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Characterizing the dynamic relationship between methamphetamine use, sleep, and sexual risk behaviors in men who have sex with men living with or at high risk of acquiring HIV in Los Angeles

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A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Allison Rosen

2022

ABSTRACT OF THE DISSERTATION

Characterizing the dynamic relationship between methamphetamine use, sleep, and sexual risk behaviors in men who have sex with men living with or at high risk of acquiring HIV in Los Angeles

by

Allison Rosen
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2022
Professor Pamina M. Gorbach, Chair

Background: Methamphetamine use is highly prevalent among men who have sex with men and particularly those living with HIV, but knowledge of the long-term dynamics and associated health outcomes is limited. This study aimed to longitudinally investigate the interdependence between methamphetamine use, sleep deficiency and sexual and HIV risk behaviors among men who have sex with men living with or at high risk of acquiring HIV in Los Angeles, CA.

Methods: All analyses used data collected between August 2014 and February 2022 from a cohort of men who have sex with men living with or at high risk of acquiring HIV in Los Angeles, CA. Chapter 2 used a multistate Markov model to compare natural histories of methamphetamine use by HIV-status and substance use treatment status. Chapter 3 used logistic regression and conditional growth curve models to investigate the association of methamphetamine use with sleep deficiency. Chapter 4 used logistic regression to examine the joint association of sleep deficiency and methamphetamine use with sexual risk behaviors, HIV risk behaviors, STI incidence, and HIV viral load.

Results: In Chapter 2, those living with HIV were less likely to transition from no to occasional methamphetamine use and from occasional to no methamphetamine use. Those who reported receiving substance use treatment at a study visit were more likely to have decreased methamphetamine use at their next study visit. In Chapter 3, those who reported methamphetamine use were more likely to experience sleep deficiency than those who reported no substance use; among those who reported methamphetamine use, depressive symptoms and unstable housing were associated with sleep deficiency. In Chapter 4, sleep deficiency, particularly among those who used methamphetamine occasionally, was associated with having at least one new anal sex partner, having concurrent partners, having exchange sex, attending a sex party, and missed HIV medications.

Conclusions: The prevalence of both methamphetamine use and sleep deficiency are high among men who have sex with men living with or at high risk of acquiring HIV. Taken together, these findings highlight the need for interventions that reduce frequency of methamphetamine use, which may in turn improve sleep hygiene and reduce risk behaviors.

This dissertation of Allison Rosen is approved.

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2022

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1 Introduction

1.1 Background

Methamphetamine use is a significant public health problem that affects both individual and community health. The United States is facing an unprecedented epidemic of substance use and overdose; further research is needed to better understand how this epidemic is affecting different regions of and subpopulations within the United States.

Not only is methamphetamine use life-threatening in itself, it is also associated with numerous negative health consequences. People with substance use disorders, including those who use methamphetamine, are at increased risk of acquiring infectious diseases such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and sexually transmitted infections (STI).[1,2] Long-term methamphetamine use has also been associated with chronic conditions such as depression, anxiety, insomnia, cognitive decline, cardiovascular disease, and cancer.[3] In comparison to the general population, men who have sex with men (MSM), and particularly MSM living with HIV are disproportionately affected by methamphetamine use. In a nationally representative survey of MSM, 12% of those living with HIV and 6% of those who were HIV-negative reported methamphetamine use.[4] Methamphetamine use is chronic and relapsing, and treatment is challenging and difficult to access. Thus, it is important to investigate factors influencing changes in methamphetamine use patterns over time, especially among MSM.

MSM are also disproportionately affected by HIV, accounting for over half of the current cases in the United States and 70% of new cases each year.[5] Given this high prevalence, it is important to consider how methamphetamine use patterns may differ for MSM living with and without HIV. The association between methamphetamine use and HIV acquisition in addition to the stigma and stress associated with having HIV over and above identifying as MSM may explain the even higher prevalence of methamphetamine use among MSM living with HIV.[6] Methamphetamine use has been linked to poor medication adherence and higher viral loads in MSM living with HIV, making it important to consider those living with HIV as an important subpopulation of MSM when studying methamphetamine use.[7-9]

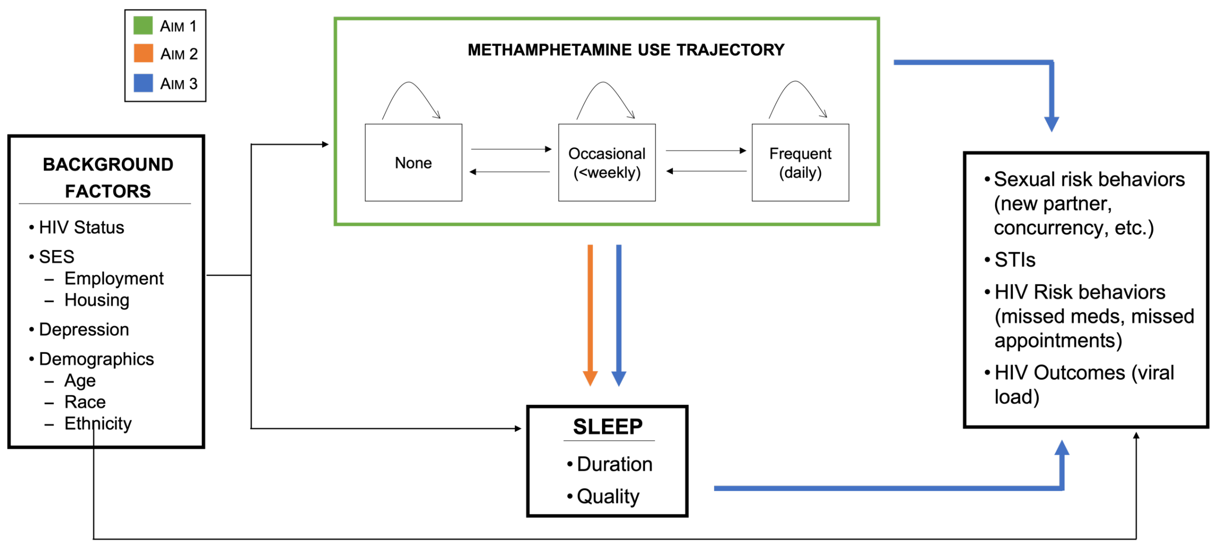
MSM with and without HIV also experience a higher prevalence of many of the negative health consequences that have been associated with substance use, including sleep problems. Nearly half of MSM may experience sleep disturbance, and MSM are more likely to report sleep disturbance than their heterosexual counterparts.[10-12] However, the extent to which methamphetamine use directly contributes to sleep deficiency is poorly understood. In addition, methamphetamine use is strongly associated with sexual and HIV risk behaviors, but the joint association between methamphetamine use and sleep deficiency among MSM is understudied, and sleep deficiency has not been linked to measurable consequences of risk behaviors such as STI acquisition and having a detectable HIV viral load.[10,13]

1.2 Study Aims and Conceptual Model

This study aimed to better understand the interdependence between methamphetamine use, sleep deficiency, and sexual and HIV risk behaviors in a cohort of MSM living with or at high risk for acquiring HIV. This analysis was guided by the conceptual model presented in **Figure 1.1**, and had three aims, which are presented in Chapters 2-4.

First, in Chapter 2, a multistate Markov model was designed to compare natural histories of methamphetamine use by HIV-status and substance use treatment status. Second, in Chapter 3, logistic regression and conditional growth curve models were used to investigate the association of methamphetamine use with sleep deficiency. Third, in Chapter 4, logistic regression was used to examine the joint association of sleep deficiency and methamphetamine use with sexual risk behaviors, HIV risk behaviors, STI incidence, and HIV viral load. The conceptual model displays the proposed relationships between methamphetamine use, sleep deficiency, and sexual and HIV risk behaviors, as well as the background factors that may influence these connections.

Figure 1.1 Conceptual Model of the interdependence between methamphetamine use, sleep deficiency, and sexual and HIV risk behaviors in MSM



2 Trajectories of methamphetamine use among men who have sex with men living with or at high risk of acquiring HIV

2.1 Abstract

Background: Methamphetamine use is highly prevalent among men who have sex with men and particularly those living with HIV, but knowledge of the long-term dynamics of methamphetamine use is limited. This study described trajectories of methamphetamine use among men who have sex with men and compared trajectories by HIV-status and substance use treatment status.

Methods: This analysis selected individuals from a cohort of men who have sex with men in Los Angeles, CA who participated in semi-annual study visits from August 2014 to February 2022. Trajectories of methamphetamine use were characterized using a continuous time multi-state Markov model with three states. States were defined using self-reported frequency of methamphetamine use in the past six months: frequent (daily), occasional (weekly or less), and never. Trajectories were compared by HIV-status. Observed transitions between states were compared for those who reported receiving current treatment for substance use and those who did not.

Results: This analysis included 2348 study visits among 285 individuals, of whom 181 (64%) were living with HIV. The average follow-up time was 4.4 years. Controlling for age and race/ethnicity, those living with HIV were less likely to transition from none to occasional use (HR: 0.67, 95% CI: 0.48 – 0.95) and from occasional to no use (HR: 0.53, 95% CI: 0.39 – 0.72). HIV-status was not associated with transition from occasional to frequent or frequent to occasional use. Among those who reported frequent use and receiving treatment at a study visit, 35% (n=14) reported continued frequent use at their next visit compared to 68.2% (n=191) of those who were not receiving treatment.

Conclusions: This study used dynamic modeling to study multiple transitions on the methamphetamine use trajectory and provides important insight into differences in methamphetamine trajectories by HIV-status as well as the potential impact of substance use treatment on future reduction of methamphetamine use.

2.2 Background

Methamphetamine use is a significant public health problem that affects both individual and community health. Between 2007 and 2019, the methamphetamine and other stimulant-involved opioid overdoses increased by 16,200% among non-Hispanic Black Americans and 4,600% among Hispanic Americans.[14] In addition, methamphetamine was involved in 37.7% of overdose deaths in the western United States in 2017, making it the most common drug involved in overdose deaths in this region.[15]

Methamphetamine use disproportionately affects men who have sex with men (MSM), people living with HIV (PLWH), and especially MSM living with HIV.[16,17] In a nationally representative survey of MSM, 12% of PLWH reported methamphetamine use compared to 6% of those who were HIV-negative.[4]

While methamphetamine use is often initiated to induce feelings of pleasure and euphoria, repeated use can result in needing to use in order to prevent adverse physical and psychological symptoms despite negative consequences of use.[18] This compulsion and loss of control is a consequence of changes to the brain that are caused by this highly addictive drug. In fact, it is well-established that addiction is associated with changes in impulse control, affect regulation, and behavioral inhibition.[19]

Both the aforementioned neurological changes and a multitude of individual and societal factors make methamphetamine use a highly dynamic behavior that involves changing patterns of use as well as periods of abstinence. Those who use methamphetamine can often be split into two groups, those who use frequently and those who use occasionally. Those who use frequently tend to be dependent on methamphetamine, while those who use occasionally tend to use methamphetamine in social and sexual settings.[20-22] In order to better understand methamphetamine use, its determinants, and potential targets for intervention, this behavior must be conceptualized as a chronic disorder and studied longitudinally.

Trajectories of methamphetamine use, and of substance use in general, are understudied. Many previous analyses of substance use trajectories focus on one transition of interest, usually injection initiation or cessation.[23-26] A number of studies have built upon those that focus on only one transition by using methods such as latent class analysis to group individuals into different stages of the substance use trajectory. The results of an analysis of individuals in Baltimore categorized participants based on frequency of use and mode of administration, finding that 53% ceased use, 16% frequently relapsed, and 32% persistently injected over time.[27] A study of African-American MSM found three states: poly substance users, alcohol/marijuana users, and unlikely problematic substance users, with 18%, 33%, and 50% membership, respectively.[28] Another analysis of MSM yielded an additional, distinctive high risk group that was defined by use of sex drugs, including methamphetamine.[29] Further analysis identified factors associated with membership in each group; many of the factors associated with membership in illicit use groups were common among studies: unstable housing, engaging in transactional sex, substance use during sexual activity, and other high-risk sexual behavior.[29]

While latent class analyses have made important contributions to the understanding of stages of the substance use trajectory, they fail to consider the dynamic nature of this behavior. These analyses assign individuals to stationary states in the trajectory based on longitudinal data rather than considering how individuals' substance use behavior changes over time. In fact, analyses that determine factors associated with group membership assume that group membership does not change over time. A study of the stability of latent classes in a population of MSM found that 26% of participants transitioned between classes. While the authors of this study concluded that this suggests relative stability of latent classes for substance use trajectories, the follow-up period for the study was only 2.5 years. In addition, the authors note that classes may be less stable in populations where substance use patterns are determined by fluctuating extrinsic factors such as income, housing, drug supply, and access to substance use treatment.[30]

Given limited research on longitudinal substance use trajectories and no specific studies of methamphetamine use trajectories to our knowledge, novel analyses that take into account the long-term, dynamic nature of methamphetamine use over time are needed to adequately characterize methamphetamine use trajectories among MSM. In addition, methamphetamine use trajectory studies have not explicitly compared the trajectories of HIV-positive and HIV-negative MSM. This study aims to describe trajectories of methamphetamine in a cohort of MSM in Los Angeles, as well as compare trajectories in PLWH and those who are HIV-negative.

2.3 Methods

Data Source

The present analysis used data from mSTUDY, a National Institute on Drug Abuse (NIDA)-funded cohort in Los Angeles based at the University of California, Los Angeles that began enrolling participants in 2014. The mSTUDY cohort includes mostly Black/African American and Latino/Hispanic MSM aged 18-45 with a history of drug use; half of participants are HIV positive. Every six months, study participants complete a behavioral survey and provide biospecimens. Due to the COVID-19 pandemic, between March 2020 and June 2021, participants completed the behavioral survey remotely and did not provide biospecimens.

Inclusion criteria for mSTUDY include being between age 18 and 45 at baseline, assigned male sex at birth, ability to provide informed consent, and willingness to return for follow-up visits. Participants must also be HIV-positive or report high risk for HIV acquisition (condomless anal intercourse with a male partner in the past six months). Having self-reported methamphetamine use at one or more study visits was also required for inclusion in the present analysis.

The University of California, Los Angeles Institutional Review Board approved the study, and all participants provided written informed consent.

Measures

Frequency of methamphetamine use was measured by self-report using a version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) that was adapted to capture substance use in the past six months.[31] Participants reported frequency of methamphetamine use as daily, weekly, monthly, less often, once, or never. For this analysis, frequent use was defined as daily use; occasional use was defined as weekly, monthly, less often, or onetime use.

Baseline HIV-status was determined by a blood test. Age was categorized using a median split in order to preserve statistical power in analyses. Race/Ethnicity was categorized as Black/African American, Hispanic/Latinx/Spanish, white, and other. Receiving substance use treatment was self-reported and the specific substance(s) was not specified.

Model Description

Trajectories of methamphetamine use were characterized using a continuous time Markov Chain, which, by definition, is stochastic. An important feature of Markov processes is that they are memory-less: the future state of the system depends only on the current state of the system.[32]

The model tracks the state, S, of an individual at time t: S(t). The ways an individual may move through the states of the model are defined by transition intensities, which represent the instantaneous risk of transition between two states. The transition intensities may be stored in a square matrix, Q, with rows and columns equal to the number of states in the model. q represents the instantaneous risk of transition from state i to state j. Q is called the transition rate matrix, and its rows sum to zero. Entries on the diagonal of Q represent the negative sum of the other intensities stored in that row. Entries in Q are set to zero if the instantaneous risk of transition from state i to state j is impossible. For a model with three states:

$$Q = \begin{bmatrix} q_{11} & q_{12} & q_{13} \\ q_{21} & q_{22} & q_{23} \\ q_{31} & q_{32} & q_{33} \end{bmatrix} = \begin{bmatrix} -(q_{12}+q_{13}) & q_{12} & q_{13} \\ q_{21} & -(q_{21}+q_{23}) & q_{23} \\ q_{31} & q_{32} & -(q_{31}+q_{32}) \end{bmatrix} \tag{1}$$

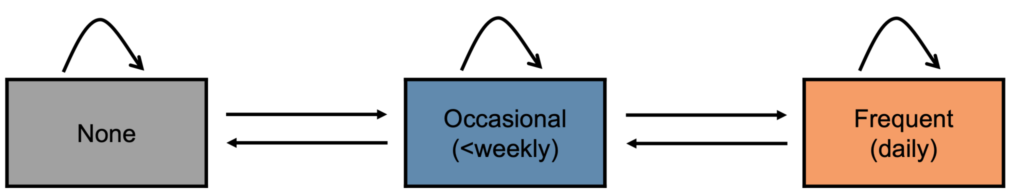
The model can be written as an equation in terms of Q and the probability distribution, p:

$$p_{s+t} = p_s e^{Qt} \tag{2}$$

where p_{s+t} is a row vector representing the probability distribution at time $s + t$. One way to explore the projected probability distribution over time is to take $t = 1$ and $s = 0, 1, 2, \ldots$ to find the probability distribution at time $1, 2, \ldots$

Trajectories of methamphetamine use were defined by three categories of frequency: none, occasional, and frequent. The model did not include an absorbing state for loss to follow-up or death; since mSTUDY began, 93% of participants remain enrolled and there has been less than 1% mortality.

Figure 2.1 Trajectories of methamphetamine use model diagram



The model was designed with seven possible transitions, as represented by the arrows in **Figure 2.1**. Participants could increase frequency from None to Occasional or Occasional to Frequent, decrease frequency from Frequent to Occasional or Occasional to None, or they could remain in each of the three respective states. It was assumed that model parameters do not change over time, and that there were no transitions between non-adjacent states in the model. Participants who reported non-adjacent transitions at time t and $t+1$ were assumed to have traveled through the adjacent state.

Parameter estimation was performed using the msm package in R.[33] Using the observed state of each participant at each study visit, maximum likelihood estimation was used to estimate the transition intensities. The estimation method assumed that the observed data were panel data from a time-homogeneous process. Panel data are data collected on a continuous time process that is observed periodically; the time of observation does not influence the observed value and thus the transition intensities. This is a reasonable assumption, as mSTUDY participants are observed biannually, and the timing of study visits do not influence frequency of methamphetamine use.

Based on **Equation (1)** and **Figure 2.1**, four transition intensities were estimated and Q was defined as:

$$Q = \begin{bmatrix} q_{NN} & q_{NO} & 0 \\ q_{ON} & q_{OO} & q_{OF} \\ 0 & q_{FO} & q_{FF} \end{bmatrix} = \begin{bmatrix} -(q_{NO}) & q_{NO} & 0 \\ q_{ON} & -(q_{ON} + q_{OF}) & q_{OF} \\ 0 & q_{FO} & -(q_{FO}) \end{bmatrix} \tag{3}$$

where None is represented by N, Occasional is represented by O, and Frequent is represented by F.

Analytic Strategy

Before modeling trajectories of methamphetamine use, univariate and bivariate analyses were used to describe the study sample. Baseline methamphetamine use, age, and race/ethnicity were compared for PLWH and those who were HIV-negative. In addition, the number of observed transitions among the total study population, PLWH, and those who were HIV-negative was computed by tabulating participants' frequency of methamphetamine use at visit $t-1$ and visit t.

Three increasingly complex multistate models were estimated. The first model estimated trajectories of methamphetamine use without covariates. The second model compared trajectories of methamphetamine use for PLWH and those who were HIV-negative. The third model built upon the second model by controlling for age and race/ethnicity; due to limited statistical power it was not possible to include a large number of covariates, and age and race/ethnicity were determined to be the most important based on background knowledge.

The estimated transition intensities from each model were used to present more intuitive parameterizations: the mean sojourn time and the probability that the next transition is to state S. Mean sojourn time was defined as the amount of time in years that individuals spend in each state before transitioning to another state. In time-homogeneous Markov models, the sojourn time is exponentially distributed with mean $-1/q_{ij}$ where $i = j$. The probability that state S is next after state R is $-q_{rs}/q_{rr}$ for each R and S.[33]

In order to compare PLWH and those who were HIV-negative, hazard ratios for the association of HIV-status and transition between states of methamphetamine frequency were computed. In addition, the projected probability distribution for PLWH and those who were HIV-negative was calculated over five years using the method described in **Equation (2)**. Model fit was assessed by using likelihood ratio tests to compare each of the three models. In addition, the observed probability distribution was compared to the probability distribution predicted by the model over five years.

Lastly, observed transitions were compared for those who reported receiving current treatment for substance use at visit $t-1$ to those who did not report receiving current treatment for substance use at visit $t-1$.

2.4 Results

This analysis included 285 unique individuals, of whom 181 (63.5%) were PLWH. Between August of 2014 and February 2022 these individuals had a combined 2348 study visits and 2063 observed transitions between states of methamphetamine frequency. On average, participants had 8.2 study visits over the course of 4.4 years. Average follow-up time was comparable for PLWH and those who were HIV-negative.

Table 2.1. Baseline characteristics of mSTUDY participants, August 2014 - February 2022

	Total[1] (n=285)	**HIV-Positive (n=181)**	**HIV-Negative (n=104)**
	n (%)	n (%)	n (%)
Methamphetamine Use[2]			
None	67 (23.5)	35 (19.3)	32 (30.8)
Occasional	164 (57.5)	106 (58.6)	58 (55.8)
Frequent	54 (18.9)	40 (22.1)	14 (13.5)
Age > 33 years old	129 (45.3)	99 (54.7)	30 (28.8)
Race/Ethnicity			
Black/African American	116 (40.8)	68 (37.6)	48 (46.6)
Hispanic/Latinx/Spanish	104 (36.6)	68 (37.6)	36 (35.0)
White	44 (15.5)	34 (18.8)	10 (9.7)
Other	20 (7.0)	11 (6.1)	9 (8.7)
Number of Visits (Mean, SD)	8.2 (3.7)	8.1 (3.5)	8.4 (4.0)
Years of Follow-Up (Mean, SD)	4.4 (1.9)	4.3 (1.8)	4.5 (2.0)

[1]Participants reported methamphetamine use during one or more visits
[2]Self-reported frequency of use in the past six months (occasional defined as weekly or less, frequent defined as daily).

At baseline, 67 (23.5%) participants reported no methamphetamine use in the past six months, 164 (57.5%) reported occasional use, and 54 (18.9%) reported frequent use. The median baseline age was 33 years old, and 116 (40.8%) identified as Black/African American, 104 (36.6%) identified as Hispanic/Latinx/Spanish, 44 (15.5%) identified as white, and 20 (7.0%) identified as another race or ethnicity. Compared to participants who were HIV-negative, more PLWH were over 33 years old, and more PLWH reported occasional or frequent methamphetamine use at baseline (**Table 2.1**).

Of 2063 observed transitions between states of frequency of methamphetamine use, it was most common to remain in the same state between visit $t-1$ and visit t. Those who reported no use at visit $t-1$ remained non-users at visit t 74.8% of the time. Those who reported occasional use at visit $t-1$ remained occasional users at visit t 65.6% of the time. Those who reported frequent use at visit $t-1$ remained frequent users at visit t 63.6% of the time. Similar trends were observed for PLWH and those who were HIV-negative, and non-adjacent transitions were relatively rare (**Table 2.2**).

Table 2.2 Observed transitions between states of frequency of methamphetamine use among mSTUDY participants, August 2014 – February 2022

		Methamphetamine Use at Visit t (To)		
		None	Occasional	Frequent
		n (%)	n (%)	n (%)
			Total (n=2063)	
Methamphetamine[1] Use at Visit t-1 (From)	None	615 (74.8)	176 (21.4)	31 (3.8)
	Occasional	213 (23.4)	596 (65.6)	100 (11.0)
	Frequent	31 (9.3)	90 (27.1)	211 (63.6)
			HIV-Positive (n=1289)	
Methamphetamine Use at Visit t-1 (From)	None	355 (76.2)	94 (20.2)	17 (3.6)
	Occasional	117 (19.4)	420 (69.7)	66 (10.9)
	Frequent	19 (8.6)	60 (27.3)	141 (64.1)
			HIV-Negative (n=774)	
Methamphetamine Use at Visit t-1 (From)	None	260 (73.0)	82 (23.0)	14 (3.9)
	Occasional	96 (31.4)	176 (57.5)	34 (11.1)
	Frequent	12 (10.7)	30 (26.8)	70 (62.5)

[1] Self-reported frequency of use in the past six months (occasional defined as weekly or less, frequent defined as daily).

When modeling trajectories of methamphetamine use without covariates, participants did not use methamphetamine for an average of 1.57 years (95% CI: 1.36 - 1.83) before transitioning to occasional use. Participants used methamphetamine occasionally for an average of 0.97 years (95% CI: 0.87 - 1.09) and then had a 0.64 (95% CI: 0.59 – 0.69) probability of transitioning to non-use and a 0.36 (95% CI: 0.31 - 0.41). probability of transitioning to frequent use. Participants used methamphetamine frequently for an average of 1.16 years (95% CI: 0.96 - 1.41) before transitioning to occasional use (**Table 2.3**).

Table 2.3 Full parameterization of continuous-time multistate Markov model

	Mean Sojourn Time		
	None	**Occasional**	**Frequent**
	Years (95% CI)	Years (95% CI)	Years (95% CI)
No Covariates	1.57 (1.36, 1.83)	0.97 (0.87, 1.09)	1.16 (0.96, 1.41)
HIV Status (crude)			
HIV-Positive	1.74 (1.43, 2.12)	1.14 (0.98, 1.32)	1.21 (0.95, 1.54)
HIV-Negative	1.36 (1.09, 1.71)	0.74 (0.62, 0.89)	1.07 (0.77, 1.47)
HIV Status (Adjusted*)			
HIV-Positive	1.73 (1.42, 2.11)	1.12 (0.97, 1.30)	1.20 (0.93, 1.53)
HIV-Negative	1.23 (0.97, 1.57)	0.71 (0.58, 0.86)	1.11 (0.78, 1.60)

	Probability state S is Next	
	None ← Occasional	**Occasional → Frequent**
	Probability (95% CI)	Probability (95% CI)
No Covariates	0.64 (0.59, 0.69)	0.36 (0.31, 0.41)
HIV Status (crude)		
HIV-Positive	0.60 (0.53, 0.67)	0.40 (0.33, 0.47)
HIV-Negative	0.70 (0.62, 0.77)	0.30 (0.23, 0.38)
HIV Status (Adjusted*)		
HIV-Positive	0.60 (0.53, 0.67)	0.40 (0.33, 0.47)
HIV-Negative	0.72 (0.64, 0.79)	0.28 (0.21, 0.36)

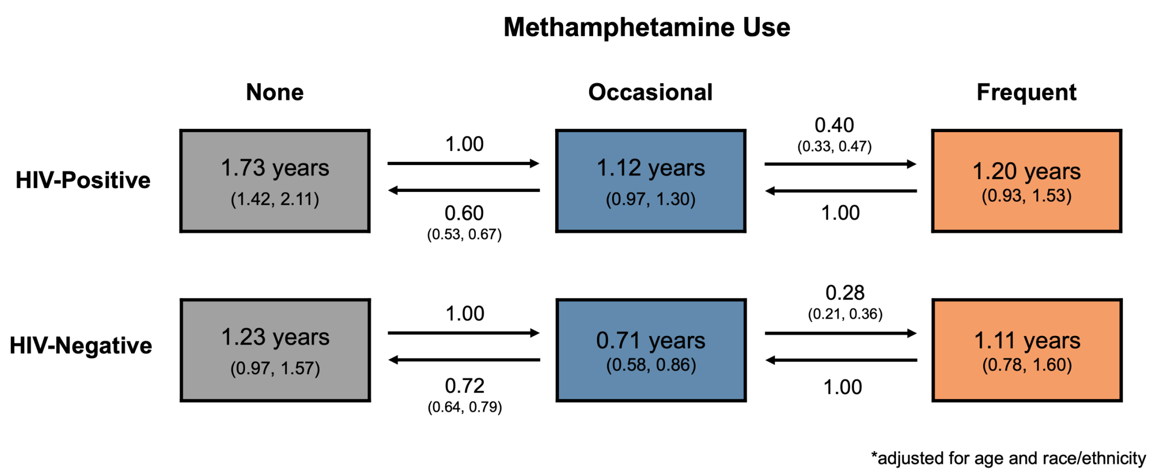
*Adjusted for age and race/ethnicity

Trajectories of methamphetamine use are compared for PLWH and those who are HIV-negative in **Table 2.3**. When controlling for age and race/ethnicity, PLWH did not use methamphetamine for an average of 1.73 years (95% CI: 1.42 – 2.11) before transitioning to occasional use. PLWH used methamphetamine occasionally for an average of 1.12 years (95% CI: 0.97 – 1.30) and then had a 0.60 (95% CI: 0.53 – 0.67) probability of transitioning to non-use and a 0.40 (95% CI: 0.33 - 0.47) probability of transitioning to frequent use. PLWH used methamphetamine frequently for an average of 1.20 years (95% CI: 0.93 - 1.53) before transitioning to occasional use.

In comparison, those who were HIV-negative did not use methamphetamine for an average of 1.23 years (95% CI: 0.97 – 1.57) before transitioning to occasional use. Those who were HIV-negative used methamphetamine occasionally for an average of 0.71 years (95% CI: 0.58 – 0.86) and then had a 0.72 (95% CI: 0.64 – 0.79) probability of transitioning to non-use and a 0.28 (95% CI: 0.21- 0.36) probability of transitioning to frequent use. Those who were HIV-negative used methamphetamine frequently for an average of 1.11 years (95% CI: 0.78 - 1.60) before transitioning to occasional use. These results are presented visually in **Figure 2.2**.

In addition, PLWH who were occasional users were 1.50 (95% CI: 1.11 – 2.02) times as likely to transition to no use than to frequent use. Those who were HIV-negative and occasional users were 2.59 (95% CI: 1.74 – 3.87) times as likely to transition to no use than to frequent use.

Figure 2.2. Visual representation of adjusted continuous-time multistate Markov model results



When controlling for age and race/ethnicity, PLWH were less likely to transition from none to occasional methamphetamine use (HR: 0.67, 95% CI: 0.48 – 0.95) and from occasional to no use of methamphetamine (HR: 0.53, 95% CI: 0.39 – 0.72) in comparison to those who were HIV-negative. HIV-status was not associated with transition from occasional to frequent or frequent to occasional methamphetamine use (**Table 2.4**)

Table 2.4.Association of HIV-status and transition between states of frequency of methamphetamine use

	Transition			
	None → Occasional	**None ← Occasional**	**Occasional → Frequent**	**Occasional ← Frequent**
	HR* (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Crude Model				
HIV-Positive	0.78 (0.58, 1.06)	**0.56 (0.42, 0.74**)	0.87 (0.59, 1.29)	0.88 (0.59, 1.31)
Adjusted Model				
HIV-Positive	**0.67 (0.48, 0.95)**	**0.53 (0.39, 0.72)**	0.95 (0.63, 1.44)	0.95 (0.61, 1.48)
Age > 33 years old	1.23 (0.87, 1.72)	1.06 (0.80, 1.42)	0.88 (0.59, 1.29)	0.72 (0.48, 1.10)
Race/Ethnicity				
Black/African American	1.39 (0.99, 1.96)	1.03 (0.75, 1.42)	1.15 (0.75, 1.77)	1.09 (0.70, 1.71)
Hispanic/Latinx/Spanish	1.00 (0.61, 1.64)	1.21 (0.79, 1.88)	0.85 (0.46, 1.57)	0.78 (0.41, 1.49)
Other	1.23 (0.70, 2.17)	1.18 (0.65, 2.15)	2.12 (1.06, 4.24)	1.00 (0.50, 1.98)
White	1.00	1.00	1.00	1.00

*HR: Hazard Ratio

Among PLWH after five years, 38.9% (95% CI: 33.4 – 44.3) are expected to not use methamphetamine, 42.8% (95% CI: 38.6 – 46.6) are expected to occasionally use methamphetamine, and 18.3% (95% CI: 14.2- 22.7) are expected to frequently use methamphetamine. Among those who are HIV-negative after five years, 47.5% (95% CI: 41.9 – 54.0) are expected to not use methamphetamine, 36.8% (95% CI: 32.1 - 41.4) are expected to occasionally use methamphetamine, and 15.7% (95% CI: 11.4 – 21.3) are expected to frequently use methamphetamine

Figure 2.3. Adjusted association of HIV-status and transition between states of methamphetamine use

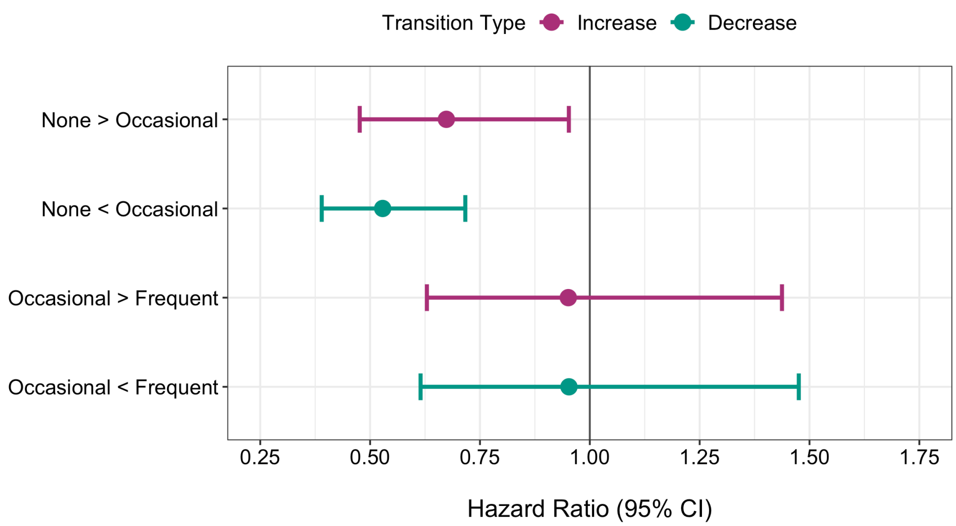
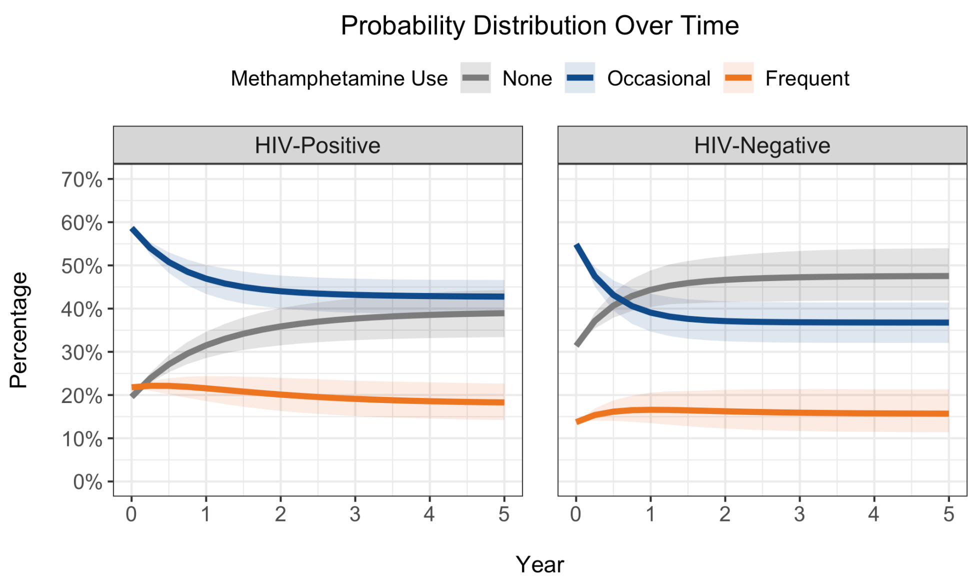


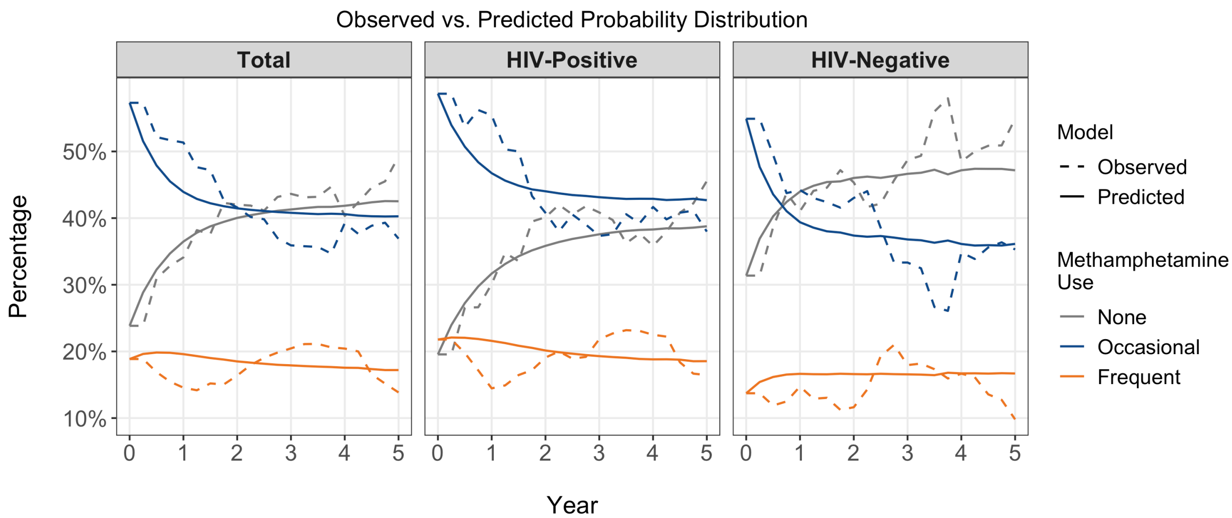
Figure 2.4. Predicted probability distribution (95% CI) of frequency of methamphetamine use over five years by HIV-Status adjusted for age and race/ethnicity



Likelihood ratio tests revealed that HIV-only model improved model fit over the model without covariates (p<0.01), but that the fully adjusted model did not improve model fit over the

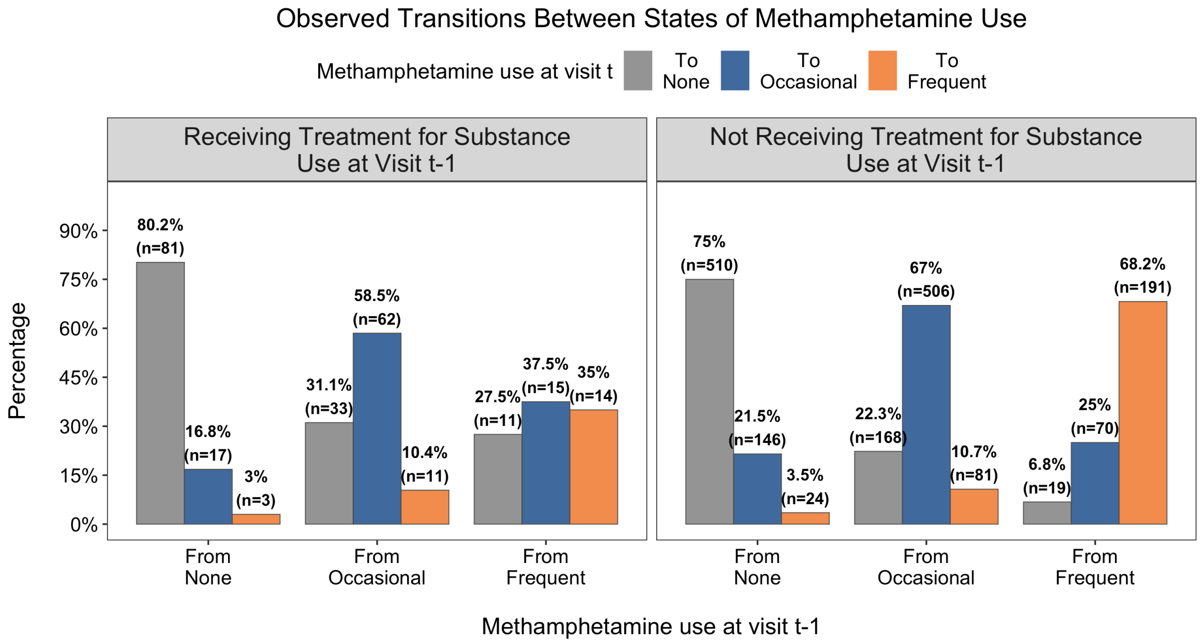
HIV-only model (p=0.47). The observed and predicted probability distributions for the fully adjusted model are shown in **Figure 2.5**. The greatest divergence from the observed occurs for those who were HIV-Negative and for frequent users of methamphetamine, all of which had the smallest sample sizes.

Figure 2.5. Observed vs. predicted probability distribution of frequency of methamphetamine use over five years by HIV-Status



Comparisons of observed transitions between states of methamphetamine use for those who did and did not report receiving current treatment for substance use at visit $t-1$ are shown in **Figure 2.6**. For those who reported frequent methamphetamine use and receiving treatment at visit $t-1$, 11 (27.5%) reported a decrease to no use at visit t, 15 (37.5%) reported a decrease to occasional use at visit t, and 14 (35%) reported continued frequent use at visit t. For those who reported frequent methamphetamine use and not receiving treatment at visit $t-1$, 19 (6.8%) reported a decrease to no use at visit t, 70 (25%) reported a decrease to occasional use at visit t, and 191 (68.2%) reported continued frequent use at visit t.

Figure 2.6.Observed transitions between states of methamphetamine use comparing those who reported receiving substance use treatment at visit t-1 compared to those who did not.



2.5 Discussion

Conclusions

In this study, a continuous-time multistate Markov model was used to better understand trajectories of methamphetamine use in a population of MSM living with HIV or at high risk of acquiring HIV. Both PLWH and those who are HIV-negative are expected to reach a steady state within five years. In both groups, the proportion who do not use methamphetamine exhibits an upward trend, and the proportions who use methamphetamine occasionally and frequently exhibit downward trends. In addition, for those both PLWH and those who are HIV-negative and who are occasional users of methamphetamine, model results suggest that transition to no methamphetamine use may be more likely than transition to frequent methamphetamine use, especially among those who are HIV-negative.

In comparison to those who were HIV-negative, PLWH were both less likely to increase frequency of methamphetamine use from none to occasional and decrease methamphetamine use from occasional to none. This may be explained by the fact that PLWH likely have a longer history of using methamphetamine heavily, as their HIV-acquisition may have been driven by methamphetamine use and they tend to be older than those who are HIV-negative.

Limitations

It is important to keep in mind the limitations of this study. First, nearly all of the data for this analysis was collected by self-report. The objectivity of self-report data cannot be guaranteed as participants may not answer all questions accurately. This social desirability bias is particularly likely when collecting data about sensitive behaviors such as substance, where participants are likely to underreport these behaviors. Unfortunately, there are currently no reliable, cost-effective biomarkers that can capture patterns of substance use over longer periods of time. The mSTUDY team works to minimize social desirability bias with a well-designed behavioral survey, by creating a welcoming environment for participants, and by using computer-assisted self-interviewing (CASI) rather than face-to-face interviews. Informal analyses found 87% agreement between self-report and urine toxicology screens for methamphetamine, suggesting that mSTUDY is collecting high quality self-report data about substance use behavior.

The model used in this analysis makes strong assumptions that must be considered. First, the model assumes that all parameters are constant over time and that all observed non-adjacent transitions occurred via travel through adjacent states. In addition, Markov models assume that the future state of the system depends only on the current state of the system; it is likely that the system is not entirely memory-less and that previous methamphetamine use has some amount of influence on transition between states. Lastly, participants were observed biannually, so if the true sojourn time for a particular state is less than six months, that could not be captured by the model.

This study is also limited by its sample size. The number of observed transitions between some states is small when stratified by HIV-status, resulting in wide confidence intervals. Only two background factors, age and race/ethnicity, could be considered as potential confounders of the relationship between HIV-status and frequency of methamphetamine use due to sparse data; additional factors, including use of other substances, treatment for substance use, mental health, and housing likely confound this association as well as mask additional heterogeneity in the estimated transition intensities. Also, age was categorized using a median split to preserve statistical power, which may result in residual confounding. Lastly, this study used covariate values at baseline, and thus does not account for HIV seroconversion and mortality from methamphetamine use or other causes. While these events are rare in the mSTUDY cohort and sensitivity analyses using HIV-status at last visit produced similar results, they should be considered in future research.

Lastly, the results of this study should be generalized with caution. mSTUDY is a convenience sample that may not be representative of all MSM in Los Angeles. In addition, mSTUDY provides connections to healthcare and other services for participants, so those who choose to remain enrolled may be more motivated to change substance use behaviors or have better access to treatment.

Significance and Future Directions

The multistate Markov model used in this study provides important insight into the rates at which individuals transition between states of frequency of methamphetamine use. Multistate Markov models are widely used in public health research to study chronic disease progression, but they have rarely been applied to studies of substance use. One previous modeling study focused on transition from cannabis use to illicit substance use, and another considered transitions from onset to regular use of alcohol and tobacco among adolescents.[34,35] However, multistate Markov models have not been previously used to study multiple transitions within a methamphetamine use trajectory, and they have not been applied to populations of MSM and PLWH.

By considering multiple transitions, rather than just cessation, this study highlights the importance of harm reduction as a part of treatment for substance use. Further research is needed to consider interventions that could increase not only the rate of transition from occasional to no use, but also the rate of transition from frequent to occasional use. This is especially important for PLWH, where frequent use of methamphetamine is more common.

While there was not sufficient power to include in the model whether individuals were receiving substance use treatment, a comparison of observed transitions for those who were vs. were not receiving substance use treatment revealed that individuals receiving treatment were more likely to report decreased frequency of use at their next visit compared to those who were not receiving treatment. This was especially apparent among those who reported frequent use; given that participants were not asked to report the substance for which they were receiving treatment or the type of treatment they were receiving, the higher reports of decreased use among frequent users may suggest that these individuals are receiving treatment specifically for methamphetamine use or that they are participating in more intensive treatment programs.

It is well-established that treatment options for methamphetamine use are limited, especially for those who report frequent use.[36-39] In addition, a previous study found that residential rehabilitation was effective at decreasing methamphetamine use only in the short term.[40] Thus further research should also use more extensive data sources with large sample sizes to consider how multiple time-varying background factors, including substance use treatment, work together to influence changes in frequency of methamphetamine use over long periods of time.

3 Association of methamphetamine use and sleep deficiency among men who have sex with men living with or at high risk of acquiring HIV

3.1 Abstract

Background: Sleep hygiene is essential to mental and physical health. Men who have sex with men, people living with HIV, and people who use methamphetamine have unique risk factors that link with sleep deficiency. This study investigated the association of methamphetamine use and sleep deficiency among men who have sex with men living with or at high risk of acquiring HIV.

Methods: This analysis selected individuals from a cohort of men who have sex with men who participated in semi-annual visits from June 2018 to June 2021. Sleep deficiency was defined as a Pittsburgh Sleep Quality Index (PSQI) score above five and frequency of methamphetamine use was self-reported. Logistic regression models with generalized estimating equations evaluated the association of methamphetamine use with sleep deficiency. Models were adjusted for age at visit, race/ethnicity, HIV-status, unstable housing, depressive symptoms, cigarette smoking, binge drinking, cannabis use, and crack or cocaine use. Conditional growth curve models examined change in PSQI score over time by methamphetamine use, depressive symptoms, and unstable housing.

Results: Analyses included 1445 visits among 382 unique participants. The average age was 36 with 41% identifying as Black/African American, 43% Latinx/Hispanic, 12% white, and 5% other. Sleep deficiency was more likely among those who reported methamphetamine use (aOR=1.89, 95% CI: 1.20-2.98) compared to those reported no substance use. The average PSQI score decreased minimally over time (-0.12, 95% CI: -0.23, -0.00), and methamphetamine use was associated with 1.80 (95% CI: 1.12, 2.48) point increase in PSQI score compared to no substance use. Among those who reported methamphetamine use, experiencing depressive symptoms was associated with a 2.41 (95% CI: 1.73, 3.09) point increase in average PSQI

score compared to those not experiencing depressive symptoms, and experiencing unstable housing was associated with a 0.91 (95% CI: 0.14, 1.68) point increase in average PSQI score compared to those not experiencing unstable housing.

Conclusions: Sleep deficiency is highly prevalent among men who have sex with men, particularly those who report methamphetamine use. Given the various adverse health outcomes associated with sleep deficiency, this study highlights the need for sleep interventions tailored to the unique needs of men who have sex with men, people living with HIV, and people who use methamphetamine.

3.2 Background

Sleep deficiency is characterized by sleep deprivation (inadequate duration of sleep), low sleep quality, timing of sleep that disrupts circadian rhythms, and sleep disorders.[41] The Centers for Disease Control and Prevention (CDC) defines sufficient sleep duration as seven or more hours per night for adults aged 18-65.[42,43] Additionally, the CDC recommends practicing good sleep hygiene, which requires implementing a regular sleep routine, a consistent bedtime, a dark and quiet place to sleep, not using electronic devices before bed, and not consuming large meals or caffeine close to bedtime.[44] Such practices promote high quality sleep that respects one's circadian rhythm and reduces the risk of sleep disorders.

Sleep deficiency can have serious short-term consequences as well as lead to long-term health problems. In addition to decreasing productivity, a lack of sleep may also increase the likelihood of accidents such as workplace errors and motor vehicle accidents.[41,45] In surveys of men who have sex with men (MSM), short sleep duration has been linked to adverse behavioral outcomes including high numbers of sexual partners, condomless anal intercourse, and substance use before sexual activity.[10,46] Sleep deficiency has also been linked to numerous chronic health conditions including obesity, diabetes, cardiovascular disease, and all-cause mortality.[47-51] In addition, sleep deficiency has also been associated with various neurologic and psychiatric health outcomes such as dementia, depression, and anxiety.[52,53]

Given the well-established associations between sleep deficiency and numerous health outcomes, further research is needed to better understand factors contributing to sleep deficiency in specific populations with unique behavioral risk factors. Results from the 2014 BRFSS suggest that up to 35% of adults in the United States experience sleep deprivation.[54] The prevalence is estimated to be even higher among certain underrepresented subgroups such as MSM and people living with HIV (PLWH).

Growing evidence suggests that MSM experience higher rates of sleep deficiency compared to their heterosexual counterparts.[11] In an internet-based survey of MSM in New York, the prevalence of sleep deprivation was 43.6%, and the prevalence of low quality sleep was 34.6%.[10] Analysis of data from the National Health Interview Survey found that in comparison to men who identify as straight or bisexual, men who identify as gay are more likely to report poor sleep quality as measured by difficulty falling asleep, using medications for sleep, and not feeling well-rested.[12] Findings from the National Longitudinal Study of Adolescent Health revealed that the odds of having trouble falling asleep among men aged 24-32 who report having mostly same-sex partners were twice that of men who identify as mostly straight.[55] Previous research suggests that factors such as stress, history of trauma, and perceived neighborhood safety may explain the high prevalence of sleep deficiency among MSM.[56-58]

It is well-established that sleep deficiency is common among PLWH.[59-63] In a sample of PLWH in the San Francisco Bay Area, 63% of participants reported poor sleep quality and actigraphy revealed that an average of 20.5% of participants' total sleep time was actually spent awake.[64] In an online survey of American MSM, 35.1% of MSM living with HIV reported bad sleep in the past month compared to 25.9% of MSM who were HIV-negative; 33.9% of MSM living with HIV had used sleep medication in the past month, compared to 26.6% of MSM who were HIV-negative.[65] In addition, the Veterans Aging Cohort Study (VACS) found that 46.3% of participants living with HIV had a restless sleep disturbance trajectory after controlling for substance use; participants' sleep was more likely to improve over time if they had a baseline viral load under 1000 copies/mL.[66] Further VACS analyses as well as a study of military beneficiaries compared HIV-positive and HIV-negative participants and found no differences in sleep deficiency; the authors posit that the relationship between HIV and sleep deficiency may be changing with the advent of modern antiretroviral therapy (ART) and its ability to improve long-term HIV outcomes.[67,68] While this analysis was conducted in a specific population that may not be generalizable to other populations, these results suggest a need to reevaluate sleep disturbance among PLWH.

Characterizing sleep in PLWH is complicated by high prevalence of comorbidities and polypharmacy in this population, which are also associated with inadequate sleep. Such comorbidities include substance use, chronic pain, post-traumatic stress disorder (PTSD), depression, anxiety, and cardiovascular disease.[66,69] Lastly, sleep disturbance is a relatively common side effect of some ART regimens.[70] In particular, at least 25% of patients taking efavirenz (EFV) report neuropsychiatric symptoms such as sleep deficiency, insomnia, and intense dreams; such sleep disturbances may remain present in half of patients six months after initiating treatment.[71-73] While the exact mechanisms by which HIV and ART affect sleep are poorly understood, it is well known that immune activation influences sleep and in turn promotes an inflammatory response.[74,75] Further investigation into the causes and consequences of sleep deficiency among PLWH is needed for clarification of the mechanism behind this well-established relationship.

Studies of the association between substance use and sleep deficiency may provide insight into the disparities in sleep deficiency among MSM and PLWH. In particular, methamphetamine use is highly prevalent in these populations, and it is strongly associated with both short-term and long-term effects on sleep health.[76-78] One study observed sleep deficiency in 65.9% of patients with methamphetamine use disorder, and another study of PLWH found that those who had a history of methamphetamine use were more likely to experience poor sleep or be considered problematic sleepers than those without a history of methamphetamine use.[76,79] Use of methamphetamine has been shown to disrupt circadian rhythms, increase difficulty falling asleep, decrease total sleep time, and increase daytime sleepiness.[77,78] In addition, sleep deficiency has been associated with initiation of substance use, suggesting a cyclic relationship between substance use and sleep deficiency.[80-83] Despite the adverse effects of substance use on sleep, there is evidence that reduction in use and abstinence may improve sleep quality, and that improved sleep may in turn reduce cravings.[84-86]

This study investigated the association of methamphetamine use with sleep deficiency in a cohort of MSM living with or at high risk of acquiring HIV in Los Angeles, CA.

3.3 Methods

Data Source

The present analysis used data from mSTUDY, a National Institute on Drug Abuse (NIDA)-funded cohort in Los Angeles based at the University of California, Los Angeles that began enrolling participants in 2014. The mSTUDY cohort includes mostly Black/African American and Latino/Hispanic MSM aged 18-45 with a history of drug use; half of participants are HIV positive. Every six months, study participants complete a behavioral survey and provide biospecimens. Due to the COVID-19 pandemic, between March 2020 and June 2021, participants completed the behavioral survey remotely and did not provide biospecimens.

Inclusion criteria for mSTUDY include being between age 18 and 45 at baseline, assigned male sex at birth, ability to provide informed consent, and willingness to return for follow-up visits. Participants must also be HIV-positive or report high risk for HIV acquisition (condomless anal intercourse with a male partner in the past six months).

The University of California, Los Angeles Institutional Review Board approved the study, and all participants provided written informed consent.

Measures

Outcome: Sleep deficiency was assessed beginning in June 2018 using the Pittsburgh Sleep Quality Index (PSQI), a widely used, validated questionnaire that measures sleep quality and disturbance in the past 30 days.[87] Measures of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction are combined into a total score that ranges from 0-21; higher scores are indicative of worse sleep.[87] Sleep deficiency was defined as a PSQI score above 5.[87]

Exposure: Methamphetamine use was measured by self-report using a version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) that was adapted to capture substance use in the past six months.[31] Participants reported frequency of methamphetamine use as daily, weekly, monthly, less often, once, or never.

For this analysis, methamphetamine use was considered in three ways. First, those who used methamphetamine were compared to those who used substances other than methamphetamine and those who did not use any substances. Those who used methamphetamine may have also used other substances. Other substances included crack or cocaine, ecstasy, party drugs, heroin, prescription opioids, cannabis, binge drinking, and cigarette smoking. Second, frequency of methamphetamine use was considered in three categories: daily; weekly, monthly, less often, or once; and no use. Lastly, methamphetamine mode of administration was categorized as injection, non-injection, or no use. Those who reported injection of methamphetamine may have also used other modes of administration.

Covariates: HIV-status was determined by a blood test. All other covariates were measured by self-report: Race/Ethnicity was categorized as Black/African American, Hispanic/Latinx/Spanish, white, and other. Unstable housing was defined as not having a regular place to stay at least one time in the past six months. Depressive symptoms were defined as a score above 23 on the Centers for Epidemiologic Studies Depression Scale (CES-

D), which measures depressive symptomology in the past seven days. Previous research suggests that 23 is a more accurate cutoff for PLWH than the more commonly used score of 16 for the general population.[88] Binge drinking was defined as having six or more drinks on at least one occasion in the past six months. All other substance use was defined as using the substance at least one time in the past six months and was measured using a version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) that was adapted to capture substance use in the past six months.[31] All covariates were measured at all study visits.

Analytic Strategy

Characteristics of the participants were first compared across visits. Sleep deficiency, socio-demographics, and substance use were compared for those who used methamphetamine, those who used substances other than methamphetamine, and those who used no substances in the past six months. Count and percentage were calculated for categorical variables, and mean and standard deviation or median and interquartile range were calculated for continuous variables. The distribution of PSQI scores was then compared using the three definitions of methamphetamine use described above.

The association of methamphetamine use with sleep deficiency was investigated using multiple logistic regression with generalized estimating equations with independent correlation structure to account for repeated observations on the same participants.[89,90] Three models were considered using the three categorizations of methamphetamine use described above. The outcome for all models was sleep deficiency, which was defined as a PSQI score above five. Based on literature review, all models included age at visit, race/ethnicity, HIV-status, depressive symptoms, and unstable housing as covariates. The models that considered frequency and mode of administration of methamphetamine also included cigarette smoking, binge drinking, cannabis use, and crack or cocaine use as covariates. Heroin, fentanyl, or prescription opioid use were not included due to low prevalence of use. Models were fit using the R package gee.[91]

Differences in the association of methamphetamine use and sleep deficiency by HIV-status, depressive symptoms, and unstable housing were investigated by viewing the data descriptively and by including interaction terms in the multiple logistic regression models.

Lastly, using PSQI score as a continuous variable, sleep patterns were explored longitudinally. An unconditional growth curve model was used to describe changes in PSQI score over time. Conditional growth curve models were used to investigate the longitudinal interaction of methamphetamine use with depressive symptoms and unstable housing. Growth curve models are used to consider longitudinal changes within and between individuals.[92,93] Models were fit using the R package lme4.[94]

3.4 Results

This analysis included 1445 visits among 382 individuals between June 2018 and February 2022. The median number of visits per participant was 4.0 and the interquartile range was 2.0-5.0. Among all visits, 476 (32.9%) were among those who reported methamphetamine use, 716 (49.6%) were among those who reported use of substances other than methamphetamine, and 253 (17.5%) were among those who reported no substance use. Among visits reporting use of substances other than methamphetamine, the most common were binge drinking (n=410, 57.3%) and cannabis use (n=468, 65.4%). Across visits, the average age of participants was 35.5, 775 (53.5%) were living with HIV, and 615 (42.6%) identified as Latinx/Hispanic/Spanish, 592 (41%) identified as Black/African American, 170 (11.8%) identified as White, and 68 (4.7%) identified as another race/ethnicity (**Table 3.1**).

Among the 476 visits where methamphetamine use was reported, 154 (35.9%) reported unstable housing, 173 (37.8%) reported unemployment, and 199 (41.8%) reported depressive symptoms. In comparison, among visits where use of substances other than methamphetamine was reported, 66 (10.3%) reported unstable housing, 131 (18.4%) reported unemployment, and 155 (21.6%) reported depressive symptoms; among visits where no substance use was reported, 26 (11.5%) reported unstable housing, 38 (15.5%) reported unemployment, and 44 (17.4%) reported depressive symptoms (**Table 3.1**).

Table 3.1 Characteristics of 1445 visits contributed by 382 mSTUDY participants, June 2018 – February 2022

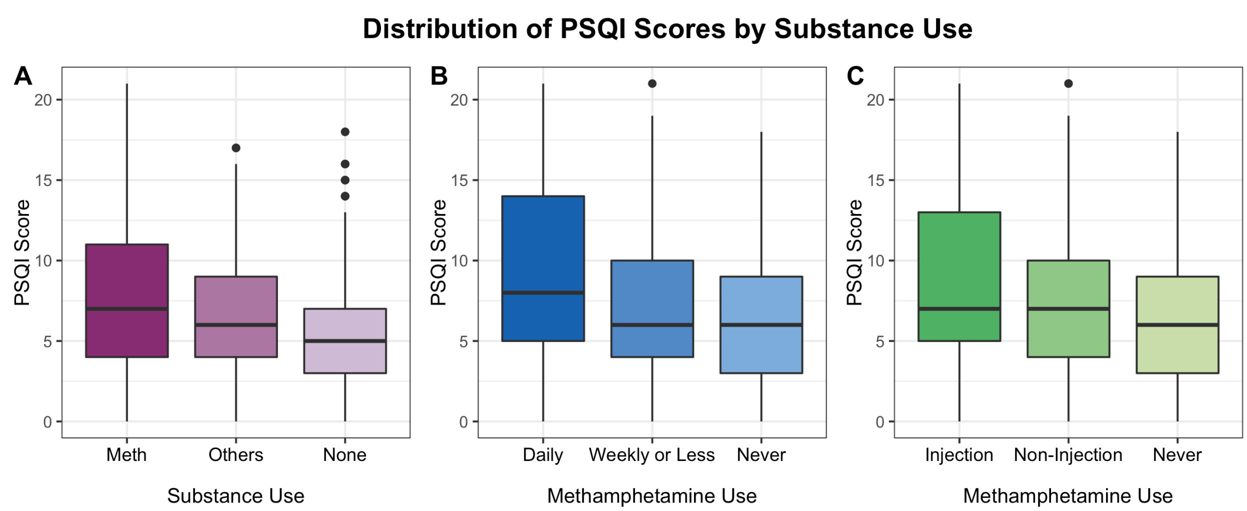
		Substance Use		
	Total (n=1445)	**Methamphetamine[1] (n=476)**	**Others[2] (n=716)**	**None (n=253)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Sleep Deficiency[3]	806 (55.8)	309 (64.9)	394 (55)	103 (40.7)
PSQI Score (median, IQR)	6.0 (4.0-9.0)	7.0 (4.0-11.0)	6.0 (4.0-9.0)	5.0 (3.0-7.0)
Socio-Demographics				
Age at Visit, (mean, SD)	35.5 (7)	36.4 (6.8)	34.4 (6.8)	37 (7.3)
Race/Ethnicity				
Latinx/Hispanic/Spanish	615 (42.6)	198 (41.6)	320 (44.7)	97 (38.3)
Black/African American	592 (41)	192 (40.3)	293 (40.9)	107 (42.3)
White	170 (11.8)	52 (10.9)	77 (10.8)	41 (16.2)
Other	68 (4.7)	34 (7.1)	26 (3.6)	8 (3.2)
HIV-Positive	775 (53.7)	324 (68.4)	295 (41.2)	156 (61.9)
Unstable Housing[4]	192 (17.4)	154 (35.9)	66 (10.3)	26 (11.5)
Unemployed	342 (24.2)	173 (37.8)	131 (18.4)	38 (15.5)
Depressive Symptoms[5]	398 (27.5)	199 (41.8)	155 (21.6)	44 (17.4)
Substance Use, past 6 mos.				
Cigarette Smoking, current	314 (21.8)	203 (42.7)	111 (15.5)	0 (0)
Binge Drinking[6]	597 (41.3)	187 (39.3)	410 (57.3)	0 (0)
Cannabis Use	728 (50.4)	260 (54.6)	468 (65.4)	0 (0)
Crack or Cocaine Use	231 (16)	116 (24.4)	115 (16.1)	0 (0)
Heroin, Fentanyl, RX Opioid Use	53 (3.7)	49 (10.3)	4 (0.6)	0 (0)
Methamphetamine Use				
Frequency				
Daily	133 (9.2)	133 (27.9)	0 (0)	0 (0)
Weekly or less	343 (23.7)	343 (72.1)	0 (0)	0 (0)

Never	969 (67.1)	0 (0)	716 (100)	253 (100)
Mode of Administration				
Injection	89 (6.2)	89 (18.7)	0 (0)	0 (0)
Non-injection	387 (26.8)	387 (81.3)	0 (0)	0 (0)
None	969 (67.1)	0 (0)	716 (100)	253 (100)

Abbreviations: SD = standard deviation, IQR = interquartile range
[1]may include other substances (cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking)
[2]other substances include cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking
[3]defined as score above 5 on Pittsburgh Sleep Quality Index
[4]defined as not having a regular place to stay at least once in past 6 months
[5] defined as Center for Epidemiologic Studies Depression Scale (CES-D) score ≥23
[6] defined as having 6 or more drinks on one occasion

Cigarette smoking, crack or cocaine use, and heroin, fentanyl, or prescription opioid use were more common at visits where methamphetamine use was reported (42.7% vs. 15.5%, 24.4% vs. 16.1%, and 10.3% vs. 0.6%, respectively). Binge drinking and cannabis use were more common at visits where substances other than methamphetamine were used (57.3% vs. 39.3% and 65.4% vs. 54.6%, respectively) (**Table 3.1**). In **Figure 3.1** comparison of the distribution of PSQI scores show potential dose-response relationships between frequency and mode of administration of methamphetamine use.

Figure 3.1 Distribution of PSQI Scores by substance use across visits, June 2018 – February 2022



Logistic regression results are displayed in **Table 3.2**. Without considering covariates, the odds of sleep deficiency among those who reported methamphetamine use were 2.69 (95% CI: 1.81 – 4.00) times that of participants who reported no substance use. The odds of sleep deficiency among those who reported daily methamphetamine use were 2.66 (95% CI: 1.57 – 4.51) times that of participants who reported no methamphetamine use and the odds of sleep deficiency among those who reported weekly or less methamphetamine use were 1.52 (95% CI: 1.11 – 2.07) times that of participants who reported no methamphetamine use. The odds of sleep deficiency among those who reported injection of methamphetamine were 1.96 (95% CI: 1.17 – 3.31) times that of participants who reported no methamphetamine use and the odds of sleep deficiency among those who reported modes of administration other than injection of methamphetamine were 1.71 (95% CI: 1.26 – 3.24) times that of participants who reported no methamphetamine use.

After adjusting for age, race/ethnicity, HIV-status, unstable housing, and depressive symptoms, the odds of sleep deficiency among those who reported methamphetamine use were 1.89 (95% CI: 1.20 – 2.98) times that of participants who reported no substance use. After adjusting for age, race/ethnicity, HIV-status, unstable housing, depressive symptoms, cigarette smoking, binge drinking, cannabis use, and crack or cocaine use, frequency of methamphetamine use and mode of administration of methamphetamine were not associated with sleep deficiency (**Table 3.2**).

Figure 3.2 shows that the prevalence of sleep deficiency among methamphetamine users who experienced depressive symptoms is 79.4% (n=158) compared to 54.5% (n=151) among methamphetamine users who did not experience depressive symptoms. The prevalence of sleep deficiency among methamphetamine users who experienced unstable housing is 69.4% (n=107) compared to 61.1% (n=168) among methamphetamine users who did not experience unstable housing.

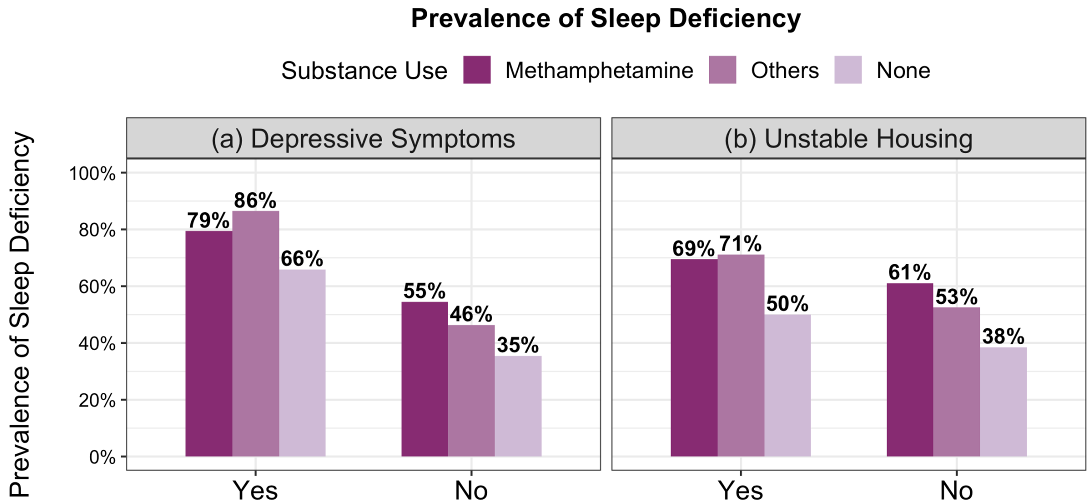
Table 3.2. Association of methamphetamine use with sleep deficiency across mSTUDY visits, June 2018 – February 2022.

	Bivariate Associations	Adjusted Association (Use)	Adjusted Association (Frequency)	Adjusted Association (Mode of Administration)
	OR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Substance Use[1]				
Methamphetamine[2]	2.69 (1.81, 4.00) **	1.89 (1.20, 2.98) **		
Other substances[2]	1.78 (1.23, 2.57) **	1.73 (1.17, 2.57) **		
None	1.00	1.00		
Frequency of Methamphetamine Use				
Daily	2.66 (1.57, 4.51) **		1.45 (0.73, 2.87)	
Weekly or less	1.52 (1.11, 2.07) **		1.11 (0.76, 1.61)	
Never	1.00		1.00	
Methamphetamine Mode of Administration				
Injection	1.96 (1.17, 3.31) *			1.21 (0.62, 2.36)
Non-injection	1.71 (1.26, 2.34) **			1.16 (0.8, 1.68)
None	1.00			1.00
Age at visit	1.00 (0.97, 1.02)	1.00 (0.97, 1.02)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Race/Ethnicity				
Black/African American	1.03 (0.62, 1.74)	0.98 (0.55, 1.74)	0.95 (0.53, 1.70)	0.95 (0.53, 1.71)
Hispanic/Latinx	1.33 (0.79, 2.23)	1.28 (0.71, 2.31)	1.31 (0.72, 2.38)	1.32 (0.72, 2.40)
Other	1.09 (0.48, 2.48)	0.68 (0.25, 1.86)	0.63 (0.23, 1.78)	0.64 (0.23, 1.82)
White	1.00	1.00	1.00	1.00
HIV-positive	1.16 (0.85, 1.57)	1.05 (0.74, 1.49)	1.11 (0.78, 1.58)	1.11 (0.78, 1.57)
Depressive Symptoms[3]	4.83 (3.46, 6.75) **	4.35 (2.97, 6.39) **	4.22 (2.88, 6.19) **	4.27 (2.91, 6.26) **
Unstable Housing[4]	1.94 (1.41, 2.68) **	1.55 (1.07, 2.25) *	1.62 (1.12, 2.35) *	1.64 (1.13, 2.38) **
Cigarette Smoking	1.6 (1.11, 2.29) *		1.04 (0.67, 1.61)	1.06 (0.68, 1.64)
Binge Drinking[5]	1.4 (1.09, 1.81) **		1.36 (1.02, 1.82) *	1.35 (1.01, 1.80) *
Cannabis Use	1.62 (1.24, 2.13) **		1.44 (1.06, 1.96) *	1.43 (1.05, 1.95) *
Crack or Cocaine Use	1.58 (1.04, 2.38) *		1.36 (0.81, 2.29)	1.37 (0.82, 2.29)

Abbreviations: OR = odds ratio, AOR = adjusted odds ratio, **p<0.01, *p<0.05

[1] all substance use reported for past 6 months unless otherwise noted
[2] includes other substances (cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge alcohol)
[3] defined as Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 23
[4] defined as not having a regular place to stay at least once in the past six months
[5] defined as having 6 or more drinks on one occasion

Figure 3.2. Prevalence of sleep deficiency by substance use, depressive symptoms, and unstable housing across visits, June 2018 – February 2022.



Data from six visits were used to investigate longitudinal patterns in PSQI scores. Among 1445 total observations, 382 were baseline visits, 215 were first follow-up visits, 224 were second follow-up visits, 200 were third follow-up visits, 173 were fourth follow-up visits, and 151 were fifth follow-up visits. The proportion of observations was similar across visits for those who reported methamphetamine use, those who reported using substances other than methamphetamine, and those who reported no substance use (**Table 3.3**).

Table 3.3. Number of observations per visit among mSTUDY participants, June 2018 – February 2022.

	Total (n=1445)	Substance Use: Methamphetamine[1] (n=476)	Others[2] (n=716)	None (n=253)
	n (row %)	n (row %)	n (row %)	n (row %)
Baseline	382 (100.0)	135 (35.3)	183 (47.9)	64 (16.8)
Follow-up visit 1	215 (100.0)	70 (32.6)	103 (47.9)	42 (19.5)
Follow-up visit 2	224 (100.0)	73 (32.6)	108 (48.2)	43 (19.2)
Follow-up visit 3	200 (100.0)	68 (34)	102 (51)	30 (15)
Follow-up visit 4	173 (100.0)	54 (31.2)	88 (50.9)	31 (17.9)
Follow-up visit 5	151 (100.0)	47 (31.1)	75 (49.7)	29 (19.2)

[1]may include other substances (cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking)
[2]other substances include cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking

Table 3.4. Growth models of longitudinal changes in PSQI score, June 2018 – February 2022.

	Unconditional Growth Model		Conditional Growth Model (Substance Use)	
	Estimate (95%CI)	P-Value	Estimate (95%CI)	P-Value
Random Effects				
Intercept	11.73 (--)	<0.01**	11.30 (--)	<0.01**
Slope	0.33 (--)	<0.01**	0.33 (--)	<0.01**
Residual	7.13 (--)	<0.01**	7.06 (--)	<0.01**
Fixed Effects				
Intercept	7.25 (6.84, 7.66)	<0.01**	6.25 (5.63, 6.87)	<0.01**
Visit	-0.12 (-0.23, -0.00)	0.04*	-0.12 (-0.23, -0.01)	0.04*
Substance Use				
Methamphetamine[1]			1.80 (1.12, 2.48)	<0.01**
Other substances[2]			0.75 (0.18, 1.33)	0.01*
None			1.00	

Abbreviations: **p<0.01, *p<0.05
[1]may include other substances (cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking)
[2]other substances include cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking

Longtiudinal model results are presented in **Table 3.4**. Without considering any covariates, the unconditional model shows that the average PSQI score was 7.25 (95% CI: 6.84 – 7.66). The average PSQI score decreased minimally over time (-0.12, 95% CI: -0.23, -0.00), though this does not represent a meaningful decrease. When considering substance use in a conditional model, methamphetamine use was associated with 1.80 (95% CI: 1.12, 2.48) point increase in PSQI score compared to no substance use. No significant interaction between substance use and time was observed (data not shown).

Additional conditional growth curve models are presented in **Table 3.5**. No significant interaction was observed between substance use and depressive symptoms or substance use and unstable housing. Based on background knowledge and limited statistical power to observe a significant interaction, interaction terms were still included in the final models. Among those who reported methamphetamine use, experiencing depressive symptoms was associated with a 2.41 (95% CI: 1.73, 3.09) point increase in average PSQI score compared to those not experiencing depressive symptoms (2.41 = 2.68 – 0.27). Among those who reported methamphetamine use, experiencing unstable housing was associated with a 0.91 (95% CI: 0.14, 1.68) point increase in average PSQI score compared to those not experiencing unstable housing (0.91 = -0.05 + 0.96).

Table 3.5. Growth curve models of longitudinal change in PSQI score by substance use, depressive symptoms, and unstable housing, June 2018 – February 2022.

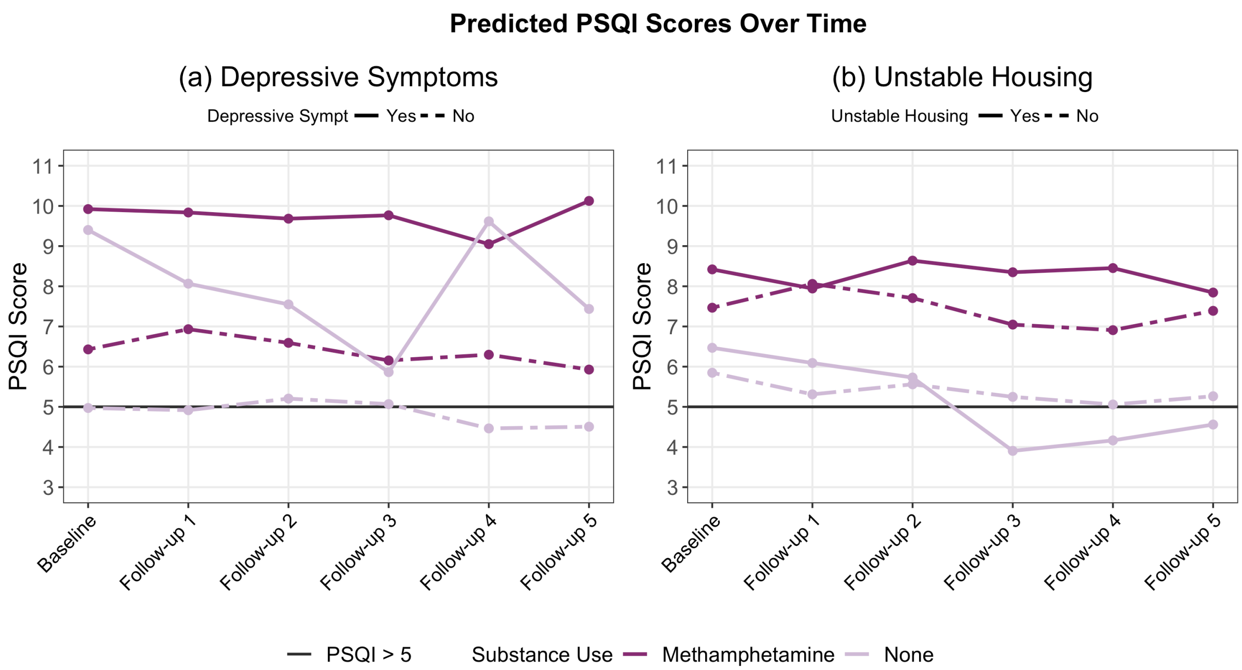
	Conditional Growth Model (Substance use * Depressive Symptoms)		**Conditional Growth Model** (Substance use * Unstable Housing)	
	Estimate (95% CI)	**P**	**Estimate (95% CI)**	**P**
Random Effects				
Intercept	8.66 (--)	<0.01**	11.48 (--)	<0.01**
Slope	0.26 (--)	<0.01**	0.38 (--)	<0.01**

Residual	6.92 (--)	<0.01**	6.90 (--)	<0.01**
Fixed Effects				
Intercept	5.57 (4.95, 6.18)	<0.01**	6.13 (5.44, 6.83)	<0.01**
Visit	-0.09 (-0.20, 0.01)	0.08	-0.1 (-0.22, 0.03)	0.14
Substance Use				
Methamphetamine[1]	1.44 (0.72, 2.17)	<0.01**	1.62 (0.83, 2.41)	<0.01**
Other substances[2]	0.59 (-0.01, 1.19)	0.05	0.66 (0.01, 1.31)	0.05
None	1.00		1.00	
Depressive Symptoms[3]	2.68 (1.55, 3.81)	<0.01**		
Substance Use * Depressive Symptoms				
Meth * Depressive Symptoms	-0.27 (-1.57, 1.02)	0.68		
Other Subs * Depressive Symptoms	0.50 (-0.78, 1.77)	0.44		
Unstable Housing[4]			-0.05 (-1.54,1.44)	0.95
Substance Use * Unstable Housing				
Meth * Unstable Housing			0.96 (-0.72, 2.64)	0.26
Other Subs * Unstable Housing			0.43 (-1.31, 2.16)	0.63

Abbreviations: **p<0.01, *p<0.05
[1]may include other substances (cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking)
[2]other substances include cocaine, ecstasy, party drugs, heroin, RX opioids, cannabis, binge drinking, cigarette smoking
[3] defined as Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 23
[4] defined as not having a regular place to stay at least once in the past six months

Lastly, all models revealed significant variation between individuals' average PSQI scores and rate of change in PSQI scores over time; this is evident from estimates of the variance of the random intercept and slope. In addition, the change in the estimated variance of the random intercept from 11.73 to 11.30 suggests that substance use accounts for 3.7% of the individual differences in PSQI score (**Table 3.4**). Substance use and depressive symptoms combined account for 26.2% of individual differences in PSQI score ([11.73-8.66]/11.73) (**Table 3.5**).

Figure 3.3. Predicted PSQI scores from conditional growth curve models by substance use, depressive symptoms, and unstable housing, June 2018 – February 2022.



Results of the models in **Table 3.5** are presented visually in **Figure 3.3**. Those who reported use of substances other than methamphetamine are omitted from the figure to increase clarity. The predicted mean PSQI score over time in **Figure 3.3(a**) is consistently the highest among those who reported methamphetamine use and depressive symptoms. In addition, the biggest difference was observed between those with and without depressive symptoms, rather than those who used methamphetamine vs. no substances. The predicted mean PSQI score over time in **Figure 3.3(b)** is consistently the highest among those who reported methamphetamine use and unstable housing, though the largest difference appears to be among those who reported methamphetamine use compared to those who reported no substance use.

3.5 Discussion

Conclusions

This study revealed important findings about the association of methamphetamine use and sleep deficiency among MSM. In comparison to those who do not use any substances, those who use methamphetamine are more likely to experience sleep deficiency. In addition, among those who use methamphetamine, experiencing depressive symptoms and/or unstable housing may further negatively impact sleep. Lastly, MSM living with or at high risk of acquiring HIV experience consistent sleep deficiency over time, especially those use who use methamphetamine and experience depressive symptoms and/or unstable housing.

Despite well-established links between HIV-status and sleep deficiency, this study did not observe association between HIV-status and sleep deficiency, regardless of substance use.[59-63] This may be explained by the fact that mSTUDY participants who are HIV-negative are at high risk of acquiring HIV and thus experience many of the same risk factors for sleep deficiency, including substance use and depressive symptomology, as PLWH.

Limitations

It is important to keep in mind the limitations of this study. First, nearly all of the data for this analysis was collected by self-report. The objectivity of self-report data cannot be guaranteed as participants may not answer all questions accurately. This social desirability bias is particularly likely when collecting data about sensitive behaviors such as substance use, where participants are likely to underreport these behaviors. Unfortunately, there are currently no reliable, cost-effective biomarkers that can capture patterns of substance use over longer periods of time. The mSTUDY team works to minimize social desirability bias with a well-designed behavioral survey, by creating a welcoming environment for participants, and by using computer-assisted self-interviewing (CASI) rather than face-to-face interviews. Informal analyses found 87% agreement between self-report and urine toxicology screens for methamphetamine, suggesting that mSTUDY is collecting high quality self-report data about substance use behavior.

This study may also be limited by forms of measurement error other than social desirability bias. The PSQI has been widely used to measure sleep deficiency in diverse populations since its creation in 1989. Despite its frequent use in studies of alcohol use disorder, it does not appear to have been specifically validated for populations who use alcohol or other substances. In addition to substance users, mSTUDY participants belong to a number of unique populations including MSM, PLWH, and people experiencing unstable housing or homelessness. The PSQI does not appear to have been validated in any of these populations, or among individuals at the intersections of these populations. To our knowledge, the closest population that the PSQI has been validated for is people with psychiatric disorders in Japan.[95] Thus, the PSQI results should be interpreted with some caution.[96]

The results of this study may also be subject to bias from unmeasured confounding. While mSTUDY captures many relevant background factors, it is limited in the data it can collect. Despite the high retention rate in mSTUDY, there may also be selection bias due to loss to follow-up. Also, most analyses in this study are cross-sectional, and the relationship between methamphetamine use and sleep deficiency is often cyclic.[81] Lastly, this study is limited by its sample size, particularly the longitudinal analyses that lacked the statistical power to detect significant interactions and account for additional covariates. These limitations will severely limit the ability to make any causal inferences from this study.

Lastly, mSTUDY is a convenience sample that is not necessarily representative of all MSM in Los Angeles. While this does not impact the internal validity of this study, caution should be taken when considering the generalizability of the results.

Significance and Future Directions

This study provides important insight into sleep patterns among MSM living with or at high risk of acquiring HIV, including those who use methamphetamine. Longitudinal analyses revealed consistent sleep deficiency in this population over time, particularly among those who use methamphetamine and experience depressive symptoms.

Frequency of methamphetamine use and methamphetamine mode of administration were not associated with sleep deficiency after controlling for relevant confounders. However, depressive symptoms and unstable housing remained strongly associated with sleep deficiency, and while unable to detect a significant interaction, these factors likely further negatively impact sleep deficiency among those who use methamphetamine. In addition, previous findings in this cohort found that methamphetamine use accounted for 10% of individual variance in depressive symptomology.[97] This suggests that depressive symptoms is an important factor in the relationship between methamphetamine use and sleep deficiency among MSM, and warrants further study.

Further research is needed to better understand how interventions focused on alleviating depressive symptoms and unstable housing could decrease the prevalence of sleep deficiency among those who use methamphetamine. This is particularly relevant, as there are well-established methods for treating depression and unstable housing, while treatment for methamphetamine use has been shown to be only moderately effective and there are no FDA approved treatments.[98]

4 Association of methamphetamine use and sleep deficiency with sexual and HIV risk behaviors among men who have sex with men living with or at high risk of acquiring HIV

4.1 Abstract

Background: The United States is facing a growing epidemic of sexually transmitted infections (STI). Methamphetamine use is a well-established determinant of STI incidence, but the relationship between sleep deficiency and STIs is poorly understood. This study investigated how sleep deficiency and methamphetamine use are jointly associated with both sexual and HIV risk behaviors as well as measurable disease outcomes related to STIs and HIV.

Methods: This analysis included individuals from a cohort of men who have sex with men who participated in semi-annual study visits between June 2018 and February 2022. Sleep deficiency was defined as a Pittsburgh Sleep Quality Index (PSQI) score above five, methamphetamine use and risk behaviors were self-reported, and STIs and HIV viral load were measured from biospecimen samples. Associations between sleep deficiency and STI and HIV outcomes of interest were investigated using logistic regression with generalized estimating equations. Differences in the association between sleep deficiency and behavioral outcomes of interest were compared across levels of methamphetamine use frequency by including interaction terms in the models. All models were adjusted for age at visit, race/ethnicity, HIV-status, unstable housing, depressive symptoms, methamphetamine use, cannabis use, binge drinking, and cigarette smoking.

Results: Analyses included 1445 visits among 382 individuals. Across visits, the average age of participants was 36, 775 (54%) were living with HIV, and 615 (43%) identified as Latinx/Hispanic/Spanish, 592 (41%) identified as Black/African American, 170 (12%) identified as White, and 68 (5%) identified as another race/ethnicity. Sleep deficiency was associated with having at least one new anal sex partner (aOR=1.63, 95% CI: 1.22-2.17), having concurrent sex

partners (aOR=1.61, 95% CI: 1.00-2.60), having exchange sex (aOR=2.74, 95% CI: 1.18-6.36), attending a circuit, hookup, or sex party (aOR=2.62, 95% CI: 1.70-4.05), and missing HIV medications (aOR=2.04, 95% CI: 1.25-3.34). Sleep deficiency was not associated with STI incidence or having a detectable HIV viral load.

Conclusions: Findings from this study reveal that sleep deficiency is independently associated with sexual and HIV risk behaviors among men who have sex with men after accounting for methamphetamine use. Additionally, associations between sleep deficiency and behavioral outcomes may be strongest among those who used methamphetamine weekly or less. The lack of link between sleep deficiency and disease outcomes may suggest that sleep deficiency is only associated with risk behaviors, but not the disease outcomes with which they are associated. Taken together these findings highlight the importance of sleep health among men who have sex with men.

4.2 Background

The United States is facing a growing sexually transmitted infection (STI) epidemic: since 2014, chlamydia, gonorrhea, and syphilis incidence has increased by 19%, 63% and 71%, respectively. While it is hard to accurately estimate STI incidence in men who have sex with men (MSM) due to difficulty in estimating the total population size, it is known that MSM share a disproportionate burden of this epidemic and likely account for well over half of gonorrhea and syphilis cases among men in the United States.[13,99] The disparity in STI incidence between MSM and the general population is likely explained by a combination of social, behavioral, and biological reasons including stigma and prevalence of high risk sexual activity that may include a large number of partners and inconsistent condom use. In addition, there is an increased risk of STI acquisition associated with receptive anal intercourse. Lastly, the chronic immune activation caused by HIV infection increases susceptibility to co-infection by other pathogens, and HIV is highly prevalent among MSM.[13]

Substance abuse has been well-established as a strong determinant of STI incidence among MSM. In particular, methamphetamine use is common during sexual activity and is associated with increased likelihood of risk behaviors such as having multiple partners and engaging in condomless anal intercourse.[100-103] In fact, a study of MSM in London found that the odds of bacterial and rectal STIs among participants who reported substance use during sexual activity compared to those who did not were 2.83 and 3.10, respectively.[104] Studies of cannabis use and STI acquisition have mixed results as to whether cannabis may be protective against STIs, warranting further research on this topic.[105,106]

In contrast to the relationship between substance use and STI incidence, the relationship between sleep deficiency and STI incidence among MSM is poorly understood. Previous studies have established relationships between sleep deficiency and sexual risk-taking, but have not linked sleep deficiency to a related, measurable health outcome such as STI incidence.[107] For example, a study of MSM found that the odds of reporting condomless receptive anal intercourse among those reporting poor sleep quality compared to those who reported good sleep quality was 2.36. In addition, the odds of having receptive anal intercourse with more partners for these two groups was 1.71.[10] Another study found positive associations between poor sleep quality, short sleep duration, problems falling asleep, and problems staying awake with sexual risk-taking behavior including condomless anal intercourse and high numbers of partners.[46]

It is well-established that sleep deficiency is common among PLWH.[59-63] In a sample of PLWH in the San Francisco Bay Area, 63% of participants reported poor sleep quality and actigraphy revealed that an average of 20.5% of participants' total sleep time was actually spent awake.[64] In an online survey of American MSM, 35.1% of MSM living with HIV reported bad sleep in the past month compared to 25.9% of MSM who were HIV-negative; 33.9% of MSM living with HIV had used sleep medication in the past month, compared to 26.6% of MSM who were HIV-negative.[65] In addition, sleep deficiency has been linked to difficulty adhering to HIV medications, which may in turn be associated with poor HIV outcomes.[108,109]

Further research is needed to expand knowledge of the established associations between sleep deficiency and sexual risk behaviors, especially among MSM who use methamphetamine. This study aims to better understand how sleep deficiency and methamphetamine use are associated with both sexual and HIV risk behaviors as well as measurable disease outcomes related to STIs and HIV.

4.3 Methods

Data Source

The present analysis used data from mSTUDY, a National Institute on Drug Abuse (NIDA)-funded cohort in Los Angeles based at the University of California, Los Angeles that began enrolling participants in 2014. The mSTUDY cohort includes mostly Black/African American and Latino/Hispanic MSM aged 18-45 with a history of drug use; half of participants are HIV positive. Every six months, study participants complete a behavioral survey and provide biospecimens. Due to the COVID-19 pandemic, between March 2020 and June 2021, participants completed the behavioral survey remotely and did not provide biospecimens for STI and HIV viral load tests.

Inclusion criteria for mSTUDY include being between age 18 and 45 at baseline, assigned male sex at birth, ability to provide informed consent, and willingness to return for follow-up visits. Participants must also be HIV-positive or report high risk for HIV acquisition (condomless anal intercourse with a male partner in the past six months).

The University of California, Los Angeles Institutional Review Board approved the study, and all participants provided written informed consent.

Measures

Outcome: Two types of behavioral outcomes and two disease outcomes were used in this analysis. Sexual and HIV risk behaviors were measured by self-report. Sexual risk behaviors included reporting a new anal sex partner in the past six months, reporting concurrent sex partners in the past six months, reporting exchange sex in the past three months, and attending a circuit, hookup, or sex party in the past six months. Exchange sex was defined as giving or getting money, drugs, or a place to stay in exchange for anal sex. HIV risk behaviors included reporting one or more missed appointments with an HIV care provider in the past six months and reporting missed HIV medication over the past weekend.

The disease outcome related to sexual risk behaviors was having a positive test for any STI. Chlamydia and Gonorrhea were assessed using urine tests, rectal swabs, and throat swabs. Syphilis was assessed using the rapid plasma regain test (RPR), with confirmatory testing using the Treponema pallidum particle agglutination test (TPPA). The result was counted as positive if it was determined to be primary, secondary, or early latent syphilis based on standard of care health department investigation of syphilis cases as specified by the Centers for Disease Control STD prevention and Treatment guidelines.[110] The disease outcome related to HIV was having a detectable viral load, defined as greater than 20 copies per milliliter.

Exposure: Sleep deficiency was assessed between June 2018 and February 2022 using the Pittsburgh Sleep Quality Index (PSQI), a widely used, validated questionnaire that measures sleep quality and disturbance in the past 30 days. Measures of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction are combined into a total score that ranges from 0-21; higher scores are indicative of worse sleep.[87] Sleep deficiency was defined as a PSQI score above 5.[87]

Covariates: All covariates except HIV-status were measured via self-report, except HIV-status which was measured with a blood test. Race/Ethnicity was categorized as Black/African American, Hispanic/Latinx/Spanish, white, and other. Unstable housing was defined as not having a regular place to stay at least one time in the past six months. Depressive symptoms were defined as a score above 23 on the Centers for Epidemiologic Studies Depression Scale (CES-D), which measures depressive symptomology in the past seven days. Previous research suggests that 23 is a more accurate cutoff for PLWH than the more commonly used score of 16 for the general population.[88] Binge drinking was defined as having six or more drinks on at least one occasion in the past six months. All other substance use was defined as using the substance at least one time in the past six months and was measured using a version of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) that was adapted to capture substance use in the past six months.[31] Methamphetamine use was also categorized as daily, weekly or less, and never to capture frequency of use.

Analytic Strategy

Characteristics of the participants were first compared across visits. Socio-demographics, substance use, sexual risk behaviors, STIs, HIV risk behaviors, and HIV outcomes were compared for those who reported sleep deficiency and those who did not report sleep deficiency. Count and percentage were calculated for categorical variables, and mean and standard deviation were calculated for continuous variables.

The association between sleep deficiency and each outcome of interest was estimated using logistic regression. Bivariate associations were first considered, and then multiple logistic regression was used to account for covariates. Logistic regression models were fit with generalized estimating equations with independent correlation structure to account for repeated observations on the same subject.[89,90] Multiple logistic regression models were adjusted for age at visit, race/ethnicity, unstable housing, depressive symptoms, methamphetamine use, cannabis use, binge drinking, and cigarette smoking. Models focused on STI-related outcomes also adjusted for HIV-status, and models focused on HIV-related outcomes included only

PLWH. Covariates were chosen based on literature review. Models were fit using the R package gee.[91]

Differences in the association between sleep deficiency and behavioral outcomes of interest were compared across levels of methamphetamine use frequency by including interaction terms in the models. The odds of the outcome of interest for those with sleep deficiency compared to those without sleep deficiency was calculated among those who reported daily, weekly or less, or no methamphetamine use. Exchange sex was not considered as an outcome in interaction analyses due to insufficient statistical power.

4.4 Results

This analysis included 1445 visits among 382 individuals between June 2018 and February 2022. Among all visits, 806 (55.8%) were among those with sleep deficiency, and 639 (44.2%) were among those without sleep deficiency. Across visits, the average age of participants was 35.5, 775 (53.7%) were living with HIV, and 615 (42.6%) identified as Latinx/Hispanic/Spanish, 592 (41%) identified as Black/African American, 170 (11.8%) identified as White, and 68 (4.7%) identified as another race/ethnicity (**Table 4.1**)

Among visits where sleep deficiency was reported, 130 (21.6%) reported unstable housing, 204 (25.8%) reported being unemployed, and 321 (39.8%) reported depressive symptoms compared to 62 (12.4%), 138 (22.2%), and 77 (12.1%) of those visits where sleep deficiency was not reported, respectively. Among visits where sleep deficiency was reported, 309 (38.3%) reported methamphetamine use, 449 (55.7%) reported cannabis use, 362 (44.9%) reported binge drinking, and 203 (25.2%) reported cigarette smoking. In comparison, among visits where sleep deficiency was not reported, 167 (26.1%) reported methamphetamine use, 279 (43.7%) reported cannabis use, 235 (36.8%) reported binge drinking, and 111 (17.4%) reported cigarette smoking (**Table 4.1**).

Table 4.1. Characteristics of mSTUDY participants across visits, June 2018 – February 2022.

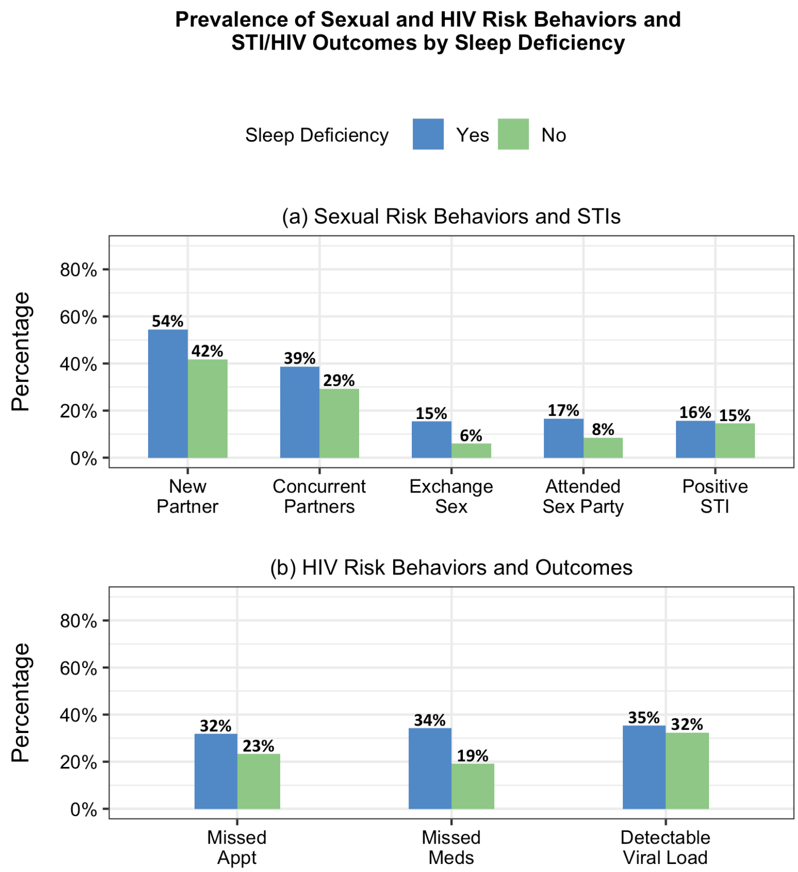
	Total (n=1445)	Sleep Deficiency[1] (n=806)	No Sleep Deficiency (n=639)
	n (%)	n (%)	n (%)
Socio-Demographics			
Age at Visit, mean (SD)	35.5 (7)	35.5 (6.9)	35.6 (7.2)
Race/Ethnicity			
Latinx/Hispanic/Spanish	615 (42.6)	365 (45.3)	250 (39.1)
Black/African American	592 (41)	315 (39.1)	277 (43.3)
White	170 (11.8)	89 (11)	81 (12.7)
Other	68 (4.7)	37 (4.6)	31 (4.9)
HIV-Positive	775 (53.7)	445 (55.3)	330 (51.7)
Unstable Housing[2]	192 (17.4)	130 (21.6)	62 (12.4)
Unemployed	342 (24.2)	204 (25.8)	138 (22.2)
Depressive Symptoms[3]	398 (27.5)	321 (39.8)	77 (12.1)
Substance Use, past 6 mos.			
Methamphetamine Use	476 (32.9)	309 (38.3)	167 (26.1)
Cannabis Use	728 (50.4)	449 (55.7)	279 (43.7)
Binge Drinking[4]	597 (41.3)	362 (44.9)	235 (36.8)
Cigarette Smoking (current)	314 (21.8)	203 (25.2)	111 (17.4)
Sexual Risk Behavior and STIs			
New anal sex partner, past 6 mos.	704 (48.9)	437 (54.5)	267 (41.8)
Concurrent sex partners, past 6 mos.	250 (34.7)	160 (38.6)	90 (29.3)
Exchange sex, past 3 mos.[5]	88 (11.3)	68 (15.3)	20 (6)
Attended circuit, hook up, or sex party, past 6 mos.	184 (13)	131 (16.6)	53 (8.5)
Positive STI (chlamydia, gonorrhea, and/or syphilis)	105 (15.2)	61 (15.7)	44 (14.5)
HIV Risk Behaviors and Outcomes[6]			
Missed ≥1 appointment with HIV care provider, past 6 mos.	213 (28.2)	138 (31.8)	75 (23.2)
Missed HIV medications, past weekend	198 (27.7)	139 (34.2)	59 (19.1)
Detectable viral load (>20 c/ml)	140 (34.1)	84 (35.3)	56 (32.4)

[1]Sleep deficiency defined as score above five on Pittsburgh Sleep Quality Index (PSQI)
[2]Unstable housing defined as not having a regular place to stay at least once in the past six months
[3]Depressive symptoms defined as a score above 23 on Center for Epidemiologic Studies Depression Scale (CES-D)
[4]Binge drinking defined as having 6 or more drinks on one occasion
[5]Exchange sex defined as gave or got money, drugs, or a place to stay in exchange for anal sex
[6]Among only participants living with HIV

As is shown in **Table 4.1**, at least one new anal sex partner was reported at 704 (48.9%) of visits, having concurrent sex partners was reported at 250 (34.7%) of visits, exchange sex was reported at 88 (11.3%) of visits, and attending a circuit, hookup, or sex party was reported at 184 (13%) of visits. A positive STI test was detected at 105 (15.2%) out of 692 visits where STI testing was conducted. Among PLWH, missing at least one appointment with an HIV care provider was reported at 213 (28.2%) of visits and missing HIV medications was reported at 198 (27.7%) of visits. A detectable HIV viral load was present at 140 (34.1%) of 411 visits where HIV viral load testing was conducted. Differences in outcomes comparing visits where sleep deficiency was reported to visits where sleep deficiency was not reported are displayed in **Figure 4.1**.

Logistic regression results are presented in **Table 4.2**. Bivariate associations were observed between sleep deficiency and all behavioral outcomes, but not between sleep deficiency and the disease outcomes. After adjusting for age at visit, race/ethnicity, HIV-status, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use, the odds of having at least one new anal sex partner among those with sleep deficiency were 1.63 (95% CI: 1.22 – 2.17) times that of those without sleep deficiency; the odds of having concurrent sex partners among those with sleep deficiency were 1.61 (95% CI: 1.00 – 2.60) times that of those without sleep deficiency; the odds of exchange sex among those with sleep deficiency were 2.74 (95% CI: 1.18 – 6.36) times that of those without sleep deficiency; the odds of attending a circuit, hookup, or sex party among those with sleep deficiency were 2.62 (95% CI: 1.7 – 4.05) times that of those without sleep deficiency; and the odds of having at least one STI among those with sleep deficiency were 1.06 (95% CI: 0.63 – 1.78) times that of those without sleep deficiency.

Figure 4.1 Prevalence of sexual risk behaviors, STIs, HIV risk behaviors, and HIV outcomes by sleep deficiency across visits, June 2018 – February 2022.



After adjusting for age at visit, race/ethnicity, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use, the odds of having missed at least one visit with an HIV care provider among those with sleep deficiency were 1.44 (95% CI: 0.88 – 2.35) times that of those without sleep deficiency; the odds of having missed HIV medications among those with sleep deficiency were 2.04 (95% CI: 1.25 – 3.34) times that of those without sleep deficiency; and the odds of having a detectable viral load among those with sleep deficiency were 1.1 (95% CI: 0.63 – 1.93) times that of those without sleep deficiency (**Table 4.2**).

Table 4.2. Association of sleep deficiency with sexual risk behaviors, STIs, HIV risk behaviors, and HIV outcomes across visits, June 2018 – February 2022.

Model Outcome[1]	OR (95% CI)	AOR (95% CI)[2]
Sexual Risk Behavior and STIs		
New anal sex partner, past 6 mos.	1.67 (1.30, 2.13) **	1.63 (1.22,2.17) **
Concurrent sex partners, past 6 mos.	1.52 (1.04, 2.21) *	1.61 (1, 2.6) *
Exchange sex, past 3 mos.[3]	2.86 (1.59, 5.11) **	2.74 (1.18, 6.36) *
Attended circuit, hook up, or sex party, past 6 mos.	2.15 (1.48, 3.10) **	2.62 (1.7, 4.05) **
Positive STI (chlamydia, gonorrhea, and/or syphilis)	1.09 (0.72, 1.68)	1.06 (0.63, 1.78)
HIV Risk Behaviors and Outcomes[4]		
Missed ≥1 appointment with HIV provider, past 6 mos.	1.54 (1.04, 2.27) *	1.44 (0.88, 2.35)
Missed HIV medications, past weekend	2.21 (1.47, 3.31) **	2.04 (1.25,3.34) **
Detectable viral load (>20 c/ml)	1.14 (0.71, 1.82)	1.1 (0.63, 1.93)

Abbreviations: OR=odds ratio, AOR=adjusted odds ratio, STI=sexually transmitted infection, *p<0.05, **p<0.01

[1]Exposure for all models was sleep deficiency, defined as score above 5 on Pittsburgh Sleep Quality Index (PSQI)

[2]Adjusted for age at visit, race/ethnicity, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use; models with sexual behavior as the outcome also adjusted for HIV-status.

[3]Exchange sex defined as gave or got money, drugs, or a place to stay in exchange for anal sex

[4]Among only participants living with HIV

Associations of sleep deficiency with behavioral outcomes by frequency of methamphetamine use are presented in **Table 4.3** and visually in **Figure 4.2** .After adjusting for age at visit, race/ethnicity, HIV-status, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use, the odds of having at least one new anal sex partner among those with sleep deficiency compared to those without sleep deficiency was 1.37 (95% CI: 0.53 - 3.52) for those who used methamphetamine daily, 1.74 (95% CI: 0.98 – 3.06) for those who used methamphetamine weekly or less, and 1.61 (95% CI: 1.14 - 2.28) for those who did not use methamphetamine; the odds of having concurrent sex partners among those with sleep deficiency compared to those without sleep deficiency was 0.94 (95% CI: 0.18 – 4.92) for those who used methamphetamine daily, 2.54 (95% CI: 1.03 – 6.27) for those who used methamphetamine weekly or less, and 1.48 (95% CI: 0.84 - 2.62) for those who did not use methamphetamine; and the odds of attending a circuit, hookup, or sex party among those with sleep deficiency compared to those without sleep deficiency was 1.85 (95% CI: 0.44 – 7.81) for those who used methamphetamine daily, 5.22 (95% CI: 1.86 – 14.63) for those who used methamphetamine weekly or less, and 2.16 (95% CI: 1.34 – 3.5) for those who did not use methamphetamine.

Table 4.3. Association of sleep deficiency with sexual and HIV risk behaviors by frequency of methamphetamine use across visits, June 2018 – February 2022.

	Daily Methamphetamine Use		**Weekly or less Methamphetamine Use**		**No Methamphetamine Use**	
Model Outcome[1]	**OR (95% CI)**	**AOR[2] (95% CI)**	**OR (95% CI)**	**AOR[1] (95% CI)**	**OR (95% CI)**	**AOR[1] (95% CI)**
New anal sex partner	1.38 (0.57, 3.33)	1.37 (0.53, 3.52)	2.05 (1.26,3.35) **	1.74 (0.98, 3.06)	1.5 (1.1, 2.03) **	1.61 (1.14, 2.28) **
Concurrent Sex partners	1.64 (0.47, 5.67)	0.94 (0.18, 4.92)	2.49 (1.21, 5.12) *	2.54 (1.03, 6.27) *	1.2 (0.75, 1.92)	1.48 (0.84, 2.62)
Attended sex party[2]	1.57 (0.46, 5.34)	1.85 (0.44, 7.81)	3.75 (1.72, 8.21) **	5.22 (1.86, 14.63) **	1.7 (1.13, 2.56) *	2.16 (1.34, 3.5) **
Missed HIV meds, past weekend	4.1 (1.35, 12.44) *	3.07 (0.84, 11.2)	1.68 (0.86, 3.28)	1.95 (0.89, 4.27)	2.19 (1.25, 3.83) **	1.94 (1, 3.76)

Abbreviations: OR=odds ratio, AOR=adjusted odds ratio, *p<0.05, **p<0.01

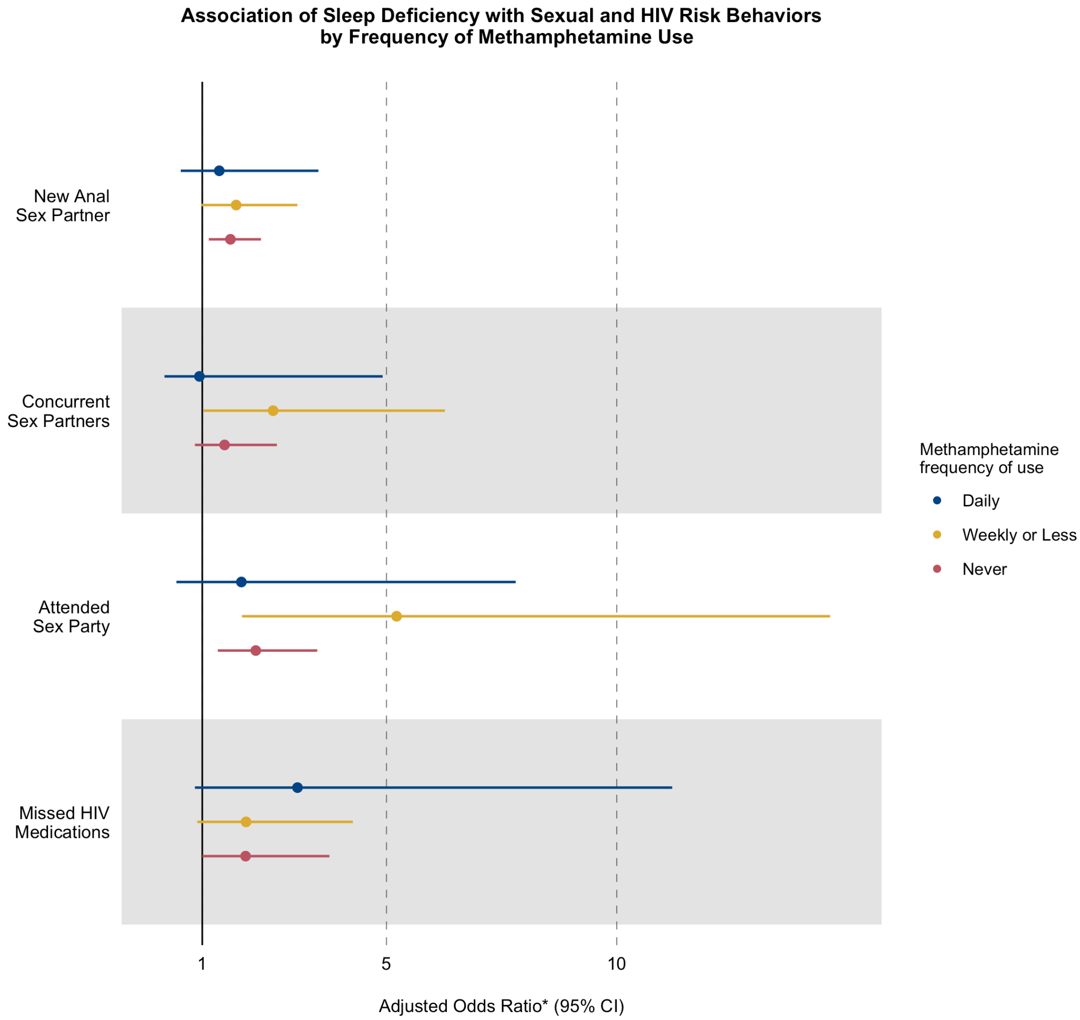
[1]All outcomes reported in past six months unless otherwise stated. Exposure for all models was sleep deficiency, defined as score above 5 on Pittsburgh Sleep Quality Index (PSQI).

[2]Adjusted for age at visit, race/ethnicity, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use; models with sexual behavior as the outcome also adjusted for HIV-status.

[3]Exchange sex defined as gave or got money, drugs, or a place to stay in exchange for anal sex

After adjusting for age at visit, race/ethnicity, unstable housing, depressive symptoms, cigarette smoking, binge drinking, and cannabis use, the odds of having missed HIV medications among those with sleep deficiency compared to those without sleep deficiency was 3.07 (95% CI: 0.84 – 11.2) for those who used methamphetamine daily, 1.95 (95% CI: 0.89 – 4.27) for those who used methamphetamine weekly or less, and 1.94 (95% CI: 1.00 – 3.76) for those who did not use methamphetamine.

Figure 4.2. Visual representation of the adjusted association of sleep deficiency with sexual and HIV risk behaviors by frequency of methamphetamine use across visits, June 2018 – February 2022.



*Adjusted for age at visit, race/ethnicity, HIV-status, unstable housing, depressive symptoms, cigarette smoking, binge drinking, cannabis use

4.5 Discussion

Conclusions

This study offers important insight in the relationship between sleep deficiency and sexual and HIV risk behaviors. After controlling for substance use and socio-demographic factors, sleep deficiency was independently associated with having at least one new anal sex partner, concurrent sex partners, exchange sex, attending a circuit, hookup, or sex party, and missing HIV medications. Sleep deficiency was not associated with disease outcomes (positive STI and detectable viral load) linked to these risk behaviors.

Additionally, descriptive differences were observed in the relationship between sleep deficiency and behavioral outcomes by frequency of methamphetamine use. While not statistically significant, those who report weekly or less methamphetamine use may be more likely to report sexual risk behaviors than those who use methamphetamine daily or not at all. This is likely explained by the fact that those who use methamphetamine on a weekly or less basis tend to use it primarily in social and sexual settings.[20-22] The odds of missing HIV medications among those with sleep deficiency compared to those without may be the highest among those who use methamphetamine daily; frequency of methamphetamine use is strongly correlated with dependence on methamphetamine, and those who use daily are likely dependent upon this highly addictive drug, which could interfere with their ability to acquire and remember to take their HIV medication.

Limitations

It is important to keep in mind the limitations of this study. First, nearly all of the data for this analysis was collected by self-report. The objectivity of self-report data cannot be guaranteed as participants may not answer all questions accurately. This social desirability bias is particularly likely when collecting data about sensitive behaviors such as sexual behavior and substance use, where participants are likely to underreport these behaviors. Unfortunately, there are currently no reliable, cost-effective biomarkers that can capture patterns of substance use over longer periods of time. The mSTUDY team works to minimize social desirability bias with a well-designed behavioral survey, by creating a welcoming environment for participants, and by using computer-assisted self-interviewing (CASI) rather than face-to-face interviews. Informal analyses found 87% agreement between self-report and urine toxicology screens for methamphetamine, suggesting that mSTUDY is collecting high quality self-report data about substance use behavior.

This study may also be limited by forms of measurement error other than social desirability bias. The PSQI has been widely used to measure sleep deficiency in diverse populations since its creation in 1989. Despite its frequent use in studies of alcohol use disorder, it does not appear to have been specifically validated for populations who use alcohol or other substances. In addition to substance users, mSTUDY participants belong to a number of unique populations including MSM, PLWH, and people experiencing unstable housing or homelessness. The PSQI does not appear to have been validated in any of these populations, or among individuals at the intersections of these populations. To out knowledge, the closest population that the PSQI has been validated for is people with psychiatric disorders in Japan.[95] Thus, the PSQI results should be interpreted with some caution.[96]

The results of this study may also be subject to bias from unmeasured confounding. While mSTUDY captures many relevant background factors, it is limited in the data it can collect. Despite the high retention rate in mSTUDY, there may also be selection bias due to loss to follow-up. Also, most analyses in this study are cross-sectional. Lastly, this study is limited by its sample size, particularly the analyses of disease outcomes and the interaction analyses. These limitations will severely limit the ability to make any causal inferences from this study. Lastly, mSTUDY is a convenience sample that is not necessarily representative of all MSM in Los Angeles. While this does not impact the internal validity of this study, caution should be taken when considering the generalizability of the results.

Significance and Future Directions

Taken together with findings from other studies, this analysis highlights the importance of sleep health among MSM living with or at high risk of acquiring HIV.[107] Not only is sleep deficiency highly prevalent in this population, but it is also linked to risk behaviors. The results of this study are especially compelling because they account for substance use (especially methamphetamine use), which is strongly associated with both sleep deficiency and sexual risk behavior and STI/HIV acquisition. Further research is needed to better understand whether interventions focused on alleviating sleep deficiency may reduce the prevalence of sexual and HIV risk behaviors. In addition, because the relationship between substance use and sleep deficiency is cyclic, reduction in sleep deficiency may in turn reduce frequency of substance use.

This study did not find a link between sleep deficiency and having an STI or a detectable viral load. This may suggest that sleep deficiency is only associated with risk behaviors, but not the disease outcomes with which they are associated. Additional research with larger sample sizes is needed to confirm this result as well as to investigate the ways in which risk behaviors may mediate the relationship between sleep deficiency and STI and HIV outcomes.

5 Concluding Remarks

This dissertation provides important insight into the dynamics of methamphetamine use, sleep deficiency, and sexual and HIV risk behaviors among men who have sex with men living with or at high risk of acquiring HIV in Los Angeles, CA. Findings from Chapter 2 revealed differences in trajectories of frequency of methamphetamine use for MSM living with HIV and those who are HIV-negative. In addition, descriptive results revealed that MSM who self-reported involvement in substance use treatment were significantly more likely to have reduced use at their next study visit, especially those who were using frequently. The analysis adds important evidence outside of clinical trials that substance use treatment may reduce methamphetamine use. Future research should incorporate substance use treatment as a time-varying covariate in models to better understand the longitudinal effects of substance use treatment on frequency of methamphetamine use.

Results in Chapter 3 highlighted a noteworthy relationship between methamphetamine use and sleep deficiency. While patterns in sleep did not significantly change over time in this cohort, average PSQI scores consistently remained above the threshold for sleep deficiency. In addition, longitudinal analyses suggested that depressive symptoms, in combination with methamphetamine use, may be an important driver of poor sleep in this population.

Lastly, Chapter 4 revealed an independent association between sleep deficiency and sexual and HIV risk behaviors after accounting for methamphetamine use. This is a significant finding given the well-established and strong associations between methamphetamine use and both sleep deficiency and risk behaviors. Additionally, this analysis suggested that the association between sleep deficiency and sexual risk behaviors may be highest among those who use methamphetamine occasionally, while the association between sleep deficiency and HIV risk behaviors may be highest among those who use methamphetamine frequently. Sleep deficiency was not associated with measurable consequences of these risk behaviors (STI and detectable HIV viral load). Additional research with increased statistical power is needed to confirm these patterns and associations. Taken together, findings from Chapter 3 and Chapter 4 highlight the high prevalence of sleep deficiency among MSM living with or at high risk of acquiring HIV. Future research should not discount the role of sleep not only in overall mental and physical health, but also in relation to substance use and sexual and HIV risk behaviors among MSM.

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