 0.004), experience physical violence (OR = 1.76, p = 0.004) and exhibit depressive symptoms (OR = 1.79, p = 0.010). In multivariate analysis, independent predictors of MA use among sexual minority males included: younger age (adjusted odds ratio [AOR] = 0.93, p = 0.011), Aboriginal ancestry (AOR = 2.59, p = 0.019), injection drug use (AOR = 3.98, p < 0.001), unprotected sexual intercourse (AOR = 1.62, p = 0.048), increased depressive symptoms (AOR = 1.67, p = 0.044), and having an area restriction influence drug use (AOR = 4.18, p = 0.008). Experiencing physical violence was included in the final model but did not reach the convention level of statistical significance (AOR = 1.47, p = 0.100).

Increased sexual HIV vulnerabilities were also observed among MA-using sexual minority females (Table 4.3). For example, females reporting recent MA use were more likely to have multiple regular or casual sex partners (OR = 1.55, p =

0.029). Several associations that were observed among MA-using males were also significant among females. For example, female MA users were younger (OR = 0.95, $p = 0.005$), more likely to inject drugs (OR = 1.68, $p = 0.011$), and more likely to report unprotected intercourse with sex trade clients (OR = 3.27, $p = 0.001$). In contrast, MA-using females were less likely to be of Aboriginal ancestry (OR = 0.41, $p = 0.012$).

In a multivariate analysis, several unique predictors of MA use emerged among sexual minority females. In contrast to males, MA-using females were more likely to reside in the DTS neighbourhood (AOR = 1.60, $p = 0.047$). Furthermore, MA use among sexual minority females was independently associated with unprotected intercourse with sex trade clients (AOR = 2.62, $p = 0.027$). Similar to males, MA-using females were more likely to inject drugs (AOR = 2.49, $p = 0.002$). Factors that remained in the multivariate model but did not reach the conventional level of statistical significance included Aboriginal ancestry (AOR = 0.55, $p = 0.137$) and non-injection cocaine use (AOR = 1.66, $p = 0.079$).

4.1 DISCUSSION

In the current study, a high prevalence of MA use among sexual minority males and females was observed. Consistent with the risk environment framework, MA use was associated with an array of individual, social, and contextual HIV-related risks and vulnerabilities among sexual minority drug users.

Although some predictors of MA use (e.g., younger age and injection drug use) were significant for both sexes, several important differences were observed. For example, unprotected intercourse involving regular or casual partners was more common among males who reported using methamphetamine, while unprotected intercourse in the context of sex work was associated with MA use among females. Furthermore, only MA-using males were more likely to experience depressive symptoms and report having area restrictions (i.e., no go zones) influence drug use. These findings may be due to the fact that sexual minority males reported heavier MA use patterns compared to females, and thus may be more likely to experience both individual (i.e., depressive symptoms) and contextual (i.e., exposure to law enforcement) MA-related sequelae. Finally, Aboriginal ancestry was positively associated with MA use among males but inversely associated with MA use females. These results demonstrate the gendered and cultural nature of MA use and suggest that MA use may augment the already pervasive structural inequities, stigma, and HIV vulnerabilities experienced by marginalised LGBT people.

Consistent with other studies [79, 207, 217-219], MA use was linked with unprotected intercourse among sexual minority men. However, in contrast to other research emphasising the pharmacologic, social and cultural aspects of MA use to enhance sexual activity among MSM [15, 78, 79], the increased exposure to sexual risk behaviour observed in this study may represent another form of oppression and

marginalisation that MA-using street-involved gay, bisexual, and transgendered men are exposed to. Although the context in which instances of unprotected intercourse occurred could not be ascertained, prior research indicates that homeless sexual minority males frequently experience sexual victimization and abuse from partners [220, 221]. Although more research is required to elucidate casual mechanisms, it is likely that the relationship between sexual risk and MA use observed among this sample of sexual minority men is less a function of desire to enhance sex but may represent a marker of increased vulnerability within sexual relationships. A similar pathway may also explain the association between MA use and experiencing physical violence observed among males in this study.

In multivariate analysis, among the subsample of females engaging in sex work, MA use was associated with unprotected intercourse with clients. This finding can be situated within a growing literature demonstrating how social and structural inequities hinder the individual agency of drug-using survival sex workers to practice HIV prevention and harm reduction with clients [222, 223]. In a recent study of female sex workers (FSW) in Vancouver, Shannon *et al*. demonstrated that MA use is associated with living and working in marginalised public spaces (e.g., industrial areas) [19]. These areas have been shown to be settings of increased risk of violence and pressure from clients to engage in unprotected sex [224]. These results support this work and indicate that MA use

may augment the adverse impact of social-structural factors in the production of HIV risk among sexual minority women involved in survival sex work.

The strongest predictor of MA use among sexual minority men was reporting that a warrant or area restriction influenced where drugs are consumed or purchased. The socio-legal regulation of public space and its negative impact on the health of homeless people and street-level drug users has been described previously [225, 226]. Recent work also suggests that the displacement of street-involved young people using warrants or area restrictions exacerbates stigma and increases sexual vulnerability and HIV risk [227]. These findings suggest that having one's movements restricted may also encourage transitions in drug use (including initiation of MA use) due perhaps to the forced removal of drug users from normative environments and social networks. This form of marginalisation (produced by policies and practices meant to *reduce* exposure to street-level drug use and violence) is one example of a population-level intervention that may *exacerbate* inequity and worsen the health of vulnerable groups [61].

These findings also support the urgent need for increased resources and programming directed towards LGBT people who use methamphetamine. In order to inform more effective interventions to reduce the harms associated with MA, researchers must clearly articulate how social processes, including the marginalisation of non-heterosexual realities through heteronormative discourses,

impact the health of sexual minorities. Once clearly identified, these factors can then be the target of broad sets of evidence-based interventions to reduce health inequities and improve overall health. For example, changes in government policy along with community mobilization and solidarity programs have been shown to be highly successful at reducing HIV risk among survival sex workers [190, 228]. Programs that support capacity-building in marginalised communities have also been shown to reduce health inequity and improve health outcomes [229, 230]. Although further research is required to elucidate the potential impact of specific enforcement practices (e.g., area restrictions) on MA use and related harms, improved coordination between policing and public health initiatives may represent another opportunity to prevent the (un)-intended consequences of public policies meant to reduce crime and street disorder [231].

To complement structural interventions, some behavioural approaches (e.g., cognitive behavioural therapy) offer promise [87]. For example, LGBT-specific substance abuse treatment programs have been found to reduce engagement in high risk sex among gay men [232]. Harm reduction programs, particularly those offering tailored services for MA users, are effective and well-received by clients [89, 233]. Finally, given the complex associations between Aboriginal ancestry, sexual orientation, and MA use observed in this study, methamphetamine-specific

programming should carefully identify the manner in which Aboriginal and sexual identities shape drug use and HIV risk within specific contexts and settings.

This study has a number of limitations that should be noted. The ARYS, VIDUS, and ACCESS cohorts are not random samples of the eligible population; thus, findings may not necessarily be generalisable to other urban areas in which MA use is prevalent. Secondly, all behaviours ascertained in this study were self-reported. Thirdly, the analyses were restricted to individuals who self-identified as a sexual minority; therefore, heterosexual-identified individuals who engaged in same-sex activity were excluded. Some authors have noted that relying on behavioural eligibility criteria (e.g., same sex activity) ignores the importance of sexual identity in HIV prevention efforts and obscures the social dimensions of sexuality that are critical for the development of effective and culturally relevant public health interventions [234]. Fourthly, motivations for MA use could not be ascertained, which if examined may have accounted some of the observed differences in the patterns of MA use between male and female participants in this study. Finally, although these data are longitudinal, this analysis does not necessarily provide thorough insight into the causal pathways linking MA use and HIV risk with broader social and structural inequities.

In summary, this study demonstrated a high prevalence of MA use among a cohort of street-involved sexual minority drug users. To my knowledge, this is the

first study to extend the risk environment approach as a theoretical foundation from which to understand the contexts of risk associated with MA use among LGBT populations. Consistent with the risk environment framework, MA use was associated with distinct sets of individual, social, and structural HIV risks and vulnerabilities among women and men, respectively; therefore, comprehensive interventions that involve sectors outside of health (e.g., housing, law enforcement), in addition to drug-specific approaches tailored to LGBT populations, are required to reduce HIV vulnerability and MA-related harms. Finally, researchers and public health practitioners must identify multi-sector population-level interventions that do not exacerbate inequity but successfully mitigate health inequities among vulnerable LGBT populations.

Table 4.1: Baseline sociodemographic characteristics and methamphetamine use patterns among study participants, stratified by biological sex at birth and sexual orientation.

	Male (*N* = 1389)				Female (*N* = 706)			
Characteristic	**Sexual Minority* (*n* = 104)**	**Heterosexual (*n* = 1285)**	**OR (95%CI)**	***p*-value**	**Sexual Minority* (*n* = 144)**	**Heterosexual (*n* = 562)**	**OR (95%CI)**	***p*-value**
Age (median, IQR)	33 (24–42)	39 (25–47)	0.97 (0.95–0.99)	0.001	31 (23–41)	35 (24–44)	0.98 (0.97–1.00)	0.053
Cohort of recruitment								
ACCESS	36 (34.6)	267 (20.8)	2.60 (1.60–4.24)	<0.001	41 (28.5)	155 (27.6)	1.16 (0.75–1.81)	0.506
ARYS	33 (31.7)	342 (26.6)	1.86 (1.14–3.05)	0.015	42 (29.2)	139 (24.7)	1.33 (0.85–2.07)	0.214
VIDUS (ref)	35 (33.7)	676 (52.6)			61 (42.4)	268 (47.7)		
Aboriginal ancestry								
Yes	42 (40.4)	305 (23.7)	2.18 (1.44–3.29)	<0.001	48 (33.3)	246 (43.9)	0.64 (0.44–0.94)	0.023
No	62 (59.6)	980 (76.3)			96 (66.7)	315 (56.2)		
Relationship status								
Single/dating	73 (70.2)	927 (72.4)	0.90 (0.58–1.39)	0.634	90 (62.5)	307 (55.4)	1.34 (0.92–1.95)	0.127
Married/regular partner	31 (29.8)	354 (27.6)			54 (37.5)	247 (44.6)		
HIV status								
Positive	42 (40.4)	272 (21.2)	2.52 (1.67–3.82)	<0.001	41 (28.5)	159 (28.3)	1.01 (0.67–1.51)	0.966
Negative	62 (59.6)	1013 (78.8)			103 (71.5)	403 (71.7)		
Any meth use†								
Yes	64 (62.1)	388 (30.5)	3.74 (2.47–5.67)	<0.001	58 (40.3)	150 (27.2)	1.80 (1.23–2.64)	0.003
No	39 (37.9)	884 (69.5)			86 (59.7)	401 (72.8)		
Any non-injection meth use†								
Yes	38 (36.5)	223 (17.5)	2.71 (1.78–4.15)	<0.001	36 (25.0)	89 (16.0)	1.75 (1.12–2.71)	0.013
No	66 (63.5)	1050 (82.5)			108 (75.0)	466 (84.0)		

	Male (*N* = 1389)				Female (*N* = 706)			
Characteristic	**Sexual Minority* (*n* = 104)**	**Heterosexual (*n* = 1285)**	**OR (95%CI)**	***p*-value**	**Sexual Minority* (*n* = 144)**	**Heterosexual (*n* = 562)**	**OR (95%CI)**	***p*-value**
Daily non-injection meth use†								
Yes	11 (10.6)	39 (3.1)	3.72 (1.84–7.50)	<0.001	8 (5.6)	20 (3.7)	1.56 (0.67–3.62)	0.296
No	93 (89.4)	1226 (96.9)			135 (94.4)	527 (96.3)		
Any injection meth use†								
Yes	43 (41.4)	262 (20.4)	2.75 (1.82–4.15)	<0.001	39 (27.1)	100 (18.0)	1.69 (1.10–2.59)	0.016
No	61 (58.6)	1021 (79.6)			105 (72.9)	455 (82.0)		
Daily injection meth use†								
Yes	17 (16.7)	45 (3.5)	5.45 (3.00–9.95)	<0.001	9 (6.4)	16 (2.9)	2.27 (0.98–5.24)	0.066
No	85 (83.3)	1229 (96.5)			132 (93.6)	532 (97.1)		

Notes: * “sexual minority” refers to lesbian, gay, bisexual, transgendered, transsexual, or other orientation; † refers to activities in the past 6 months.

Table 4.2: Longitudinal analysis of factors associated with methamphetamine use† among sexual minority* males

Characteristic	Odds Ratio	95% CI	*p*-value	Adjusted Odds Ratio	95% CI	*p*-value
Sociodemographic Characteristics						
Age (per year)	0.92	0.89 – 0.96	<0.001	0.93	0.88 – 0.98	0.011
Aboriginal ancestry (yes vs. no)	2.37	1.17 – 4.79	0.016	2.59	1.17 – 5.77	0.019
Relationship status (single/dating vs. married/partner)	0.96	0.65 – 1.42	0.842			
HIV status (positive vs. negative)	0.50	0.24 – 1.00	0.051			
Drug Use						
Non-injection cocaine use† (yes vs. no)	2.44	1.09 – 5.44	0.029			
Crack use† (yes vs. no)	1.47	0.89 – 2.43	0.133			
Any injection drug use† (yes vs. no)	2.31	1.30 – 4.11	0.004	3.98	1.85 – 8.57	<0.001
Overdose† (yes vs. no)	1.52	0.83 – 2.77	0.172			
Sexual Activities						
Number of sex partners† (>1 vs. ≤1)	1.91	1.28 – 2.86	0.002			
Unprotected intercourse† (yes vs. no)	1.86	1.22 – 2.84	0.004	1.62	1.01 – 2.60	0.048
Sex trade work† (ref = no sex trade work)						
Protected intercourse with clients† (yes vs. ref)	2.79	1.62 – 4.82	<0.001			
Unprotected intercourse with clients† (yes vs. ref)	3.25	1.44 – 7.37	0.005			
Violence & Depression						
Experience physical violence† (yes vs. no)	1.76	1.20 – 2.59	0.004	1.47	0.93 – 2.32	0.100
Clinical depression (CES-D‡ ≥16 vs. <16)	1.79	1.15 – 2.79	0.010	1.67	1.01 – 2.76	0.044
Contextual Factors						
Downtown South residency (yes vs. no)	1.45	0.90 – 2.34	0.124			
Homeless† (yes vs. no)	1.76	1.00 – 3.09	0.050			
Area restrictions influence drug use (yes vs. no)	4.02	0.87 – 18.54	0.075	4.18	1.46 – 11.95	0.008
Use drugs in public† (≥ most often vs. < most often)	1.53	0.96 – 2.43	0.073			

Notes: multivariate model adjusted for cohort of recruitment; * "sexual minority" refers to lesbian, gay, bisexual, transgender, transsexual, or other orientation; † refers to activities in the past 6 months; ‡ CES-D refers to the Center for Epidemiologic Studies Depression Scale.

Table 4.3: Longitudinal analysis of factors associated with methamphetamine use† among sexual minority females.

Characteristic	Odds Ratio	95% CI	*p*-value	Adjusted Odds Ratio	95% CI	*p*-value
Sociodemographic Characteristics						
Age (per year)	0.95	0.92 – 0.99	0.005			
Aboriginal ancestry (yes vs. no)	0.41	0.21 – 0.82	0.012	0.55	0.25 – 1.21	0.137
Relationship (single/dating vs. married/partner)	1.07	0.76 – 1.49	0.708			
HIV status (positive vs. negative)	0.62	0.90 – 1.30	0.209			
Drug Use						
Non-injection cocaine use† (yes vs. no)	1.79	1.06 – 3.04	0.030	1.66	0.94 – 2.92	0.079
Crack use† (yes vs. no)	0.95	0.71 – 1.27	0.730			
Any injection drug use† (yes vs. no)	1.68	1.13 – 2.50	0.011	2.49	1.42 – 4.39	0.002
Overdose† (yes vs. no)	1.47	0.90 – 2.41	0.126			
Sexual Activities						
Number of sex partners† (>1 vs. ≤1)	1.55	1.05 – 2.30	0.029			
Unprotected intercourse† (yes vs. no)	0.97	0.65 – 1.45	0.897			
Sex trade work† (ref = no sex trade work)						
Protected intercourse with clients† (yes vs. ref)	1.30	0.88 – 1.93	0.189	1.16	0.72 – 1.87	0.543
Unprotected intercourse with clients† (yes vs. ref)	3.27	1.60 – 6.68	0.001	2.62	1.12 – 6.14	0.027
Violence & Depression						
Experience physical violence† (yes vs. no)	1.24	0.88 – 1.75	0.210			
Clinical depression (CES-D‡ ≥16 vs. <16)	0.85	0.66 – 1.09	0.204			
Contextual Factors						
Downtown South residency (yes vs. no)	1.45	1.00 – 2.10	0.053	1.60	1.01 – 2.54	0.047
Homeless† (yes vs. no)	1.19	0.86 – 1.64	0.299			
Area restrictions influence drug use (yes vs. no)	0.59	0.28 – 1.23	0.160			
Use drugs in public† (≥ most often vs. < most often)	1.18	0.77 – 1.81	0.446			

Notes: multivariate model adjusted for cohort of recruitment; * "sexual minority" refers to lesbian, gay, bisexual, transgender, transsexual, or other orientation; † refers to activities in the past 6 months; ‡ CES-D refers to the Center for Epidemiologic Studies Depression Scale.

CHAPTER 5

FREQUENT METHAMPHETAMINE INJECTION PREDICTS EMERGENCY DEPARTMENT UTILISATION AMONG STREET-INOLVED YOUTH

5.1 INTRODUCTION

Homeless and street-involved youth experience many health problems and face a variety of structural and social barriers while seeking appropriate care to address them [235]. Among the most common health concerns identified by street-involved youth include pregnancy and sexually transmitted infections (STIs), depression and other mental health concerns, dental problems, acute trauma and injuries, and substance-related disorders [236-238]. Youth who are homeless (as opposed to those who are sheltered or unstable housed) are often uninsured and have unmet health needs [239]; furthermore, longer durations of homelessness tend to exacerbate underlying health conditions [240]. Street-involved youth who manage to access care tend to over-rely on emergency departments as opposed to ambulatory clinics and other primary health care services [236]. One study, consisting of a nationally representative sample of sheltered and street-based youth in the US, found that approximately one third had been treated in an emergency

department in the previous year [241]. Two-thirds of street youth who accessed the emergency department reported that the visit was related to substance use.

Methamphetamine (MA) use is a continuing public health concern in many urban settings due to large increases in its production, trafficking, and consumption over the past decade [5, 33]. The increasing use of MA among street-involved youth has been noted in numerous settings [22, 145]. Several studies have also demonstrated that adult MA users utilise emergency departments and hospital resources more frequently than other drug-using populations [92, 242]. Although fewer studies have examined MA use among street-involved youth, its consumption has been shown to be associated with deteriorating physical and mental health and an increased risk of bloodborne disease acquisition [20, 44, 45, 78]. Given the preliminary evidence indicating that MA use may exacerbate health problems experienced by street youth, the objective of this study was to determine whether frequent MA injection was an independent risk factor for emergency department (ED) utilisation among a prospective cohort of street-involved youth in a setting with universal access to health care. The reasons for ED admissions among street-involved youth who inject MA were also examined.

5.2 METHODS

This study utilised data from the ARYS cohort. Detailed sampling and recruitment procedures are provided in Section 1.4. For this analysis, the sample was restricted to individuals less than 24 years of age in order to be consistent with prior studies that have assessed homeless youths' access to emergency health services and primary care [241, 243]. All ARYS participants between 14 and 24 years of age and who completed a baseline survey between September 2005 and January 2007 were eligible for inclusion in this analysis.

The primary endpoint for this study was time to first ED visit at St. Paul's Hospital (SPH) — a major inner-city teaching hospital located in downtown Vancouver. SPH is the primary hospital for the street-involved and drug-using population in the city [242]. A confidential linkage to the SPH ED health records database was conducted to ascertain the exact date of first ED visit following enrolment into the ARYS cohort. The SPH ED database also contains information regarding the primary presenting diagnosis, including internal ED codes (e.g., "ID" = infectious disease, "GI" = gastrointestinal disorder) and string data describing the reason for the ED visit. These data were manually sorted and categorized by the primary author (BDLM) based on an *a priori* defined list of common ED presentations that have been described and published elsewhere [242]. Each classification was then reviewed independently by a second author (JAB) until all

diagnoses were appropriately categorised. The most common classifications among daily MA injectors and non-injectors were then compared using Fisher's exact test. The SPH ED database includes data regarding the time and day of ED utilisation; this information was categorised to represent visits that took place during standard business hours (i.e., Monday through Friday between 9:00am and 5:00pm) versus those in the evenings, nights, and on weekends. Finally, to determine what proportion of visits led to hospital admission, discharge data, including whether the individual was transferred to acute care, discharged with approval, or discharged without service or against advice was examined.

The primary independent variable was self-reported MA injection in the past 6 months, defined as a categorical variable with the following levels: no MA injection, less than daily (i.e., infrequent) MA injection, and at least daily (i.e., frequent) MA injection. The following sociodemographic covariates were examined as potential confounders in the association between MA injection and ED utilisation: age (per year older), sex (female vs. male), and Aboriginal ancestry (yes vs. no). Aboriginal ancestry was defined as all participants who self-identified as First Nations, Inuit, Métis, or Aboriginal. This variable was included in the study to reflect the higher prevalence of HIV and other co-morbidities among Aboriginal street youth in this setting [244]. The following potentially confounding covariates were also assessed: homelessness (yes versus no), crack use (yes versus no), heavy

alcohol use (defined as consuming on average ≥ four drinks per day [yes versus no]), frequent cocaine injection (≥daily versus <daily), frequent heroin injection (≥daily versus <daily), non-fatal overdose (yes versus no), engagement in sex work (yes versus no), enrolment in addiction treatment (yes versus no), and recent suicide attempt (yes versus no). Depressive symptomatology was also adjusted for, based on a cut-off of ≥22 on the 20-item Center for Epidemiologic Studies Depression (CES-D) scale. The CES-D is a validated instrument for measuring depressive symptoms, and a higher cut-off of ≥22 as opposed to ≥16 has been found to be reliable among samples of adolescents [245]. Unless otherwise indicated, all variables refer to behaviours or activities in the 6 months prior to the date of the baseline interview.

To determine the cumulative incidence of ED utilisation over the study period, the Kaplan-Meier method was used to generate the survival function of frequent MA injectors, non-frequent MA injectors, and non-MA injectors. The log-rank test was used to compare the survival distributions of the three groups. Cox proportional hazards models were constructed to estimate the associations between each variable and the outcome of interest. As the primary objective of this analysis was to determine the independent association between MA injection and ED utilisation, a series of confounding models were fit based on an approach described by Maldonado and Greenland [246]. As a first step, bivariate screenings were conducted, based on a conservative *p*-value of less than 0.20. All covariates that

achieved this cut-off were then included in a "full" multivariate model. Starting with this model, variables that did not alter the coefficient of the primary explanatory variable by more than 10% were removed in a sequential fashion. Since baseline MA injection was a categorical variable with a reference and two modeled levels, covariates were considered significant if their removal from the "full" model altered one or both coefficients by more than 10%. This method has been described previously and used successfully by several authors [247, 248].

As a final confirmatory sub-analysis, the mean number of visits over the study period among frequent MA injectors, non-frequent MA injectors, and non-MA injectors were compared using ANOVA. All statistical analysis were conducted using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina), and all *p*-values are two-sided.

5.3 RESULTS

Between September 2005 and January 2007, 427 eligible individuals were enroled in the ARYS cohort. The median age of the sample was 20.9 (interquartile range [IQR]: 19.1 – 22.5), 154 (36.1%) were female, and 81 (19.0%) were of Aboriginal ancestry. In total, 211 (49.4%) reported using MA in the past six months, among whom 65 (30.8%) reported MA injection. One-third (n = 22, 33.8%) of MA injectors reported doing so at least daily. The majority (n = 50, 76.9%) of MA injectors also

reported using MA through other modes of consumption (e.g., snorting, smoking) at least once in the past six months. Baseline sociodemographic characteristics and methamphetamine use patterns are presented in Table 5.1. No deaths or HIV seroconversions were observed during the study period.

Among the 427 participants, 163 (38.2%) visited the ED at least once within the year following the date of their baseline interview. Approximately three quarters of these visits (n = 122, 74.9%) occurred outside of regular business hours. The vast majority (n = 132, 81.0%) led to a discharge with approval, while 6 (3.7%) were discharged against advice and 6 (3.7%) led to admission. Notably, 18 (11.0%) visits resulted in a discharge without service.

The incidence density of ED utilisation was 53.7 (95%CI: 45.9 – 62.5) per 100 person-years. In a Kaplan-Meier analysis stratified by baseline MA injection frequency (see Figure 5.1), significant differences in the survival distributions between the groups were observed (log-rank p = 0.004). Among participants reporting daily or greater MA injection, the cumulative incidence of ED utilisation was 68% — approximately twice that of non-daily MA injectors (35%) and non-MA injectors (37%), respectively.

In bivariate Cox regression analyses, frequency of MA injection was significantly associated time to first ED visit (type-III p-value = 0.006). Although the hazard of ED utilisation among non-daily MA injectors was similar to that of non-

MA injectors (unadjusted hazard ratio [HR] = 1.00, 95%CI: 0.89 – 1.71, p = 0.999), frequent MA injectors were at a significantly increased risk of an ED visit during the study period (HR = 2.39, 95%CI: 1.40 – 4.08, p = 0.001). Other factors associated with time to first ED utilisation are shown in Table 5.2. Frequent MA use through non-injection routes of consumption (i.e., smoking or snorting) was not associated with ED utilisation (HR = 1.37, 95%CI: 0.87 – 2.17, p = 0.177).

In a multivariate model adjusting for other variables observed to confound the relationship between MA injection and time to first ED visit, frequent MA injection was associated with an elevated hazard of ED utilisation (adjusted hazard ratio [AHR] = 1.84, 95%CI: 1.04 – 3.25, p = 0.036). Older age (AHR = 1.09 per year, 95%CI: 1.01 – 1.17, p = 0.026) was also significant in the final confounding model (see Table 5.2).

The most common presenting diagnoses at first ED visit among study participants are presented in Table 5.3. Among non-MA injectors, the most common types of diagnoses included: musculoskeletal injuries; abscesses, cellulitis, and other skin infections; and psychiatric disorders. Abscesses, cellulitis, and other skin infections were also most common among non-daily MA injectors. The most common ED presentations among daily MA injectors were those related substance misuse. These presentations were significantly more common among those who

reported injecting MA at least daily compared to the non-MA injecting group (Fisher's exact test p=0.020).

In a sub-analysis examining ED utilisation over the entire study period, 163 participants were found to contribute 599 unique visits. The large majority (n = 508, 84.8%) led to a discharge with approval, while only 21 (3.5%) led to admission. Results of an ANOVA comparing the mean number of annual visits among frequent, non-frequent, and non-MA injectors demonstrated significant heterogeneity between the groups (F-test p=0.018). The mean number of ED visits was greatest among frequent MA injectors (mean = 3.1, standard error [SE] = 0.69) compared to only 1.9 (SE = 0.50) and 1.2 (SE = 0.17) among non-frequent and non-MA injectors, respectively.

5.4 DISCUSSION

A significantly increased risk of ED utilisation was observed among street-involved youth who reported frequent methamphetamine injection. Within one year of enrolment, the cumulative incidence of ED utilisation among frequent MA injectors was approximately 70%, compared to only 35% among occasional MA injectors and non-MA injectors. Furthermore, in a confirmatory sub-analysis, a dose-response relationship was found to exist between the mean number of annual ED visits and frequency of MA injection. The most common ED presentations

among frequent users of MA were those related to substance dependence, misuse, or overdose, followed by psychiatric disorder diagnoses. These findings support recent research indicating that substance-related conditions including those related to MA use are significant contributors of ED utilisation in North America, and that acute injuries, overdose, and psychiatric problems are among the most common presentations among substance users [249-251]. These findings may inform public health interventions that more effectively reduce the negative health consequences of frequent MA use, and improve access to appropriate health services for street-involved youth who require care.

Although the health and social consequences of chronic MA use among adult populations have been well-described, there exists little evidence to inform effective interventions to address health issues experienced by MA-using youth [96]. The results of this study demonstrate that street-involved youth who inject MA, particularly those who do so frequently, may require a comprehensive set of interventions to address and reduce MA-related co-morbidities. The finding that frequent MA injectors are more likely to visit the ED for substance-related disorders has important implications for interventions that seek to improve the health of this population. The utilisation of emergency care services for substance dependence and misuse may indicate that youth are unable to access other forms of treatment modalities; the absence of treatment programs for MA-dependent youth in this

setting is noted [252]. A scale-up of residential and outpatient programs that meet the needs of this patient population is thus urgently required. While some studies have demonstrated that mechanisms which formally link addiction treatment services with direct access to primary medical care are effective in some emergency settings [253], studies that evaluate similar programs for MA-using youth are lacking. Although integrated service models may be as equally effective for young people as for adults, providers must address multiple barriers that street-involved youth experience while attempting to access traditional health services. These include, but are not limited to, confusion over issues regarding confidentiality and consent, transportation problems, and lack of respect and perceived judgmentalism from service providers [241, 254]. Further examples of structural barriers include services that are perceived as being too rigid (e.g., by appointment only), inflexible (e.g., require ID), or inaccessible (i.e., inconvenient hours of operation) [255]. Improved integration of health services with addiction treatment and other social services accessed by homeless youth has been proposed as one mechanism to reduce barriers to care among this population [241].

In the United States, lack of insurance has been found to be a primary barrier experienced by street youth who attempt to access care [254]. Although health care in Canada is publicly funded and thus all patients have universal access to hospital and primary care services, disparities in health service utilisation, particularly

among the most disadvantaged, continue to exist [256]. This study characterises the ED utilisation patterns of a population of youth who are among the most marginalised, and thus likely experience some of the greatest disparities in access to care. While clinics and services designed specifically for street-involved young people may help to reduce health inequities and over-reliance on acute services, some studies have shown that many programs are heavily underutilised by youth in greatest need of care [241]. For these reasons, interventions which aim to reduce MA-related harms and connect MA-using street youth with appropriate primary care should seek not only to provide youth-friendly services but commit to the meaningful engagement of young people in the development, implementation, and evaluation of these programs. Furthermore, given that the vast majority of ED visits occurred outside of standard clinic operating hours, expanding the range of services for young patients presenting with substance use problems within the ED setting may be more cost effective and address this population's health concerns more appropriately than the additional provision of youth-friendly ambulatory clinics.

This study has several limitations. Firstly, the true burden of ED utilisation is likely underestimated, as participants may have received care at other settings not evaluated in this analysis. However, there is no reason to believe that individuals receiving care at other hospitals would differ with respect to MA use from those who accessed SPH. Secondly, although ED utilisation was determined with

certainty through a confidential linkage to ED records, all other variables were self-reported. However, previous studies have established the validity of self-reported drug use among adolescents [159]. Finally, it was not possible to determine what proportion of ED visits observed in this sample were a suitable use of emergent care, or whether the health concern may have been more appropriately treated in a primary care setting. For example, "psychiatric disorders" could not be disaggregated into acute psychotic episodes and those related to chronic conditions.

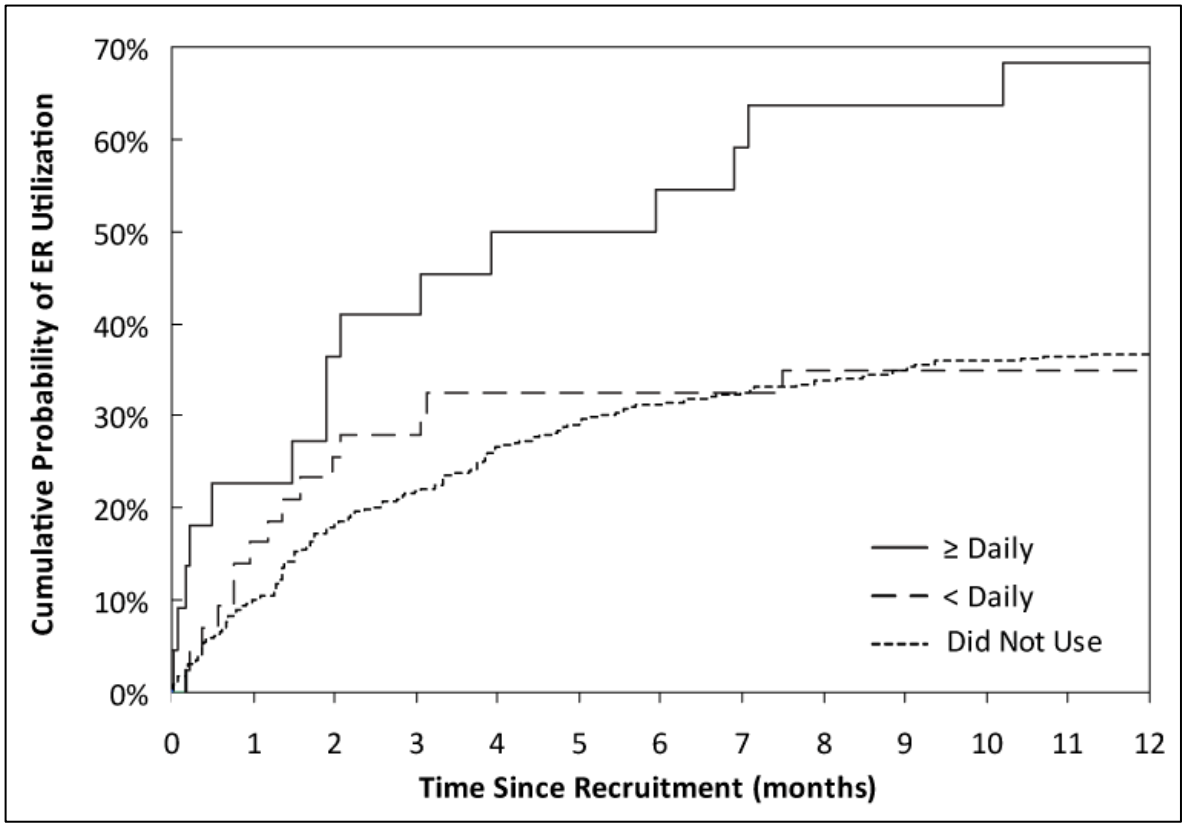
In summary, street-involved youth who report frequently injecting methamphetamine were found to be at an increased risk of ED utilisation. Effective interventions to reduce the adverse health consequences of MA use and improve access to subacute and ambulatory settings will require not only the integration of services to address underlying health concerns experienced by this population, but also the meaningful engagement of youth to lessen barriers to care.

Table 5.1: Baseline sociodemographic characteristics and methamphetamine use among a cohort of street-involved youth (*n* = 427).

Characteristic	*N* (%)
Age (median, IQR)	20.9 (19.1 – 22.5)
Sex	
Female	154 (36.1)
Male	273 (63.9)
Ethnicity	
Aboriginal	81 (19.0)
Other	346 (81.0)
Homeless†	
Yes	335 (78.5)
No	92 (21.5)
Non-injection MA use†	
None	238 (55.7)
< Daily	139 (32.6)
≥ Daily	50 (11.7)
Injection MA use†	
None	362 (84.8)
< Daily	43 (10.1)
≥ Daily	22 (5.1)

Note: † refers to activities in the past 6 months prior to the baseline interview.

Figure 5.1: Kaplan-Meier analysis of time to emergency department utilisation among a cohort of street-involved youth



Note: log-rank *p*-value = 0.004

Table 5.2: Factors associated with time to emergency department utilisation among a cohort of street-involved youth (*n* = 427).

Characteristic	Unadjusted HR* (95% CI)	*p* - value	Adjusted HR* (95% CI)	*p* - value
Injection MA use† (ref: None)				
Infrequent (< Daily)	1.00 (0.89 – 1.71)	0.999	0.83 (0.47 – 1.44)	0.498
Frequent (≥ Daily)	2.39 (1.40 – 4.08)	0.001	1.84 (1.04 – 3.25)	0.036
Sociodemographic Characteristics				
Age (per year older)	1.11 (1.03 – 1.19)	0.006	1.09 (1.01 – 1.18)	0.026
Sex (female vs. male)	0.86 (0.62 – 1.20)	0.373		
Ethnicity (Aboriginal vs. other)	1.05 (0.71 – 1.54)	0.821		
Homeless† (yes vs. no)	1.12 (0.77 – 1.64)	0.556		
Other Drug Use Variables				
Crack use† (yes vs. no)	1.24 (0.91 – 1.70)	0.170		
Heavy alcohol use† (yes vs. no)	0.72 (0.53 – 0.99)	0.040	0.78 (0.57 – 1.08)	0.141
Cocaine injection† (≥daily vs. <daily)	2.73 (0.68 – 11.00)	0.159	2.77 (0.66 – 11.59)	0.164
Heroin injection† (≥daily vs. <daily)	1.21 (0.70 – 2.09)	0.501		
Overdose† (yes vs. no)	0.85 (0.51 – 1.40)	0.516		
Other Variables				
Sex work† (yes vs. no)	1.69 (1.10 – 2.59)	0.016	1.47 (0.94 – 2.30)	0.089
Addiction treatment† (yes vs. no)	1.05 (0.74 – 1.49)	0.799		
Experience violence† (yes vs. no)	0.90 (0.66 – 1.22)	0.481		
Depression (CES-D ≥22 vs. <22)	0.87 (0.63 – 1.19)	0.380		
Attempted suicide† (yes vs. no)	1.24 (0.76 – 2.02)	0.390		

Note: * HR = hazard ratio; † refers to activities in the past 6 months.

Table 5.3: Primary reasons for visiting the emergency department among a cohort of street-involved youth.

Characteristic	No MA Use† (*n* = 133) *N* (%)	< Daily MA Use† (*n* = 15) *N* (%)	≥ Daily MA Use† (*n* = 15) *N* (%)
Musculoskeletal injuries	21 (15.8)	1 (6.7)	1 (6.7)
Abscesses, cellulitis, & other skin infections	16 (12.0)	4 (26.7)	1 (6.7)
Psychiatric disorders	16 (12.0)	2 (13.3)	2 (13.3)
Gastrointestinal & urological disorders	14 (10.5)	2 (13.3)	1 (6.7)
Wounds, lacerations & contusions	8 (6.0)	0 (0.0)	0 (0.0)
Cardiac & circulatory system diseases	7 (5.3)	0 (0.0)	0 (0.0)
Dental pain	7 (5.3)	2 (13.3)	0 (0.0)
Substance dependence, misuse, & overdose‡	6 (4.5)	1 (6.7)	4 (26.7)
Neurological disorders, seizures & headaches	6 (4.5)	0 (0.0)	1 (6.7)
Medication refills & aftercare	6 (4.5)	1 (6.7)	0 (0.0)
Respiratory infections and disorders	5 (3.8)	1 (6.7)	2 (13.3)
Miscellaneous bacterial and viral infections	4 (3.0)	0 (0.0)	1 (6.7)
Trauma (blunt or penetrating)	4 (3.0)	0 (0.0)	0 (0.0)
Fractures and dislocations	1 (0.8)	0 (0.0)	0 (0.0)
Other	12 (9.0)	1 (6.7)	2 (13.3)

Note: † refers to use in the past 6 months; ‡ note: significantly more common among ≥daily MA injectors compared to non-MA injectors (Fisher's exact test $p = 0.020$).

CHAPTER 6

DIFFICULTY ACCESSING SYRINGES MEDIATES THE RELATIONSHIP BETWEEN METHAMPHETAMINE USE AND SYRINGE SHARING AMONG YOUNG INJECTION DRUG USERS

6.1 INTRODUCTION

The sharing of non-sterile injecting equipment remains an important risk factor for HIV acquisition and other blood-borne diseases, despite impressive declines in injecting-related risk behaviour observed among injection drug users (IDU) in several settings [257-259]. Substantial evidence exists to suggest that needle and syringe programs (NSPs) have played an important role in reducing HIV risk behaviour and HIV seroconversion among IDU who use these programs [260, 261]. However, recent studies have raised concerns that a high prevalence of injection risk (including receptive and distributive syringe sharing) persists among new injectors and young IDU [262-264]. Younger injectors are less likely than adults to use NSPs, and those who do access these services use them infrequently [265, 266]. Furthermore, young IDU are less likely to return to NSPs after an initial visit, with geographic proximity being a particularly important predictor of retention [267]. Research that identifies the evolving risk factors for syringe sharing among young IDU and their barriers to accessing HIV prevention programs is therefore required

to inform more effective interventions to reduce the risk of blood-borne disease acquisition among this population.

The use of methamphetamine (MA) via injection among adults has been associated with a variety of adverse health and social consequences, including elevated rates of mortality in some settings [94, 105]. Behavioural studies have also shown that adult MA injectors are more likely to report sexual- and injection-related risk behaviour compared to other injectors [33-35]. Although much less research has been conducted examining the health and behavioural consequences of MA injection among youth, a recent systematic review concluded that young MA injectors experience an increased risk of psychopathology and other drug-related harms including overdose [96].

The primary hypothesis of the present analysis was that young people who inject MA would be more likely to report syringe sharing as compared to young IDU who inject other substances. Drawing on a growing literature demonstrating that social and structural barriers to accessing NSPs and other harm reduction interventions are important drivers of HIV risk behaviour among IDU populations [268-270], it was also hypothesized that reporting difficulty accessing sterile syringes would mediate the association between MA injection and syringe sharing. Mediation analysis permits the examination of potential mechanisms through which independent variables impact health behaviours [271], and was thus appropriate for

this analysis. These findings may inform the development of more effective behavioural and public health interventions aiming to reduce syringe sharing and resultant infectious disease transmission among young MA injecting populations.

6.2 METHODS

6.2.1 Study Design and Participants

Data derived from all three cohorts were used for these analyses; detailed sampling and recruitment procedures are described in Section 1.4. All three cohorts were combined to achieve sufficient power to examine the predictors of syringe sharing among young participants who reported active injection drug use. All individuals who completed a baseline survey between October 2005 and May 2008 were eligible for inclusion. For this study, individuals less than 30 years of age at enrolment were eligible for inclusion. The sample was also restricted to active IDU (i.e., participants who reported injecting at least once in the six months prior to the baseline interview or one of four follow-ups during the study period).

6.2.2 Measures

All variables examined in these analyses were assessed consistently and equivalently across the three cohorts. The dependent variable in this analysis was syringe sharing (yes versus no), defined as answering affirmatively to either, "In the

past six months, have you fixed with a rig that had already been used by someone else?" or "In the past six months, have you lent your used rig to someone else?". The primary independent variable of interest was injecting MA (either alone or in combination with other drugs) at least once in the six months prior to the interview (yes versus no). The potential mediator assessed in this study was "difficulty accessing sterile syringes", which was assessed by examining responses to the question, "Do you find it hard to get new rigs when you need them?" Participants who answered "yes" or "sometimes" were coded as having difficulty accessing syringes versus those who reported "no".

The following covariates were assessed as potential confounders: age (<24 versus ≥24), sex (male versus female), ethnicity (Caucasian versus other), current relationship status (single/dating versus married/regular partner), and baseline HIV status (positive versus negative). These variables have been shown in previous studies to be important risk factors for syringe sharing and HIV incidence among IDU [263, 272-275], and were thus included in all regressions as *a priori* potentially confounding variables. Scores derived from the self-efficacy for limiting HIV risk behaviour (LHRB) scale were also examined. The self-efficacy for LHRB is a validated nine-item instrument that has high levels of internal consistency and validity among at-risk youth [276]. Items included in the scale assess both self-efficacy to limit sexual risk (e.g., "How sure are you that you could… use a condom

correctly if your partner wanted to?") and injection-related risk behaviour (e.g., "…refuse to use a needle that had already been used by a friend?"). Participants rate each item on a 10-point scale from 0 (i.e., "cannot do at all") to 10 ("certain can do"). Due to the negatively skewed distribution of the scores, responses were categorized based on the sample quartiles. Finally, the number of years participants reported injecting, non-injection MA use, non-injection crack use, injection cocaine use, and injection heroin use were also examined in order to compare the drug use patterns between MA injectors and non-injectors.

6.2.3 Statistical Analysis

As a preliminary analysis, the characteristics of those who did and did not report injecting MA at baseline was compared using Pearson's χ^2-square test for dichotomous variables and the Kruskal-Wallis test for continuous variables. As a next step, a mediation analysis according to the procedures recommended by Baron and Kenny was conducted [271]. Generalised estimating equations (GEE) with a logit link for binary outcomes were used for all regressions. GEE were appropriate for this analysis since the factors associated with syringe sharing, including the independent variable and proposed mediator, were dichotomous, serial (i.e., time-dependent) variables. Since GEE account for the correlation between repeated measures for each subject, valid estimates of association and standard errors are obtained [216]. Furthermore, these methods permitted the inclusion of all data

collected in any survey during which active injection drug use was reported (i.e., participants did not need to report injecting drugs over the entire study period to be eligible).

In accordance with the techniques proposed by Baron and Kenny, three multivariate longitudinal regressions were conducted to determine the relationship between: (1) path *a*, the independent variable (i.e., injecting MA) and the mediator (i.e., difficulty accessing syringes); (2) path *b*, the mediator and the dependent variable (i.e., syringe sharing), adjusting for the effect of the independent variable; and (3) path *c*, the independent variable and the dependent variable. To determine the extent to which difficulty accessing syringes mediated the association between injecting MA and syringe sharing, a final model with both the mediator and independent variable as predictors of the dependent variable was conducted to estimate coefficient *c′*. If mediation is present, the magnitude and significance of *c′* should be less than *c*. In the case that the relationship is explained entirely by the mediated pathway (i.e., full mediation), *c′* should equal zero. If the coefficient remains positive, partial mediation is present, which indicates that although the mediator may be important, it does not fully account for the relationship between the dependent and independent variables. Finally, to determine the statistical significance of the proposed mediation pathway, a Sobel test was conducted [277]. This conservative test is used to determine whether the indirect effect of the

independent variable on the dependent variable via the mediator is significantly different from zero. All statistical analyses were conducted using SAS version 9.1.3 and all p-values are two-sided.

6.3 RESULTS

6.3.1 Descriptive Statistics

Among 756 young participants recruited, 384 (50.8%) reported injecting over the study period and were thus eligible for inclusion in this analysis. The majority of eligible participants were recruited from ARYS (n = 203, 52.8%), followed by VIDUS (n = 137, 35.7%) and ACCESS (n = 44, 11.5%). The median age of eligible respondents was 24.2 (interquartile range [IQR]: 22.0 – 26.8), 214 (55.7%) were male, and 244 (63.5%) were of Caucasian ethnicity. At baseline, 187 (48.7%) reported injecting MA at least once in the past six months. The median number of years participants reported injecting was 7 (IQR: 4 – 10). Other sociodemographic, behavioural, and drug use information stratified by baseline self-reported MA injection is reported in Table 6.1.

6.3.2 Bivariate Analyses

Several significant differences between MA injectors and non-MA injectors were observed. The former group reported significantly fewer years injecting: six

versus eight, respectively (χ^2 = 11.0, *df* = 1, *p* = 0.001). As shown in Table 6.1, MA injectors were more likely to be less than 24 years of age (53.8% vs. 41.4%, *p* = 0.016), male (62.7% vs. 51.0%, *p* = 0.023), Caucasian (71.9% vs. 57.8%, *p* = 0.004), and single or casually dating (75.9% vs. 65.0%, *p* = 0.020). Drug use patterns also varied significantly between the two groups, with MA injectors more likely to report non-injection MA use (59.5% vs. 11.2%, *p* < 0.001), but less likely to report non-injection crack, injection cocaine, or injection heroin use (see Table 6.1). At baseline, syringe sharing (25.3% vs. 14.7%, *p* = 0.010) and having difficulty accessing sterile syringes (50.9% vs. 30.9%, *p* = 0.008) were significantly more common among participants who injected MA. No significant differences between groups with respect to HIV status (10.8% vs. 15.1%, *p* = 0.217), or self-efficacy for LHRB (χ^2 = 3.44, *df* = 3, *p* = 0.328) were observed. Odds ratios and confidence intervals for each association are provided in Table 6.1.

6.3.3 Longitudinal Mediation Analyses

The results of the mediation analyses are shown in Figure 6.1. In a longitudinal model adjusting for age, sex, ethnicity, HIV status, relationship status, and self-efficacy for LHRB, MA injection was independently associated with syringe sharing (*c* = 0.48, adjusted odds ratio [AOR] = 1.62, *p* = 0.022). MA injectors were also more likely to report having difficulty accessing syringes (*a* = 0.82, AOR = 2.27, *p* < 0.001), after adjusting for the same set of covariates. When MA injection was

controlled for, difficulty accessing syringes was positively associated with syringe sharing (b = 0.45, AOR = 1.56, p = 0.029). After controlling for difficulty accessing syringes, the coefficient for MA injection lost significance and decreased in magnitude (c' = 0.33, AOR = 1.39, p = 0.134), indicating partial mediation. A Sobel test to examine the indirect effect of difficulty accessing syringes on the relationship between injecting MA and syringe sharing confirmed the significance of the mediation pathway (p = 0.048).

6.4 DISCUSSION

Consistent with previous studies [33, 35, 278], a positive and significant association between MA injection and syringe sharing was observed. Furthermore, participants who injected MA were over twice as likely to report having difficulty accessing sterile syringes compared to other active IDU. In a series of longitudinal regression analyses, the relationship between MA injection and syringe sharing was shown to be largely mediated by difficulty accessing syringes; in fact, when this variable was included in the models, the association between injecting MA and syringe sharing became non-significant. These results suggest that the high prevalence of injecting-related risk behaviour observed among young MA users may be driven predominately by ongoing social and structural barriers to accessing HIV prevention programs.

Previous studies have demonstrated that reporting difficulty accessing sterile syringes is one of the primary risk factors for syringe sharing, even in the presence of well-established syringe exchange programmes [268, 279]. In Vancouver, programmatic barriers, including restrictive (i.e., one-for-one) exchange policies, were historically among the most common reasons for having difficulty accessing these services [279, 280]. In response to these concerns, the health authority began a series of NSP policy reforms in 2000, including: a shift to syringe distribution and recovery instead of one-for-one exchange; decentralising services to expand the number of sites distributing supplies; and diversifying the delivery of these services to include fixed-site programs, outreach, foot patrols, peer-run programs, and the distribution of supplies at all local health clinics and pharmacies. These policy changes have recently been shown to have resulted in large reductions in syringe sharing among IDU and have contributed to declining HIV incidence [257].

It is concerning however that young MA injectors continue to report having difficulty accessing sterile syringes in an era of high coverage, widespread syringe distribution programmes. Further research will be required to determine the most common individual, social, and structural barriers experienced by young people who inject MA, although it is likely that some of the factors previously reported by adult IDU [265, 267] also affect this population's access to HIV prevention interventions. For example, since geographic proximity to NSPs is an important

predictor of programme utilization and risk behaviour [280, 281], it is possible that many MA injectors either are not in close proximity to NSPs or avoid areas where they are located. For example, ethnographic work in this setting has shown how youth perceive neighbourhoods with extensive open drug scenes (and thus a concentration of NSPs and other HIV prevention services) as being environments of exceptional danger and risk and actively seek to avoid it [282]. Other ethnographic research conducted in the United States indicates that MA injectors are less likely to be in contact with outreach programs, due to the fact that they are younger and belong to more segregated social networks [283]. MA injectors may be more likely to use drugs and thus require sterile injecting equipment when many services are closed, including at night or early in the morning. Finally, young MA injectors may feel uncomfortable or unwelcome accessing HIV prevention programs that cater largely to adult opioid users [284].

While structural barriers clearly contribute to ones' (in)-ability to access HIV prevention services, other individual factors and social influences may be operating to prevent MA injectors from obtaining sterile syringes. For example, MA users may have difficulty accessing safer injecting equipment while on multi-day drug "binges" or during periods of MA-induced psychological distress [285]. Prior research has also shown that MA injectors (compared to heroin users) are more likely to inject in groups or with friends, which may promote the sharing of syringes

and other injecting equipment [286]. Future research will be required to identify at what level barriers to service access are operating, and how these individual, social, and structural barriers intersect to produce HIV-related harms.

The results of this study have a number of important implications for future interventions that seek to address injection-related risk behaviour among young MA injectors. These results suggest, as do others [283, 287], that MA users are younger and more likely to be segregated from well-established injection drug using social networks. Interventions and policies that promote secondary syringe distribution (i.e., receiving supplies from peers who access NSPs) are therefore recommended. Youth-driven models of syringe distribution, including fixed and outreach-based services run by or catered specifically to youth, have also been shown to be successful in numerous settings [77, 288]. In order to meet the needs of MA injectors, current youth-specific services should develop harm reduction-based policies and interventions that can accommodate young people who are actively injecting drugs in addition to operating programmes that seek to prevent injection initiation among high-risk youth. Given the effectiveness of supervised injecting facilities (SIFs) at reducing syringe sharing among hard-to-reach and hidden populations [274], the development of youth-friendly SIFs that are acceptable to individuals injecting MA should also be considered. Furthermore, interventions that harness social influence and promote positive peer norms among young IDU

networks are effective at reducing risk behaviour and may encourage uptake of HIV prevention and other health services [289, 290]. Efforts must be made to develop effective HIV prevention strategies tailored specifically to MA injectors, given the unique injecting practices and health issues experienced by this population [5]. Finally, future research in this area may benefit from the incorporation of novel methodologies (including for example geographic information systems [GIS]) to determine the geographic distribution, operation hours, and coverage of services that would most effectively meet the needs of this vulnerable IDU subpopulation. For example, a recent study in New York City used GIS methodology to demonstrate substantial cross-neighbourhood variation in NSP access [291], although it remains to be determined whether specific subgroups of injectors (including young IDU and MA users) are disproportionately affected by the inequitable geographic distribution of services in this setting.

When drawing conclusions from this study, several limitations should be noted. The ARYS, VIDUS, and ACCESS cohorts are not random samples of the populations they seek to represent; therefore, generalisability to the larger drug-using community or other settings may be limited. It is important to note however that the sociodemographic characteristics of these samples are similar to other street youth and injection drug-using studies that have been conducted in Canada [292, 293]. A second limitation is that all behaviours assessed in this study were self-

reported, and it is possible that stigmatized behaviours including syringe sharing may have been underreported. However, there is no reason to believe the magnitude of this bias would differ between MA injectors and non-injectors; therefore, if present, socially desirable reporting would attenuate these results towards the null. Previous studies involving young people have also shown that self-reports are reliable measures of drug use and other HIV risk behaviours [161, 162]. Thirdly, the models could not be adjusted for a robust set of potential confounders, due to a small sample size and concerns regarding over-fitting. Finally, although the statistical methods used in these analyses preclude inference regarding causality, the longitudinal nature of the study design demonstrates the temporal stability of the observed relationships. Longer-term studies are required to determine whether improvements in syringe access mitigate injection risk behaviours among young people who inject MA.

Young MA injectors continue to be at an increased risk of syringe sharing, even in the presence of well-established, high coverage syringe distribution programmes. A series of meditational analyses revealed that having difficulty accessing sterile syringes is frequently reported by young MA-using IDU, and that these barriers largely accounted for the relationship between injecting MA and syringe sharing. Novel, youth-driven interventions, including the expansion of current services to adequately meet the needs of this population, are urgently

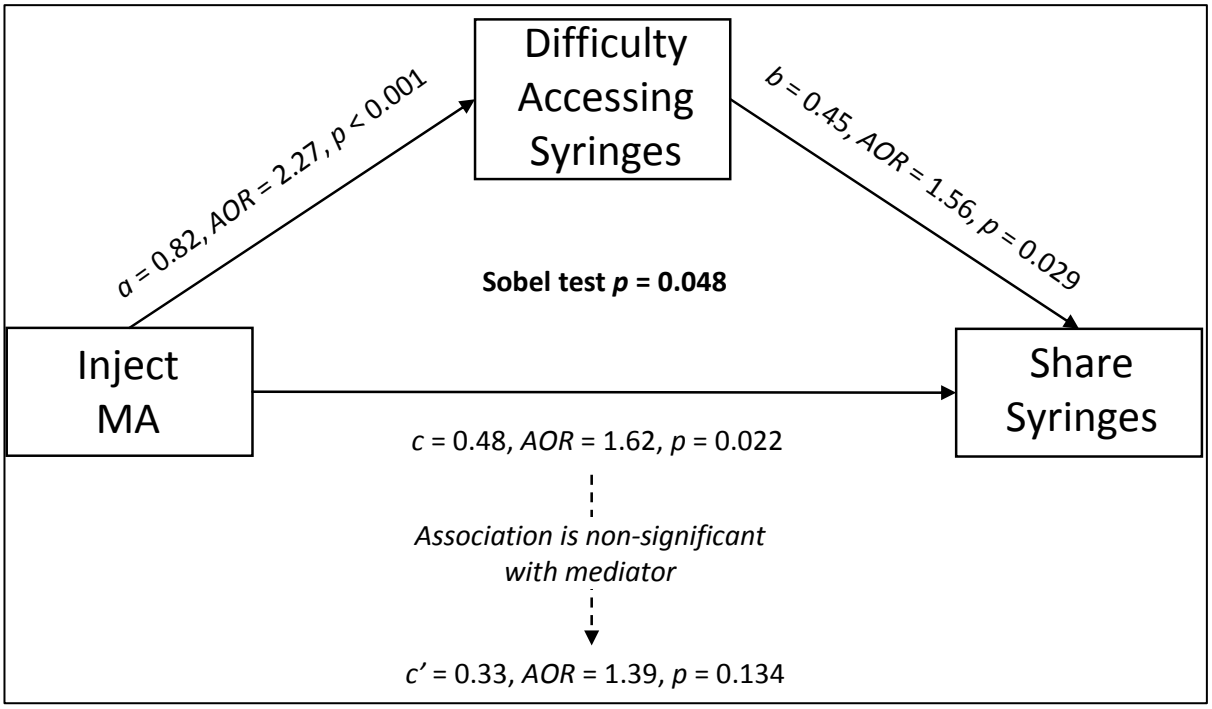
required to reduce blood-borne disease transmission among young people who inject methamphetamine.

Table 6.1: Baseline characteristics of young injection drug users stratified by self-reported methamphetamine injection (*n* = 384).

Characteristic	Inject MA (*n* = 187) (*N*, %)	Did not inject MA (*n* = 197) (*N*, %)	OR (95%CI)	*p*-value
Age				
<24	99 (53.8)	79 (41.4)	1.64 (1.10 – 2.50)	0.016
≥24	85 (46.2)	112 (58.6)		
Sex				
Male	116 (62.7)	98 (51.0)	1.61 (1.06 – 2.44)	0.023
Female	69 (37.3)	94 (49.0)		
Ethnicity				
Caucasian	133 (71.9)	111 (57.8)	1.87 (1.21 – 2.87)	0.004
Other	52 (28.1)	81 (42.2)		
Relationship status				
Single/dating	142 (75.9)	126 (65.0)	1.70 (1.09 – 2.66)	0.020
Married/regular partner	45 (24.1)	68 (35.0)		
HIV status				
Positive	20 (10.8)	29 (15.1)	0.68 (0.37 – 1.25)	0.217
Negative	165 (89.2)	163 (84.9)		
Non-injection MA use†				
Yes	110 (59.5)	22 (11.2)	11.60 (6.81 – 19.74)	<0.001
No	75 (40.5)	174 (88.8)		
Non-injection crack use†				
Yes	126 (67.4)	151 (77.0)	0.62 (0.39 – 0.97)	0.035
No	61 (32.6)	45 (23.0)		
Injection cocaine use†				
Yes	56 (30.6)	82 (42.3)	0.60 (0.39 – 0.92)	0.019
No	127 (69.4)	112 (57.7)		
Injection heroin use†				
Yes	111 (61.3)	157 (80.1)	0.39 (0.25 – 0.63)	<0.001
No	70 (38.7)	39 (19.9)		
Syringe Sharing†				
Yes	47 (25.3)	29 (14.7)	1.96 (1.17 – 3.28)	0.010
No	139 (74.7)	168 (85.3)		
Difficulty Accessing Syringes†				
Yes	89 (50.9)	56 (30.9)	2.31 (1.50 – 3.56)	0.008
No	86 (49.1)	125 (69.1)		

Notes: not all cells add to 100% due to missing values; † during the six months prior to the date of the first interview during which injection drug use was reported over the study period.

Figure 6.1: Mediation analysis of the direct and indirect effects of injection methamphetamine (MA) use on syringe sharing among young injection drug users (*n* = 384).



Note: all models adjusted for age, sex, ethnicity, HIV status, relationship status, and self-efficacy for limiting HIV risk behaviour.

CHAPTER 7

DISCUSSION, IMPLICATIONS, DIRECTIONS FOR FUTURE RESEARCH, AND CONCLUSIONS

7.1 SUMARY OF STUDY FINDINGS

The purpose of this research project was to conduct a series of epidemiologic studies examining the full spectrum of MA initiation, use, and harms among injection drug users and street-involved youth. Chapter 2 includes the results of a systematic review that sought to characterise the known adverse health outcomes associated with MA use among young people. The intention of this review was three-fold: to guide the development of empirical analyses and examine outcomes that are understudied; to evaluate systematically scientific evidence suggesting associations between MA use and specific health problems; and finally, to inform the development of interventions that effectively prevent and mitigate MA-related harms.

Drawing on the risk environment framework, subsequent quantitative research papers examined the combinations of individual, social, environmental, and structural factors that predicted MA initiation, influenced patterns of MA use, and exacerbated exposure to MA-related harms. In Chapter 3, a longitudinal analysis of MA initiation was presented, demonstrating a high incidence of MA

injection among young IDU, stimulant users, homeless individuals, and those involved in the city's open drug scene. These findings were consistent with the risk environment framework, which posits that micro- and macro-level factors intersect to exacerbate drug-related risks, and in this case, increase the likelihood of initiating MA injection.

The considerable body of literature examining sexual risk behaviour and HIV transmission among men who have sex with men (MSM) informed the research described in Chapter 4. The primary objective of this analysis was to extend the conceptualisation of MA-related HIV risks to include not only individual behaviour, but also gendered social interactions and structural vulnerabilities. As in previous studies [47, 98, 209], MA use was found to be greatly elevated among sexual minority individuals. Of note, this particular analysis revealed that differential sets of HIV risks and vulnerabilities were observed for males and females. For example, the strongest predictor of MA use among sexual minority males was having a legal order or area restriction. In contrast, the strongest predictor of MA use among sexual minority females was sexual vulnerability in the context of sex work. These results suggest that interventions addressing MA-related harms among sexual minorities may need to be informed by more nuanced understandings of the intersections between drug use, social-structural HIV vulnerabilities, and gender/sexual identities.

In Chapter 5, the impact of MA injection on emergency department utilisation was examined. Although accessing emergency health care does not necessarily imply the existence of MA-related health issues per se, it is an important marker of acute co-morbid conditions and MA-associated health care utilisation patterns, and therefore has significant implications for policy and programme development. Of particular concern was the greatly increased hazard of ER utilisation among youth who frequently inject MA. Although prior research has examined the impact of MA use on rates of emergency care [242, 250], this is the first study to show an independent association between MA injection and ED utilisation among street-involved youth. Furthermore, the high rate of ED visits directly related to substance dependence and overdose highlight the need for improved integration of youth-friendly addiction treatment services within emergency care settings.

The analysis presented in the penultimate chapter sought to examine further the previously observed relationship between MA use and syringe sharing [33-35]. Given that having difficulty accessing syringe distribution programmes is a primary driver of injection-related risk among adult IDU [268, 279], I hypothesised that syringe access barriers would mediate the relationship between MA injection and syringe sharing among drug-using youth. Consistent with this hypothesis, a formal mediation analysis demonstrated that the increased risk of syringe sharing observed among young MA injectors was driven largely by difficulties accessing sterile

syringes. Although further research is required to clarify at what level(s) these barriers may be operating, these results point to the importance of developing new interventions to reduce service barriers and ameliorate MA-related risks experienced by this population.

7.2 STUDY STRENGTHS & UNIQUE CONTRIBUTIONS

Collectively, these research findings offer novel and important insights into the epidemiology of methamphetamine use among marginalised populations in Canada. Through an exploration of MA initiation, trajectories, and related harms, these results have the ability to guide both the timing and targets of future public health interventions. Furthermore, it is my hope that this research will inform the development of a broad set of evidence-based policies and programmes, including those that involve vulnerable subpopulations such as sexual minority groups and youth, to prevent MA initiation and reduce MA-related harms.

This project has been guided by the social epidemiologic theories of HIV transmission and substance use, which explicitly posit that interactions amongst individual, social, and structural factors shape both the population distribution of vulnerability and one's individual propensity for engagement in risk behaviour within these contexts [294, 295]. In doing so, this research extends the extensive body of literature examining MA use among MSM, which has largely sought to

uncover the psychological and cultural factors that influence MA use and dependence [78, 86, 106]. The primary theoretical contribution of this work is therefore to advance the conceptual context of MA-related research so as to include not only individual-level behavioural risk factors as the important levers in mitigating MA-related harms, but also to bring into focus aspects of the context in which these behaviours occur.

The improved integration of social epidemiologic approaches within MA research will undoubtedly point to novel areas of intervention, including those traditionally conceived as being outside the health sector. Although the notion of combination interventions (e.g., biomedical, behavioural, and structural) are increasingly recognized as instrumental in mounting effective responses to HIV epidemics among marginalised groups [296, 297], research involving MA has only recently begun to adopt similar frameworks [298]. Furthermore, current population-level strategies to reduce MA use and prevent health and social harms are often of limited effectiveness. For example, existing policy strategies, including precursor control regulations, generally tend to have restricted and transient effects [56, 298]. The state of evidence regarding universal preventive interventions for adolescents is of similar equivocality [72, 154]. By examining a comprehensive range of individual, social, environmental, and structural factors, this research illuminates several novel

targets of intervention (discussed in detail in section 7.4) that might more effectively address MA use among vulnerable populations.

As demonstrated in Chapter 2, many inferences regarding the impact of MA use on health rely upon cross-sectional studies of convenience or treatment samples. The limitations of cross-sectional designs have been well described, particularly in terms of assessing the direction of causality between independent and dependent variables [299]. This issue is of great salience in substance use research involving young people. For example, some authors have noted the failure of many epidemiologic studies to resolve the direction of causality between cannabis use and onset of psychotic symptoms in adolescents [300]. Research involving MA use has been subjected to similar criticisms [301, 302]. Therefore, an important contribution of this research is to demonstrate that longitudinal analytic techniques are increasingly necessary to address many outstanding research questions and more appropriately inform the development of MA prevention and intervention strategies. Although all analyses described in this dissertation are longitudinal, definitive causal inferences remain limited; thus, further innovation is required to develop methods that elucidate causal pathways and underlying mechanisms.

7.3 LIMITATIONS

Although specific limitations are presented in the discussion section of each research chapter, several general cautions when interpreting these finds are warranted. One of the primary limitations of these studies is that the majority of independent variables and outcomes relied on self-report. Retrospective self-reporting of stigmatised activities and behaviours is prone to a wide array of biases, including recall bias and socially desirable reporting [303, 304]. A number of techniques were used to mitigate the magnitude of these potential biases. For example, calendars, prompts, and other memory tools are used during all VIDUS, ACCESS, and ARYS interviews. These techniques have been shown to reduce the tendency to "telescope" rare events into the recall period of interest (i.e., past six months) and to under-report everyday activities [305]. Furthermore, sensitive questions are placed later in the questionnaire in order to allow subjects to become comfortable with the interview process and to build rapport with the interviewers. Several reliability studies have also demonstrated the validity of IDU and adolescent self-report of drug use and other behaviours [159, 306-308]. For these reasons, it is anticipated that the impacts of these biases (if present) are negligible. Finally, some variables such as HIV status and ED utilisation were not collected via self-report and thus are not subject to recall bias or socially desirable reporting.

A second important limitation is that the cohorts from which the data were derived are not random samples of the populations they seek to represent. However, extensive efforts were taken to maximise the representativeness of the samples, including close collaboration with relevant service agencies to identify eligible individuals, snowball sampling, and street-based outreach conducted in a variety of local neighbourhoods where drug users are known to congregate.

7.4 RECOMMENDATIONS

Specific recommendations are provided at the conclusion of each chapter; therefore, I focus here on the overarching recommendations arising from the cumulative body of research. These recommendations are informed by themes that have appeared throughout this dissertation and will be elaborated upon in this section. They include: the implementation of combination multi-level approaches; the creation of population-specific versus universal interventions; the meaningful engagement of young people in service provision; and the evaluation of interventions using rigorous scientific approaches.

Services that are comprehensive and integrated across health and other sectors are now thought to produce the most significant and sustained reductions in HIV risk and transmission at a population level [297, 309]. For example, a recently published consensus statement by the United Nations Office

of Drugs and Crime (UNODC), UNAIDS, and the World Health Organization (WHO) emphasises the provision of comprehensives packages of evidence-based interventions to ensure universal access to HIV prevention and treatment services for IDU [310]. It is not surprising then that combinations of approaches (including those at the individual, community, and policy level) are also recommended to address global MA consumption and related harms [6, 298].

Although combination interventions, particularly those with sufficient scientific evidence base, are certainly worthy of implementation, the results of this research suggest that some caution is warranted. For example, within integrated MA approaches, the relative distribution of resources across program components is rarely explicated. Several analyses have shown significant disparities in funding allocations within "comprehensive" drug control strategies, often resulting in an over-reliance on law enforcement initiatives at the expense of evidence-based treatment and harm reduction interventions [55]. Furthermore, attempts to implement supply control strategies in the absence of effective demand reduction interventions can result in unintended consequences. The displacement of MA production and consumption from the United States to Mexico following the implementation of strict precursor regulations in the former is one such example [6]. A recent analysis of Canadian hospital admissions also confirmed that these regulations were

associated with an *increase* in MA-related acute care visits in Canada, due perhaps to shifts in MA production from small-scale operations to larger organizations that tend to produce higher purity MA [56]. Of further concern is that the unintended adverse impacts of these population-level approaches are likely concentrated among individuals who already experience substantial health inequity and systemic barriers to accessing care. It is therefore recommended that future combination interventions not only allocate resources based upon the best-available evidence, but also include special consideration for vulnerable groups (e.g., street-involved youth, LGBT communities) most likely to engage in and experience harms from MA use.

Many population interventions that have been implemented (e.g., regulation of precursor chemicals, mass media campaigns) are rarely subjected to rigorous evaluation; furthermore, the small number of studies that have been conducted tend to demonstrate transient or minimal effects [58, 103, 154, 298]. Additionally, universal approaches may fail to reach hidden populations or meet the needs of specific vulnerable subpopulations [311]. Throughout this thesis, I have argued that interventions specifically designed for MA users and affected communities should constitute a central component of comprehensive prevention, treatment, and harm reduction strategies. For example, the analysis presented in Chapter 6 demonstrated that compared to other young IDU, MA

injectors experience unique barriers to accessing harm reduction and HIV prevention programmes. Although interventions designed specifically for young MA users exist (e.g., peer-led outreach, tailored addiction treatment services and harm reduction programmes), there is a scarcity of research to inform policy in this area [312, 313]. Increased funding for MA-specific interventions (specifically those involving marginalised populations) and strengthened research capacity to evaluate these interventions are required. Furthermore, these approaches should be integrated within larger multi-level interventions to prevent unintended impacts such as shifts from MA use to other the use of drugs that may be of equal or greater harm.

Public health interventions that aim to reduce MA-related harms and connect youth with appropriate care and services should seek to meaningfully engage young people in the development, implementation, and evaluation of these programs. The youth engagement model suggests that incorporating youths' perspectives of the contexts, use, and harms of MA into harm reduction programs and health services is an integral component of effective strategies to address underlying needs [314]. These models of intervention are not without challenges. Peer-based education and support models have been critiqued by several authors, noting for example that peer education approaches may only further essentialise behaviour as "safe" or "risky" [201]; furthermore, they may

fail to recognize the social/structural context within which these activities take place. To guide intervention research and practice in this area, the evaluation of successful youth-driven programmes that can serve as best-practice models to address MA use among youth are recommended.

7.5 FUTURE RESEARCH DIRECTIONS

This project has several important implications for future directions in substance use research. The collective body of findings highlights the importance of longitudinal data in monitoring evolving community drug use patterns. Although changes in community MA use patterns have been observed in other settings [39, 173], the studies presented herein are somewhat unique in that they captured a period of rapidly escalating MA prevalence and harms [33, 50]. Long-term studies will now be required to determine the factors that influence the direction of MA "epidemics" (i.e., whether use remains stable among some populations, continues to increase or declines). Several indicators have suggested that the prevalence of MA use in some areas of North America is decreasing [7], and further research is required to elucidate the drivers of these population-level reductions in MA consumption.

A second area of future research is the examination of multiple substance use and the extent to which polydrug use exacerbates exposure to health risks and

complicates our understanding of treatment for substance dependence. Some studies have demonstrated that MA use often co-occurs with that of other drugs [32, 315]; furthermore, MA users who report higher levels of polydrug use are more likely to engage in sexual and injection-related HIV risk behaviour [302, 316]. For these reasons, future studies should seek to contextualise the use and harms of MA within trajectories and typologies of drug use that more accurately reflect true patterns of use in the population. While the use of multiple substances over time can and has been analysed quantitatively, (random effects growth models and latent class analyses for example), these models can be difficult to construct and interpret [315]. Future research is therefore needed to guide the development of conceptual frameworks and analytic approaches that can be used to improve our understanding of the relationships between the use of multiple drugs and the impact that polydrug use has on individuals and their communities.

Many authors have noted the absence of effective pharmacologic and behavioural therapies for the treatment of MA use, particularly among adolescents [132, 317, 318]. In accordance with the combination intervention approach, further research is needed to determine whether pairing these strategies with structural interventions (e.g. increased access to stable housing, drug policy changes, reforms to law enforcement practices) may be most effective at preventing MA initiation and simultaneously reducing harm. Evaluations of combination interventions (that

include structural components) are not without difficulty; however, these challenges are not insurmountable, and several evaluations of structural interventions (primarily within HIV prevention) have been conducted [319, 320]. The evaluation of "natural experiments" is also an important means of evaluating population-level impacts of (un)-intended policy or program changes and should be considered. For example, time-series analyses have been used to demonstrate that a sharp reduction in heroin supply in Australia was associated with subsequent increases in MA use among some populations [321].

This dissertation has focused exclusively on MA use and its relationship to HIV acquisition and risk for transmission. Further research is needed to determine the relationship between MA use and HIV pathogenesis among HIV-infected users. For example, while very preliminary research indicates that MA users receiving highly active antiretroviral therapy (HAART) are less likely to achieve viral load suppression [322], the causal pathways underlying this association remain to be determined. Although biologic mechanisms and drug interactions have been proposed by several authors [322, 323], the extent to which adherence and other individual, social, and environmental factors mediate the relationship between MA use and HIV pathogenesis have yet to be investigated.

Finally, although the conceptualisation of much HIV and substance use research is now firmly rooted in the risk environment approach, quantitative

methodological advances are required to more accurately depict the influence and interaction of variables operating at differing levels. For example, although quantitative multi-level frameworks are becoming increasingly popular in some areas of social epidemiology [324], they have yet to contribute significantly to the substance use disciplines. Several recent studies can provide direction [325, 326], but further research is required to address the discord between quantitative methods and conceptual models in this area.

7.6 CONCLUSIONS

This thesis has brought together a collection of quantitative epidemiologic studies investigating the initiation, use, and harms of MA use among marginalised populations in Vancouver. MA users in this setting are at an increased risk of a host of health behaviours and harms, although perhaps not to the extent that some public and academic discourses have previously suggested. Collectively, these findings indicate that comprehensive interventions need to be implemented to more effectively address the health and social inequities experienced by people who use methamphetamines. In order to avoid further stigmatisation of MA users and prevent increased vulnerability of street-entrenched young people, it is imperative that future interventions be based on sound evidence and be evaluated to the highest standards of scientific rigour.

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APPENDIX 1: Electronic search strategy to identify studies examining health outcomes associated with methamphetamine use

Database	Search Strategies
Ovid MEDLINE® 1950 to Present with Daily Update **Searched:** **January 2, 2009** **472 results, 48 duplicates = 424 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25 to (english language)
Ovid MEDLINE® In-Process & Other Non-Indexed Citations **Searched:** **January 2, 2009** **37 results, 20 duplicates = 441 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25 to (english language)
All EBM Review – Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED **Searched: January 2, 2009** **36 results, 0 duplicates = 477 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25 to (english language)
EMBASE 1988 to 2008 Week 52 **Searched: January 2, 2009** **395 results, 136 duplicates = 736 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25 to (english language)
International Pharmaceutical Abstracts 1970 to Nov 2008 **Searched: January 2, 2009** **4 results, 3 dupliates = 737 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25 to (english language)
Journals@Ovid Full Text Dec 31, 2008 **Searched:** **January 2, 2009** **616 results, 27 duplicates = 1326 potentially relevant studies**	1. (meth?amphetamine$ or metamphetamine$ or methylamphetamine$ or "crystal meth$" or metamfetamine$ or "d-methamphetamine$" or "dextro-methamphetamine$").mp. 2. randomized controlled trial.pt. 3. controlled clinical trial.pt. 4. "randomi?ed controlled trial$".mp. 5. "random allocation".mp. 6. "double blind method".mp. 7. "single blind method".mp. 8. clinical trial.pt. 9. exp Clinical Trial/ 10. ((clin$ or control$) adj25 trial$).ti,ab. 11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 12. Placebos/ 13. placebo$.ti,ab. 14. random$.ti,ab. 15. Research Design/ 16. Comparative Study/ 17. exp case-control studies/ or exp cohort studies/ or exp longitudinal studies/ or exp follow-up studies/ or exp prospective studies/ or exp evaluation studies/ or exp cross-sectional studies/ 18. (cohort or "case?control$" or control$ or observational or prospectiv$ or retrospectiv$ or "time series" or "time?series" or "case comparison" or "case?comparison" or "case referent" or "case?referent" or "cross sectional" or "cross?sectional" or risk$ or effectiveness or "multi cent$" or multi?cent$ or multi?site or "multi site").ti,ab. 19. multicenter study.pt 20. (ct or di or ep or et or pc or rh or th or dm).fs. 21. exp Risk Factors/ or exp Causality/ or exp Behavior Therapy/ or exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ 22. or/2-21 23. 22 and 1 24. (child$ or schoolchild$ or p?ediatric or adolescent$ or juvenil$ or teen$5 or youth$ or "young adult$" or

Database	Search Strategies
	highschool$ or "high school$").mp. 25. 24 and 23 26. limit 25
CINAHL with Full Text (EBSCOhost) **Searched:** **January 3, 2009** **199 results, 57 duplicates = 1468 potentially relevant studies**	S1. (MH "Methamphetamine+") S2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" S3. S2 or S1 S4. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" S5. S4 and S3 S6. S5 limit language: English
PsychINFO (EBSCOhost) **Searched:** **January 3, 2009** **402 results,** **145 duplictes =** **1725 potentially relevant studies**	S1. MJ "Methamphetamine*" or DE "Methamphetamine*" S2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" S3. S2 or S1 S4. S3 limit publication year: 1990-2009; language: English S5. S4 limit population group: Human, Male, Female, Inpatient, Outpatient S6. S5 limit age groups: Childhood (birth-12 yrs), School Age (6-12 yrs), Adolescence (13-17 yrs), Young Adulthood (18-29 yrs) S7. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" S8. S5 and S7 S9. S6 or S8
Science Citation Index Expanded and Social Sciences Citation Index (via Web of Science®) **Searched:** **January 3, 2009** **206 results,** **125 duplicates =** **1806 potentially relevant**	1. TS=(meth$amphetamine* or metamphetamine* or methylamphetamine* or "crystal meth*" or metamfetamine* or "d-methamphetamine*" or "dextro-methamphetamine*" or "meth amphetamine*") 2. TS=("randomi$ed controlled trial*") 3. TS=("controlled clinical trial*") 4. TS=("random allocation") 5. TS=("double blind" OR "single blind*") 6. TS=("clinical trial*") 7. TS=(placebo* or random*) 8. TS=("research design") 9. TS=("comparative stud*" or "evaluation stud*" or "follow$up stud*" or "prospective stud*" or "controlled

Database	Search Strategies
studies	trial*") 10. TS=(cohort or "case$control*" or "case control" or control* or observational or prospectiv* or retrospectiv* or "time series" or "time$series" or "case comparison" or "case$comparison" or "case referent" or "case$referent" or "cross sectional" or "cross$sectional" or risk* or effectiveness or "multi cent*" or multi$cent* or multi$site or "multi site" or longitudinal or predict* or prevent* or risk* or causal*) 11. #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 12. #11 AND #1 13. TS=(child* or schoolchild* or p$ediatric or adolescent* or juvenil* or teen* or youth* or "young adult*" or highschool* or "high school*") 14. #13 AND #12 15. #14 AND Language=(English) AND Document Type=(Article OR Correction, Addition OR Correction, Addition OR Database Review OR Discussion OR Editorial Material OR Letter OR Meeting Abstract OR Meeting Summary OR Meeting-Abstract OR Proceedings Paper OR Reprint OR Review)
CAB Direct (CAB Abstracts and Global Health) – Dec 24, 2008 **Searched:** **January 3, 2009** **47 results, 33 duplicates = 1820 potentially relevant studies**	1. child* or youth* or adolescen* or "young adult" 2. methamphetamine* 3. methylamphetamine* 4. 2 or 3 5. 4 and 1
ERIC **Searched:** **January 3, 2009** **23 results,** **1843 potentially relevant studies**	1. methamphetamine* or "crystal meth" or "meth amphetamine" or "meth-amphetamine" or metaphetamine* or methylamphetamine* or metafetamine* 2. publication types: journal articles and/or numerical/quantitative data OR reports descriptive OR reports evaluative OR reports research
PubMed ® **Searched:** **January 4, 2009**	1. methamphetamine[MeSH] 2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or methylamphetamine* or "crystal meth*" or metamfetamine* or "d-methamphetamine*" or "dextro-methamphetamine*" 3. #2 or #1

Database	Search Strategies
446 results, 336 duplicates = 1953 potentially relevant studies	4. child or children or schoolchild* or pediatric* or paediatric* or adolescent* or juvenil* or teen* or youth* or "young adult*" or highschool* or "high school*" 5. #4 and #3 6. #5 Limits: Publication Date from 1990/01/01 to 2009/01/04, Humans, Clinical Trial, Letter, Meta-Analysis, Randomized Controlled Trial, Review, Classical Article, Comparative Study, Controlled Clinical Trial, Corrected and Republished Article, English Abstract, Evaluation Studies, Government Publications, Historical Article, Journal Article, Lectures, Multicenter Study, Validation Studies, English
Sociological Abstracts **Searched: January 9, 2009** **61 results, 21 duplicates = 1993 potentially relevant studies**	1. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or methylamphetamine* or "crystal meth*" or metaphetamine* or metafetamine* 2. child* or schoolchild* or pediatric* or paediatric* or adolescent* or juvenil* or teen* or "young adult*" or youth*
SocINDEX with Full Text (EBSCOhost) **Searched: January 9, 2009** **121 results, 27 duplicates = 2087 potentially relevant studies**	1. SU methamphetamine 2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" 3. S2 or S1 4. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" 5. S4 and S3 6. limit S5: Document Type: Abstract, Article, Book Chapter, Book Entry, Conference Paper, Dissertation, Editorial, Erratum, Essay, Letter, Proceeding, Report
Academic Search Complete (EBSCOhost) **Searched: January 9, 2009** **97 results, 59 duplicates = 2125 potentially relevant studies**	1. SU methamphetamine 2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" 3. S2 or S1 4. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" 5. S4 and S3 6. limit S5: Scholarly (Peer Reviewed) Journals; 7. random* or control* or trial* or blind* or placebo* or comparative* or "case-control" or "case control" or cohort or longitudinal or "follow-up" or "time series" or "time-series" or prospective or retrospective or "case

Database	Search Strategies
	comparison" or "case-comparison" or "case referent" or "case-referent" or "cross sectional" or "cross-sectional" or risk* or effectiveness or evaluation or "multi cent*" or "multi-cent*" or "multi-site" or "multi site" or epidemiol* or "public health" or observational 8. S7 and S6
LGBT Life with Full Text **Searched:** **January 19, 2009** **8 results, 0 duplicates = 2133 potentially relevant studies**	1. SU methamphetamine 2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" 3. S2 or S1 4. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" 5. S4 and S3 6. limit S5 to Publication Type: Academic Journal
Biomedical Reference Collection: Comprehensive (EBSCOhost) **Searched:** **January 19, 2009** **11 results, 0 duplicates = 2144 potentially relevant studies**	1. SU methamphetamine 2. methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" 3. S2 or S1 4. child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*" 5. S4 and S3
ProQuest Dissertations and Theses – Full Text **Searched:** **January 19, 2009** **30 results, 9 duplicates = 2165 potentially relevant studies**	1. (methamphetamine* or "meth amphetamine*" or "meth-amphetamine*" or metamphetamine* or methylamphetamine* or "crystal meth*" or metafetamine) AND (child* or schoolchild* or pediatric or paediatric or adolescent* or juvenile* or teen* or youth* or "young adult*" or highschool* or "high school*")
Conference Papers Index **Searched:**	1. (methamphetamine* or ("meth amphetamine*") or "meth-amphetamine*") or (metaphetamine* or ("crystal meth*") or methylamphetamine*) 2. (child* or schoolchild* or pediatric*) or (paediatric* or adolescent* or juvenile*) or (teen* or youth* or

Database	Search Strategies
January 19, 2009 **20 results, 0 duplicates = 2185 potentially relevant studies**	("young adult*") 3. 1 and 2
Native Health Research Database **Searched: January 19, 2009** **2 results, 0 duplicates = 2187 potentially relevant studies**	1. methamphetamine 2. limit 1 to publication type: journal article, research manuscript, conference paper, evaluation study, comment, conference report, special studies/intiatives, review, multidisciplinary case study, commentary, review article, report, validation study, journal article comment, statistical report
BioMed Central **Searched: January 31, 2009** **20 results, 0 duplicates = 2207 potentially relevant studies**	1. (methamphetamine* OR "meth amphetamine*" OR "meth-amphetamine*" OR metamphetamine* OR methylamphetamine* OR "crystal meth*" [TIAB]) 2. (child* OR schoolchild* OR pediatric OR paediatric OR adolescent* OR juvenile* OR teen* OR youth* OR "young adult*" OR highschool* OR "high school*") [TIAB] 3. 2 and 1
NLM Gateway Meeting Abstracts **Searched: January 31, 2009** **107 results, 1 duplicates = 2313 potentially relevant studies**	1. methamphetamine

*** 228 additional duplicates found = 2085 potentially relevant unique records found**

APPENDIX 2: Checklist for quality assessment of eligible studies in systematic review

Domain	Criteria	Scoring
Reporting	Is the hypothesis/aim/objective of the study clearly described?	yes (1) or no (0)
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	yes (1) or no (0)
	Are the characteristics of the individuals included in the study clearly described?	yes (1) or no (0)
	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	yes (1) or no (0)
	Are the main findings of the study clearly described?	yes (1) or no (0)
	Does the study provide estimates of the random variability in the data for the main outcome (IQR, standard deviation, etc.)?	yes (1) or no (0)
	Have actual probability values been reported (e.g., 0.035 rather than <0.05 for the main outcomes except where the probability value is <0.001?	yes (1) or no (0)
External Validity	Were the subjects that were asked to participate in the study representative of the entire population from which they were recruited?	yes (1), no (0) or undetermined (0)
	Were those subjects who were prepared to participate in the study representative of the entire population from which they were recruited?	yes (1), no (0) or undetermined (0)
Internal Validity – Bias	If the results of the study were based on "data dredging", was this made clear?	yes (1), no (0) or undetermined (0)
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the exposure and outcomes the same for cases and controls?	yes (1), no (0) or undetermined (0)
	Were the statistical tests used to assess the main outcomes appropriate?	yes (1), no (0) or undetermined (0)
	Were the main outcome measures used accurate (valid and reliable)?	yes (1), no (0) or undetermined (0)

Domain	Criteria	Scoring
Internal Validity – Confounding	Were the patients in different groups (trials or cohort studies) or were cases and controls (case-control studies) recruited from the same population?	yes (1), no (0) or undetermined (0)
	Were study subjects in different groups (trial and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	yes (1), no (0) or undetermined (0)
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	yes (1), no (0) or undetermined (0)
	Were losses to follow-up taken into account?	yes (1), no () or undetermined (0)
Power	Did the study have sufficient power to detect a significant different between the two groups (trial and cohort studies) or cases and controls (case-control studies)?	yes (1), no (0) or undetermined (0)
Total		**/18**