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Sleep Disturbance as a Predictor of Time to Drug and Alcohol Use Treatment in Primary Care

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Abstract

Background—Sleep Disturbances (SDs) are a symptom common to mental health disorders (MHD) and substance use disorders (SUD). We aimed to identify the value of SD as a predictor for subsequent treatment of illicit drug and alcohol use disorders (SUDs) in primary care and relative to the predictive value of mental health disorders (MHDs).

Methods—We used electronic health records data from ambulatory primary care in a safety net Boston area healthcare system from 2013-2015 (n=83,920). SUD (separated into illicit drug use disorder and alcohol use disorder) and MHD were identified through ICD-9 codes and medical record documentation. We estimated Cox proportional hazard models to examine the risk of SUD across four comparison groups (SD only, SD and MHD, MHD only, and neither SD nor MHD).

Results—Compared to patients with no sleep or MHD, patients with SD had a greater risk for subsequent SUD treatment. Approximately one-fifth of patients with SD were treated for an illicit drug use disorder and approximately 12% were treated for alcohol use disorder. Risk for SUD treatment, estimated at over 30% by the end of the study, was greatest for patients with a MHD,

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either alone or comorbid with SD. Risk was greater for older patients and men, and lower for minority patients.

Conclusions—SD and MHD, individually and comorbid, significantly predict subsequent treatment of illicit drug and alcohol use disorder in primary care. Screening and evaluation for SD should be a routine practice in primary care to help with identifying SUD risk.

Keywords

sleep disturbance; substance use disorder; adequate care

1. Introduction

Sleep disturbances (SD) include inability to sleep (insomnia), excessive sleepiness (hypersomnia), daytime sleepiness, abnormal movement or behavior during sleep, or inability to fall asleep at the appropriate time (Harvey & Asarnow, 2014). Sleep disturbances are considered as symptoms of other diagnoses, such as psychiatric disorders including major depressive disorder, bipolar disorder, and autism (Baker & Richdale, 2015; Cohen & Sharkey, 2017) or medical illness, such as diabetes, obesity, and cardiovascular disease (Kamath, Prpich, & Jillani, 2015). SDs are a symptom of virtually all mental health disorders (MHD) and substance use disorders (SUD), most commonly insomnia or hypersomnia (Arnedt, Conroy, & Brower, 2012; Chokroverty, 2000; Krystal, Thakur, & Roth, 2008; Vandrey, Babson, Herrmann, & Bonn-Miller, 2014). Studies examining the effects of alcohol, cocaine, cannabis, opiates, and other addictive substances on sleep clearly indicate they are associated with, and contribute to, disordered sleep (Garcia & Salloum, 2015). Although SD is most often a symptom of another illness or syndrome, primary disorders such as obstructive sleep apnea, chronic insomnia, and restless leg syndrome are commonly first diagnosed in primary care settings rather than in specialty behavioral health care (Bailes et al., 2016). If SDs are indicators of risk for SUDs, screening for and identifying SD and related distress and morbidity in primary care could be helpful in providing early identification of risk for drug and alcohol use problems.

SD in childhood is associated with the early onset of alcohol use disorders (AUD) in adolescence (Hasler, Kirisci, & Clark, 2016; Wong, Brower, Fitzgerald, & Zucker, 2004; Wong, Brower, & Zucker, 2009). One way this has been interpreted is that subjects with SD may have the tendency to self-medicate with alcohol and tranquilizers to promote sleep, or abuse stimulants to stay awake during the day (Aira, Hartikainen, & Sulkava, 2008). Other theories suggest that SD might be part of a prodromal predisposition of an individual who is at risk for SUD (Wong et al., 2004) or that poor sleep exacerbates existing MHDs such as depression or ADHD, which in turn leads to substance use risk (Morse, MacMaster, Kodad, & Robledo, 2014). However, the predictive value of SD as an indicator of risk for SUDs in adults is less understood. If SDs have predictive value for identifying adult individuals in primary care who may be at risk for later needing treatment for SUDs, this would provide an important opportunity to address that risk early. SDs that are not clearly linked to a behavioral health disorder are usually identified and treated in primary care settings rather than in specialty behavioral health services. The potential benefit of screening for SDs in primary care is especially important given the movement towards behavioral health

treatment integration in primary care (Stoop, Nefs, Pommer, Pop, & Pouwer, 2015) which can include the implementation of brief interventions for sleep (Chung, Lee, Yeung, Chan, Chung, & Lin, 2017).

SDs can have implications for both new onset and relapse SUDs. Adults in recovery from alcohol and illicit drug use may continue to have sleep problems long after achieving abstinence, and persistent SD may be predictive of SUD relapse (Babson, Boden, Harris, Stickle, & Bonn-Miller, 2013; Brower, Krentzman, & Robinson, 2011; Kaplan, McQuaid, Primich, & Rosenlicht, 2014). Studies suggest the monitoring of adults who use alcohol to fall asleep (alcohol as a hypnotic), as this use may be representative of how sleep problems evolve into SUD (Kolla et al., 2015). SD may pre-date and potentially be a predictor for SUD in at least a subset of primary care patients. Both SD and SUD are often under-identified and untreated (Bartlett, Marshall, Williams, & Grunstein, 2008; Teplin, Raz, Daiter, Varenbut, & Tyrrell, 2006), but SD may be even more likely to be missed than SUD. One study found that while questions about smoking and alcohol use were asked in 100% of routine visits, at least one question about sleep health (How is your sleep?) was asked in only 40% of visits (Sorscher, 2008).

In this paper, we report on a study evaluating sleep disturbances (SD) as potential predictors of later SUD diagnosis and treatment in an adult primary care sample within a large safety-net hospital that offers care for indigent and uninsured patients. Our objectives are to understand the predictive value of SD associated with substance use problems in adult populations, and whether identifying SD could be helpful for screening and intervening early in the risk for SUD, and identify which group of patients would most benefit from screening. We hypothesize that persons with sleep disturbance are more likely to be subsequently diagnosed and treated for a SUD as compared to individuals without sleep disturbance, regardless of whether SD is comorbid with a MHD.

2. Methods

This study is part of the International Latino Research Partnership (ILRP; NIDA R01DA034952 and NIMH R01MH100155). Data for this study consisted of electronic health records (EHR) data from January 1, 2013 - September 1, 2015. We collected EHR data from primary care sites associated with a large Boston area safety net and academic community health care system serving over 140,000 patients in primary care, specialty care, emergency services, hospital care, maternity care, and behavioral health. The system serves vulnerable populations and engages a community psychiatry and public health mission in its practice and medical training. The patient population is multicultural, and approximately 40% of patients speak a language other than English, most commonly Spanish, Portuguese, and Haitian Creole. The study was approved by the institutional review boards of the participating institutions.

We limited the current study sample to four distinct adult populations: patients with no sleep disorder and no mental health disorder; patients with a diagnosis of a sleep disorder (SD) but no mental health disorder, patients with a diagnosis of sleep and mental health disorder, and patients with mental health disorder only. Patients in these groups "enter" the data on the day

of their first visit for treatment of the SD and are followed until September 1, 2015. The fourth group was the lower risk comparison group and included patients that never received a diagnosis for SD or mental health disorder during the 32 months of data collection. These patients "enter" the data at the time of their first medical or behavioral health care visit, and are followed until September 1, 2015. The EHR sample was comprised of 60.06% female and 39.94% male patients; and diverse across race/ethnicity (46.06% White, 16.44% Black, 28.84% Latino, 7.67% Asian).

Because of our specific interest in the progression from SD and MHD to SUD (separated into alcohol abuse and illicit drug use disorder), we excluded from this sample patients with prior treatment for SUD that preceded treatment for SD. To ensure that patients in the sample were regular patients at the health care system under study, we excluded individuals if they had less than three primary care visits between 2013 and 2015. Other than age (patients less than 18 years of age not included), no other exclusion criteria were used.

We identified SD in the EHR through treatment linked to the International Classification of Diseases, Ninth Revision (ICD-9) codes (780.5X unspecified sleep disturbance or 327.3X Circadian rhythm sleep disorders). We identified mental health disorder through service use linked to the behavioral health International Classification of Diseases, Ninth Revision (ICD-9) codes 291, 292, and 295-314, with the exception of the substance use disorder ICD-9 codes described below. This includes a range of psychiatric disorders including unipolar and bipolar affective disorders, anxiety disorders, Attention Deficit Hyperactivity Disorder among other common psychiatric diagnoses.

We examined two dependent variables (follow-up treatment for illicit drug use disorder, and alcohol use disorder), using the following ICD-9 codes: illicit drug dependence (304.XX, 648.3X, 655.5X, 760.72, 73, 75, 779.5, 965.0X), illicit drug abuse (292.XX; 305.20-23, 30-33, 40-43, 50-53, 60-63, 70-73, 80-83, 90-93), alcohol dependence (303.9X; 357.5; 425.5; 535.3; 571.0, 1, 2, 3; V11.3), and alcohol abuse (291.XX; 303.00-03; 305.00-03; V79.1; 790.3). Given the established associations between age, sex, race/ethnicity and rates of substance use (Compton, Thomas, Stinson, & Grant, 2007), we adjusted for these variables in multivariate Cox proportional hazard models, an analytic approach increasingly used to identify risk factors for developing alcohol and substance disorders (Gowin, Sloan, Stangl, Vatsalya, & Ramchandani, 2017). Sex was categorized as female or male, race/ethnicity as non-Latino White, non-Latino Black, non-Latino Asian, and Latino, and age was entered into the regression models as a continuous variable. We included three physical health conditions prevalent in primary care and associated with risk for SD, MHD and SUDs (Young, Skatrud, & Peppard, 2004): HIV (ICD-9 codes of 042.XX), cardiovascular disease (ICD-9 codes of 429.2X, 401.XX, or 402.XX), and diabetes (ICD-9 code of 250.XX) as control variables. The variables indicating diagnosis of these illnesses are not mutually exclusive, ie, patients with multiple disorders can be coded as a "1" for multiple conditions. Benzodiazepine prescriptions and pain medications are also adjusted for given their significant association with SUD and mental health disorder (Darke & Hall 1995; SAMHSA, 2012) and their potential for confounding the relationship between sleep and MH disorder and SUD.

2.1. Analytical Methods

First, we conducted chi-square analyses to compare the probability of receiving treatment for SUD, split into illicit drug use disorder and alcohol use disorder across the four groups of interest, as well as differences between the groups in the covariates described above.

Next, we estimated Kaplan-Meier survival function curves to account for SD/MHD group differences in the amount of exposure time (ie, patients "enter" the data at different time periods during 32 months of data collection and therefore have different time windows of risk of being diagnosed with SUD), and the right-censoring of patients (to account for the probability that treatment for a SUD diagnosis could occur after September 1, 2015) (Hosmer & Lemeshow, 2008). These curves graphically demonstrate the difference in time to treatment for a SUD diagnosis. Separate curves were created for each of the four groups, plotting at day-long intervals the proportion of the number of cases with SUD over the number of cases without SUD remaining in each time period. The hazard rates associated with these curves were calculated and statistically compared using the nonparametric log-rank test of equality (Mantel, 1966).

We then estimated Cox proportional hazard models to examine the risk of SUD, comparing hazard rates across our four groups (SD only, SD and MHD, MHD only, and no SD or MHD), adjusting for the covariates described above. We considered all individuals that had not yet received treatment for SUD to be right-censored at the end of our data (September 1, 2015). We assessed the Cox proportional hazards assumption using tests of Schoenfeld (1982) residuals and by visual estimation of log-log plots of the estimated survival curves. We used Wald tests (Korn & Graubard, 1990) to test significance in group hazard rate differences. All analyses were conducted using Stata 14 (StataCorp, 2014).

3. Results

Table 1 identifies differences between the four groups; 12.31% were treated for illicit drug use disorder over the study time period and 7.04% were treated for alcohol use disorder. Illicit drug use was further broken down to show that 7.33% were treated for cocaine, a third of a percent (0.33%) were treated for marijuana use, and 6.79% were treated for illicit prescription drug use. Chi-square results indicated that those with co-morbid sleep and mental health disorders were most likely to have alcohol or illicit drug use disorder treatment. The breakdown of type of sleep disorder within those diagnosed with sleep disorder was 6.9% circadian rhythm sleep disorder; 21.4% sleep disturbance; 1.3% sleep apnea; 63.5% insomnia, unspecified; 7.3% hypersomnia; and 0.9% disruption of 24-hour sleep wake cycle (the total is greater than 100% because several patients had multiple diagnoses).

Figures 1 and 2 present Kaplan-Meier survival curves for illicit drug use disorder and alcohol use treatment, respectively. These curves represent the different survival functions, or the different hazard over time of receiving treatment for illicit drug use disorder or alcohol use disorder by sleep/mental health group. In both cases, SD alone significantly predicted both alcohol and illicit drug use disorder, and the group with comorbid sleep and mental health disorder had the greatest hazard of treatment for subsequent alcohol use

disorder (approximately 15% of the sample by the end of the study period) and illicit drug use disorder (approximately 30% of the sample by the end of the study period). Mental health disorder alone was associated with a greater risk for illicit drug use compared to sleep disturbance alone, however, risk patterns for alcohol use disorder were similar for sleep disturbance and mental health disorder.

After covariate adjustment, Cox proportional hazard model results show that SD was associated with a greater overall risk of treatment for alcohol or illicit drug use disorder diagnosis as compared to those without sleep or mental health disorder, after adjustment for race, gender, age, and other covariates (Tables 2 and 3). The results were similar in direction and significance for alcohol use disorder, and were similar in direction but not significance for illicit drug use disorder. In addition, the greater hazard rates for those with both MHD and SD compared to those with no mental health or SD persist in Cox proportional hazard models of alcohol use disorder and illicit drug use disorder.

4. Discussion

Results of this study highlight important considerations in the identification, treatment, and potential risk for alcohol and illicit drug use disorders in patients with SD, and comorbid SD and MHD, and as compared to having MHD alone. Our hypothesis that persons with various sleep disturbances are more likely to be later diagnosed and treated for SUD was supported by study findings for alcohol disorders, but only partially supported in findings for illicit drug use disorders.

Sleep complaints are highly prevalent in primary care populations (Foley, Ancoli-Israel, Britz, & Walsh, 2004) and research has consistently shown that patients with the highest risk for SD are those with pain, limited activity, and poor overall physical and mental health (Dinges et al., 1999; Mundt, Eisenschenk, & Robinson, 2017). Because SD are associated with significant health impacts (Drager, McEvoy, Barbe, Lorenzi-Filho, & Redline, 2017; Lillis et al., 2017), screening positive for symptoms of SD should prompt further diagnostic evaluation (Teplin et al., 2006). A meta-analysis found that SD can even be associated with suicidal ideation, a relationship that did not show risk moderation by depression being present (Pigeon, Pinquart, & Conner, 2012). Although we tried to include individuals whose SD pre-dated the initiation of documented diagnosis and treatment for drug or illicit drug use disorder, it is likely that some of the individuals in the sample had prior substance use, and that in those cases our observations reflected SD predicting alcohol/illicit drug use disorder relapse. However, screening may be helpful regardless of whether SD predicts initial incidence or relapse.

4.1. Limitations

A limitation of our study is the use of the hospital electronic medical records, which rely on clinician comprehensiveness and accuracy regarding the identification and coding of SD, SUD and MHD. Because of variability in clinicians' attention to sleep symptoms and use of screening tools, under-identification and under-diagnosis of SD in the sample is likely. This study did not examine the possible role that psychiatric factors might play in mediating between sleep related problems and SUD. In addition, our SD variable represents a variety

of sleep problems including obstructive sleep apnea, insomnia, and restless leg syndrome and is not representative of a homogenous group. The sample that receives care in this safety net hospital is more vulnerable than the general population, with higher representation of women and Latinos. This may lead to an underestimate of SUD, which is more prevalent for White individuals, and may highlight mental health disorders more prevalent in women and vulnerable populations (Compton et al., 2007). This study should be replicated using data from populations in less adverse circumstances. Our data also cannot capture those individuals who have SD and need but never seek substance use treatment, our primary outcome.

4.2. Clinical Implications

The treatment of SD should include monitoring for the development of alcohol and illicit drug use towards early identification, non-narcotic medication treatment, and non-pharmacological interventions for substance use problems (Arnedt, Conroy, Armitage, & Brower, 2011; Babson, Feldner, & Badour, 2010; Britton et al., 2010). Providers in mental health and primary care should consider routine screening and identification of SD so that treatment can be initiated effectively and early (Teplin et al., 2006). Using brief screening tools for mental health disorders (eg, PHQ-9; Kroenke, Spitzer, & Williams, 2002) can help in identifying sleep problems which are symptoms of a mental health disorders such as depression (ie., questions about insomnia and hypersomnia which are part of the depression disorder symptom criteria). Conversely, patients with SD should be thoroughly evaluated for mental health disorders. Symptoms suggestive of SD are common, but are not routinely and specifically screened for in the primary care setting. Validated questionnaires and screening tools that have been developed for identifying shift work related SD can efficiently identify patients at risk for common SD in this setting (Barger et al., 2012). A study in Australia found that a subjective screening measure of sleep difficulty was helpful and feasible in identifying individuals in a community pharmacy setting with likelihood for obstructive sleep apnea, insomnia, and/or restless leg syndrome, the most common sleep disturbances encountered in primary care settings (Fuller et al., 2014). Other available screening measures include the Cleveland Sleep Habits questionnaire (CSHQ; Mustafa, Erokwu, Ebose, & Strohl, 2005), Berlin questionnaire (Chung et al., 2008), and Epworth Sleepiness Scale (ESS; Johns, 1991). Objective and mobile markers of sleep exist through rest/activity cycle-measuring wrist band devices (Dijk, 2016), and these can supplement other more subjective measures including self-reported sleep latency, duration of sleep, and restfulness. Patients who screen positive for SD and present with subjective complaints regarding their sleep, may warrant further questioning about whether they are self-medicating, or have a history of SUD. In our sample, individuals prescribed benzodiazepines or pain medication and/or who had medical comorbidity also showed increased risk of needing treatment for AUD and SUD. The Michigan Alcohol Screening Test (MAST; Selzer, 1971) and the Drug Abuse Screening Test (DAST; Skinner, 1982) or Alcohol Use Identification Test (AUDIT; Reinert & Allen, 2002) can identify alcohol and drug problems among patients presenting with SD, both alone or comorbid with mental health problems (Boschloo et al., 2010). In addition, interventions that address SD among patients with and without comorbid mental health problems are needed (Conroy & Arnedt, 2014; Kaplan et al., 2014), especially those that can be delivered or initiated in primary care, and that can address behavioral, medical, and

psychiatric comorbidity. In primary care, clinical encounters, a limited sleep history should be conducted followed by documentation of any identified SD, a brief intervention such as sleep hygiene counseling, a referral to a sleep evaluation if initial brief interventions are not helpful, and a referral to a psychiatry clinic for any significant comorbid diagnosis or symptoms.

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidenced-based practice used to identify, reduce, and prevent problematic use, abuse, and dependence on alcohol and drugs (Aldridge, Linford, & Bray, 2017). SBIRT can be easily used in primary care settings and enables healthcare professionals to systematically screen and assist patients who may not be seeking help for a SUD, but whose drinking or drug use may cause or complicate their ability to successfully handle health, work, or family issues. In a landmark report, the Institute of Medicine specifically cited the SBIRT model as a promising practice for SUD treatment (Institute of Medicine, 2001). SDs are not usually specifically screened as part of SBIRT practice, although screening for SD could identify an important potential indicator that a patient is at risk for subsequent SUD in primary care. This SBIRT approach could offer patients a comprehensive response to a significant health problem, while promoting healthy sleep, and the prevention of alcohol and substance use problems. Our study sheds light on the issue of SD as an indicator of risk of SUD. Future research is needed to more clearly understand the relationship between SD, SUD, and MHD to continue to better inform prevention and intervention efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Patients with sleep disturbances have a higher risk for SUD treatment

- Patients with a mental health disorder had the greatest risk for SUD treatment

- Screening for sleep disturbances may help identify SUD risk in primary care
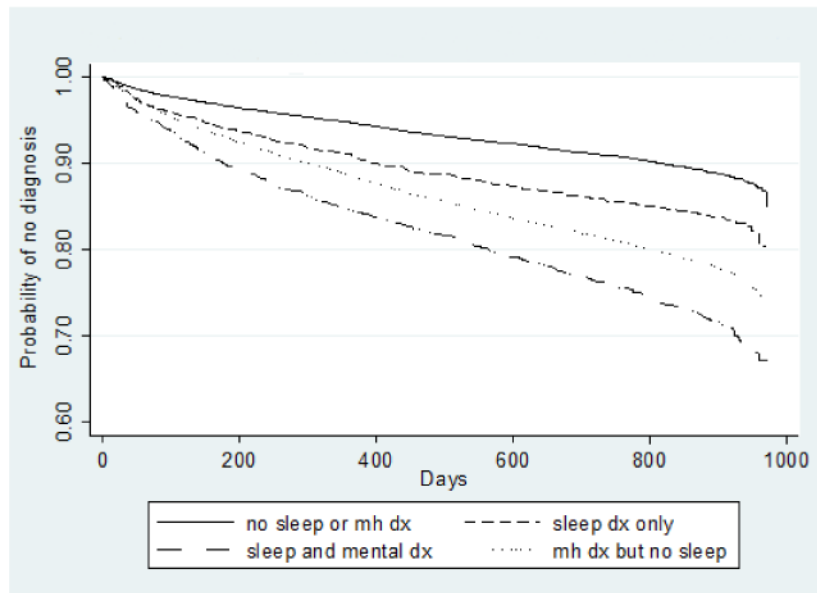
Fig. 1.
Kaplan-Meier survival curves for time to diagnosis of illicit drug abuse or dependence. dx = diagnosis.
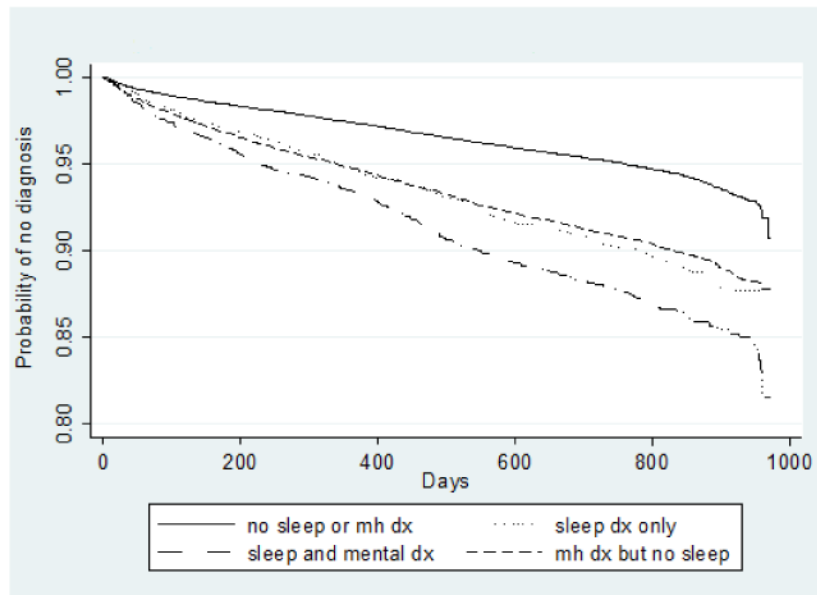
Fig. 2.
Kaplan-Meier survival curves for time to diagnosis of alcohol abuse or dependence. dx = diagnosis.

Table 1

Descriptive statistics (in percent unless otherwise noted) for total sample and four comparison groups, with chi-square tests for differences between the four groups of patients (N=83,920).

	Total Sample	With no sleep or mental health disorder	Sleep disorder only	With Comorbid Sleep Disorder and Mental Health Disorder	Mental Health Disorder only	*p*-value for tests between 4 groups
Number of primary care visits over data collection period	13.50	11.58	19.11	27.51	16.39	.0001
Alcohol Use Disorder = Yes	7.04	5.16	10.72	15.39	10.68	.0001
Illicit Drug Use Disorder = Yes	12.31	9.30	14.78	24.68	18.66	.0001
Cocaine Use Disorder = Yes	7.33	6.49	11.64	13.42	8.40	.0001
Marijuana Use Disorder = Yes	0.33	0.17	0.17	0.92	0.69	.0001
Prescription Drug Abuse = Yes	6.79	4.14	7.12	17.16	12.62	.0001
Race/Ethnicity						
White	46.06	41.94	42.63	58.12	56.06	.0001
Black	16.44	18.16	18.59	11.37	12.20	.0001
Latino	28.84	29.56	30.70	26.53	26.99	.0001
Asian	7.67	9.23	7.50	3.38	4.00	.0001
Female	60.06	58.49	46.27	58.92	65.93	.0001
Male	39.94	41.51	53.73	41.08	34.07	.0001
Diabetes = 1	28.08	25.51	44.05	46.66	31.05	.0001
Cardio = 1	5.11	4.25	9.25	12.14	6.11	.0001
HIV = 1	9.11	8.02	9.88	14.07	11.38	.0001
Pain Medication	34.48	31.00	42.34	53.62	40.67	.0001

Table 2

Hazard ratios from survival analysis of time to diagnosis of illicit drug use disorder

VARIABLES	(1) Full Sample	(2) Excluding those with a prior illicit drug use disorder
No Sleep, No Mental Health DX (referent)		
Sleep DX only	1.294[***] (0.0762)	1.101 (0.0700)
Sleep DX + Mental Health DX	2.115[***] (0.0962)	1.899[***] (0.0904)
Mental Health DX only	1.889[***] (0.0470)	1.887[***] (0.0470)
Age	1.003[***] (0.000676)	1.003[***] (0.000679)
Female	0.811[***] (0.0180)	0.810[***] (0.0182)
White (reference)		
Black	0.896[***] (0.0280)	0.897[***] (0.0282)
Asian	0.753[***] (0.0373)	0.755[***] (0.0375)
Latino	0.769[***] (0.0207)	0.767[***] (0.0208)
Cardio DX	1.029 (0.104)	1.025 (0.104)
HIV DX	1.791[***] (0.109)	1.793[***] (0.109)
Diabetes DX	2.947[***] (0.0753)	2.943[***] (0.0758)
Any pain medication	1.468[***] (0.0335)	1.472[***] (0.0338)
Any benzodiazepine	1.326[***] (0.0352)	1.330[***] (0.0355)

Hazard ratios represent the change in the expected log of the hazard ratio relative to a one unit change in the covariate of interest, adjusting for all other predictors

Standard errors of the hazard ratios are reported in parentheses.

[***] Statistically significant at $p<0.001$ level

[**] $p<0.01$

[*] $p<0.05$

Table 3

Hazard ratios from survival analysis of time to diagnosis of alcohol use disorder

VARIABLES	(1) Full Sample	(2) Excluding those with a prior alcohol use disorder
No Sleep, No Mental Health DX (referent)		
Sleep DX only	1.493 *** (0.106)	1.296 *** (0.0764)
Sleep DX + Mental Health DX	1.692 *** (0.106)	2.113 *** (0.0964)
Mental Health DX only	1.586 *** (0.0550)	1.889 *** (0.0470)
Age	1.010 *** (0.000920)	1.003 *** (0.000676)
Female	0.531 *** (0.0161)	0.811 *** (0.0181)
White (reference)		
Black	0.730 *** (0.0349)	0.895 *** (0.0280)
Asian	0.714 *** (0.0517)	0.753 *** (0.0373)
Latino	1.011 (0.0355)	0.770 *** (0.0207)
Cardio DX	1.459 *** (0.171)	1.030 (0.104)
HIV DX	1.290 ** (0.128)	1.792 *** (0.109)
Diabetes DX	1.470 *** (0.0589)	2.949 *** (0.0754)
Any pain medication	1.963 *** (0.0621)	1.468 *** (0.0335)
Any benzodiazepine	1.494 *** (0.0532)	1.325 *** (0.0352)

Hazard ratios represent the change in the expected log of the hazard ratio relative to a one unit change in the covariate of interest, adjusting for all other predictors.

Standard errors of the hazard ratios are reported in parentheses.

*** Statistically significant at $p<0.001$ level

** $p<0.01$

* $p<0.05$