Characterisation of the genetic relationship between the domains of sleep and circadian-related behaviours with substance use phenotypes

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Abstract
Sleep problems and substance use frequently co-occur. While substance use can result in specific sleep deficits, genetic pleiotropy could explain part of the relationship between sleep and substance use and use disorders. Here we use the largest publicly available genome-wide summary statistics of substance use behaviours (N = 79,729–632,802) and sleep/activity phenotypes to date (N = 85,502–449,734) to (1) assess the genetic overlap between substance use behaviours and both sleep and circadian-related activity measures, (2) estimate clusters from genetic correlations and (3) test processes of causality versus genetic pleiotropy. We found 31 genetic correlations between substance use and sleep/circadian related measures after Bonferroni correction. These patterns of overlap were represented by two genetic clusters: (1) tobacco use severity (age of first regular tobacco use and smoking cessation) and sleep health (sleep duration, sleep efficiency and chronotype) and (2) substance consumption/problematic use (drinks per day and cigarettes per day, cannabis use disorder, opioid use disorder and problematic alcohol use) and sleep problems (insomnia, self-reported short sleep duration, increased number of sleep episodes, increased sleep duration variability and diurnal inactivity) and measures of circadian-related activity (L5, M10 and sleep midpoint). Latent causal variable analyses determined that horizontal pleiotropy (rather than genetic causality) underlies a majority of the associations between substance use and sleep/circadian related measures, except one plausible genetically causal relationship for opioid use disorder on self-reported long sleep duration. Results show that shared genetics are likely a mechanism that is at least partly responsible for the overlap between sleep and substance use traits.

KEYWORDS
genetic correlations, sleep, substance use

1 | INTRODUCTION

Sleep disturbances are one of the most common complaints in substance use disorder treatment1,2 and there is substantial comorbidity between substance use disorders (SUD) and sleep disorders3,4.
Attempting to quit substances and the consequent cravings and withdrawal are often associated with sleep disturbances, and these sleep deficits can in turn be reciprocally linked to substance use relapse. For example, sleep difficulties and insomnia are common clinical features of withdrawal from alcohol, nicotine and cannabis. Further complicating this relationship, common substances such as alcohol and cannabis are often used to self-medicate sleep issues. Cannabis and alcohol are frequently considered sleep aids despite strong cross-sectional evidence demonstrating positive correlations between increased use and sleep deficits. Relatedly, tobacco is often used as a stress and tension reliever even though tobacco use before sleep is associated with sleep disturbances.

Research suggests that circadian mechanisms contribute to the association between sleep issues and substance use/disorder and that substance use may also impact circadian rhythms, further disturbing sleep. While circadian rhythm is a multifaceted biological construct, one measurable feature is self-report chronotype, a preference between either evening or morning activity, wake-up and bedtime. An evening chronotype has been associated with higher alcohol and cannabis use. In addition to the standard self-report measure of chronotype, activity-related proxies (measured via actigraphy or accelerometer) can function as objective circadian-related measures. Research on the relationship between circadian-related activity measures and substance use is scarce and yet to be fully understood.

Sleep and substance use behaviours seem to interact dynamically, and there is evidence of a bidirectional relationship between the domains of substance use and sleep deficits, particularly during development. There is indication that early sleep problems and an evening chronotype predict later substance use, and both early substance use and problematic substance use predict later sleep issues.

Reconciling these cross-sectional associations and bidirectional patterns, it is likely that a third variable, such as genetic pleiotropy, is driving manifestations of sleep and substance use comorbidity. Heritability ($h^2$) is the measure of the phenotypic variance associated with additive genetic contributions. Both substance use disorders (e.g., alcohol use disorder: $h^2 = 0.50–0.64$; nicotine use disorder: $h^2 = 0.30–0.70$; cannabis use disorder (CUD): $h^2 = 0.51–0.59$; and opioid use disorder (OUD): $h^2 = 0.50$) and sleep traits (e.g., insomnia: $h^2 = 0.39$; sleep duration: $h^2 = 0.46$) are heritable. Genetic pleiotropy implies that sleep and substance use disorders share genetic factors; that is, some of the same genes influence both traits. Genetic pleiotropy would thus imply that persons with vulnerability to substance use disorders might also have increased risk for sleep problems because of a shared genetic factor. While substance use may induce acute changes in sleep, and sleep disturbances may, in a state-dependent manner, exacerbate and prolong substance misuse (e.g., withdrawal-related insomnia may impede smoking cessation), evidence for genetic pleiotropy would suggest that, even prior to onset of substance use, individuals with a genetic predisposition may experience sleep difficulties.

Prior studies implicate shared genetic influences on sleep and substance use as likely contributors to their comorbidity. Twin studies focused on sleep/circadian-related outcomes and substance use are scarce but a few have found genetic correlations between earlier regular cannabis use and both shorter sleep duration and increased insomnia symptoms as well as genetic correlations between an evening chronotype with increased alcohol quantity and binge drinking. Modern designs using results from genome-wide association studies (GWAS) have found genetic correlations among self-report sleep deficits and common substance use behaviours including tobacco behaviours such as smoking initiation, smoking cessation and increased cigarettes per day, increased alcohol involvement via scores on the Alcohol Use Disorders Identification Test (AUDIT), OUD, and cannabis-related measures, such as lifetime cannabis use and CUD. Despite these findings, the relationship between the multitude of available substance use and both chronotype and circadian-related activity measures has yet to be comprehensively explored. Still, the current genetically informed results imply that the genes that could be contributing to sleep deficits and circadian-related measures might contribute to substance use and misuse (or vice versa).

Genetic studies can further be used to inform causality. For example, Mendelian Randomisation uses genetic variants to approximate random assignment in a randomised control trial, where the genetic variants are used in an instrumental variable design. A prior study explored the pair-wise associations between sleep and substance use disorders using Mendelian Randomisation, finding that insomnia had a potential positive causal influence on tobacco smoking, alcohol dependence and cannabis initiation, while smoking initiation was potentially causal for insomnia. This design has also shown that insomnia may have a potential influence on increasing smoking heaviness. Further, more cigarette use may causally influence chronotype. However, the effects of insomnia on both alcohol dependence and cannabis initiation were partially driven by pleiotropic single nucleotide polymorphisms (or SNPs) (rather than genetic causality), suggesting caution in causal inference and the possibility of a shared genetic liability.

There has yet to be a comprehensive genomic study to include a multitude of alcohol, tobacco, cannabis and opioid use and use disorder behaviours as well as both a collection of self-report and objective sleep/circadian-related measures. Sleep itself is a highly heterogenous set of behaviours, encompassing many subdomains. Substance use and use disorder may interfere with sleep generally, with sleep efficiency, duration and circadian rhythm or with the sleep cycle to produce sleep problems. Further, different substances may show unique relationships with any one domain of sleep specifically. Therefore, it is important to explore subdomains of substance use, misuse and sleep behaviours in order to localise the causes of such deficits.

Sleep health promotes well-being and likely interrupts progression to misuse of nearly all substances. Within users, a majority of substances, when used heavily and often, result in acute state-dependent changes in sleep behaviours. When such heavy substance use persists, the accumulating deficits in sleep health may begin to appear...
stable and trait-like, rather than being temporally delimited to periods of heavy substance use. In addition, pleiotropy also accounts for sleep disturbances in individuals at genetic risk for substance use disorders, even in the absence of substance use. Despite the ubiquity of the substance-sleep associations, there is considerable variability in how individual substances may influence state-dependent and possibly stable alterations in sleep health, and these important distinctions may be evident in examination of pleiotropy versus causality. For example, tobacco and alcohol have differing effects on short term sleep. But it is possible that these mechanisms could be causal and act through substance-specific pathways or that a shared etiological mechanism that is unrelated to acute effects of these substances (pleiotropic risk that is independent of substance exposure) underlies these associations. Thus, studying multiple substances provides a framework for being able to disentangle specific and shared mechanisms of association.

The goals of the current study are to (1) investigate the shared genetic relationship between a multitude of substance use and sleep/activity measures utilising cross-trait genetic correlations, (2) estimate clusters among the genetic associations of substance use and sleep/activity traits using K-means clustering and (3) investigate the potential causal versus shared genetic relationships responsible for these associations using latent causal variable (LCV) analysis.

2 | METHODS

2.1 | Measures

2.1.1 | Self-report and objective sleep and circadian-related measures

Our analyses used summary statistics from several large-scale GWAS focused on self-reported sleep phenotypes and objective accelerometer-derived sleep/activity phenotypes. Self-report sleep phenotypes included insomnia, chronotype, self-report sleep duration, self-report short sleep duration and self-report long sleep duration. Objective accelerometer-derived sleep/circadian-related activity phenotypes included sleep duration, standard deviation of sleep duration (a measure of sleep variability), sleep efficiency, number of sleep episodes, diurnal inactivity (inactive states such as napping and wakeful rest), sleep midpoint (a proxy of chronotype), least active 5 h of the day (L5 timing, indication of a preference for going to bed earlier or later in the day) and most active 10 h of the day (M10 timing, indication of whether a person is most active earlier or later in the day). Diurnal inactivity can be conceptualised as a sleep problem due to increased naps/rest/inactivity that are a compensatory behaviour for nonrestful sleep. L5 and M10 and sleep midpoint will be conceptualised as activity measures that are circadian-related proxy measures. All sleep and circadian-related GWAS discovery cohorts were of European ancestry. Table S1 details sleep/activity traits in terms of type of measure, measure construct, coding and GWAS discovery sample.

2.1.2 | Substance use measures

Our analysis used summary statistics from several of the largest GWAS of substance use behaviours. Alcohol behaviours included alcoholic drinks per week and problematic alcohol use. Tobacco behaviours included lifetime tobacco use, age of first becoming a regular smoker, smoking cessation and cigarettes per day. Cannabis behaviour included lifetime cannabis use and CUD. Lastly, we included OUD. All substance-related GWAS discovery cohorts were of European ancestry. Table S1 details each substance use trait in terms of type of measure, measure construct, coding, and GWAS discovery sample. Table S2 describes the SNPheritabilities for each phenotype.

2.2 | Analyses

2.2.1 | Linkage disequilibrium score regression (LDSC) to estimate genetic correlation

We used LDSC to estimate genetic correlations between traits. SNPs from GWAS summary statistics were retained if they had minor allele frequency (MAF) > 0.01 and imputation information score (INFO) > 0.70. All duplicated rs (reference SNP) numbers or SNPs that were multi-allelic, strand ambiguous or indexed deletions/insertions were removed. Alleles were merged with the HapMap 3 reference panel (the major histocompatibility complex region was removed due to complex linkage disequilibrium (LD) patterns). Beta weights and LD scores were pregenerated from 1000 Genomes European genetic data included in the LDSC software download. LDSC regresses chi-square statistics from the summary statistics of the GWAS of the trait of interest on SNP LD scores. Genetic correlations were estimated using overlapping SNPs from filtered summary statistic files. LDSC accounts for possible sample overlap and additional sources of confounding (e.g., population stratification). We estimated a pair-wise genetic correlation matrix that included all sleep/activity and substance use measures (Figure 1). Due to the large number of genetic correlations estimated, we utilised Bonferroni correction to adjust for potential false positives (correcting for 231 tests) due to multiple testing.

2.2.2 | K-means clustering of the genetic correlations between sleep and substance use

K-means clustering is an unsupervised machine learning clustering technique that uses a centroid or distance-based algorithm to assign correlations to a cluster of a predefined number. After assigning the K number of clusters, the algorithm shuffles the data to clusters and assigns them to initial random centroids. It then determines the sum of squares (or distance) between each data point and the initial centroids and does a series of reassignments to the centroids until the algorithm is finished with the appropriate cluster assignments.
attempting to make data in the clusters similar while making each individual cluster separate from the others. By comparing the distance (sum of squares) between cluster solutions (i.e., 1 vs. 2 and 2 vs. 3), we can estimate a silhouette coefficient that identifies the ideal number of clusters to account for patterns in the data, that is, the cluster solution that allows for the smallest sum of squares across clusters.

An advantage of K-means over other clustering algorithms is that clustering is done at the variable level with the correlation matrix (unlike mixture modelling or density-based spatial clustering of applications with noise) in a hypothesis-free format (unlike a confirmatory factor analysis in genomic structural equation modelling [GenomicSEM]). For the current analyses, the genetic correlation matrix was read into the K-means algorithm. We could have created a similar procedure by combining GenomicSEM and exploratory factor analysis. However, exploratory factor analysis requires setting the number of factors, selecting a model, and then confirming the fit via a confirmatory factor analysis. This is a multistep process that can be useful when there is a strong theoretical foundation for suspecting overlap between all variables. When this is not the case, it is possible to conduct these analyses in a single step and select the best solution because K-means has an objective measure of fit, the silhouette coefficient. Thus, for the current analyses, the genetic correlation matrix was read into the K-means algorithm. We could have created a similar procedure by combining GenomicSEM and exploratory factor analysis. However, exploratory factor analysis requires setting the number of factors, selecting a model, and then confirming the fit via a confirmatory factor analysis. This is a multistep process that can be useful when there is a strong theoretical foundation for suspecting overlap between all variables. When this is not the case, it is possible to conduct these analyses in a single step and select the best solution because K-means has an objective measure of fit, the silhouette coefficient. Thus, for the current analyses, the genetic correlation matrix was read into the K-means algorithm. The silhouette coefficient determined how many centres were needed to keep each substance use and sleep measure closest together, compared with other potential cluster solutions. K-means clustering was conducted in R using the R packages “cluster” v1.0.7 and “factoextra” v2.1.2.

2.2.3 Latent Causal Variable analysis to assess pleiotropy versus genetic causality

To examine evidence for genetic causality between sleep and substance use/misuse phenotypes, we used LCV analysis on genetic correlations that survived Bonferroni correction. LCV allows genetic correlations between two traits to be mediated by a latent variable with a causal effect on each trait. This model was designed to account for genetic pleiotropy by partitioning the genetic correlation into pleiotropy versus partial causality. This is done using the fourth moments (i.e., kurtosis) from the LD score distribution. The proportion of kurtosis is larger than the marginal effect sizes for SNPs with larger effect on a trait. Thus, if trait 1 has a causal effect on trait 2, the effects of SNPs with a large effect on trait 1 will have a proportional influence on trait 2. Using this model, causality is implied when trait 1 is more strongly correlated with the causal latent variable (compared with trait 2) or vice versa. If trait 1 is perfectly genetically correlated with the latent variable, it can be considered fully genetically causal for trait 2. The extent to which the LCV causes trait 1 versus trait 2 is expressed as a ratio, referred to as the genetic causality proportion (gc). The gc is an estimate of the degree to which each trait is correlated with the latent genetic variable with a score that can range from 0 (reflecting no genetic causality) to 1/0 (signifying full genetic causality).
trait 1. For the current analyses, the sleep/activity measure is trait 1 and the substance use measure is trait 2.

While LCV is similar to other methods for determining genetic causality in that it utilises SNPs to derive instrumental variables (like traditional Mendelian Randomisation), LCV has advantages over other methods for estimating genetic causality. First, sample overlap is accounted for by the LDSC intercept. Second, the model produces a gcp that is the proportion of genetic effects that are consistent with a model of genetic causality, allowing us to account for partial overlap. Third, the gcp is robust to pleiotropy, which is accounted for using LDSC. Fourth, pleiotropic effects across the entire genome are accounted for, rather than only at a few SNPs. Indeed, simulation designs show that the method outperforms Mendelian Randomisation when the genetic correlation between traits is nonzero. Considering that many of our samples overlap and that we want to account for pleiotropy, LCV is ideal in this analysis. Despite these advantages, LCV has several limitations worth noting, including its inability to detect bidirectional causal relationships between traits and potential confounding in the presence of additional intermediaries. Despite these limitations, LCV provides a robust approach for analysing genetic relationships between traits.

To complement and corroborate evidence of genetic causality, all pair-wise associations that had significant LCV results were also tested for significance using two-sample Mendelian Randomisation via MR base under a range of assumptions. Due to the low number of genome-wide significant SNPs for both traits, we used a genome-wide significance threshold of 5e-6 for SNP inclusion for the genetic model of genetic causality, allowing us to account for partial overlap. Focusing on measures of chronotype, in addition to the circadian-related sleep midpoint relationships mentioned above, significant genetic correlations were found between self-reported chronotype and lifetime cannabis use, lifetime tobacco use and drinks per week (absolute values of rGs between 0.08 and 0.25).

### 3.2 K-means clustering within and between sleep and substance use domains

A silhouette coefficient determined that two clusters were optimal to explain the overlap between sleep/circadian-related activity and substance use dimensions (Figure 2). Figure 3 displays our optimal cluster solution. We refer to the first cluster as the “tobacco use severity and sleep health” cluster, which grouped the substance use behaviours of age of initiation of regular smoking and smoking cessation with elements of sleep health such as self-report long sleep duration, self-report sleep duration, accelerometer-derived sleep duration, sleep efficiency, and self-report chronotype. The traits most central to this cluster included sleep efficiency (sleep duration divided by the time between the start and end of the first and last nocturnal inactivity period) and self-reported sleep duration. The second cluster reflected “substance consumption/problematic use and sleep problems” and contained common substance use behaviours (lifetime tobacco use and lifetime cannabis use), consumption (cigarettes per day and drinks per week), as well as problematic substance use (CUD, OUD and problematic alcohol use), measures of sleep difficulties (insomnia, self-report short sleep duration, increased number of sleep episodes, increased standard deviation of accelerometer-derived sleep duration, and diurnal inactivity) and circadian-related activity measures (L5, M10 and sleep midpoint). The traits most central to this cluster included drinks per week, problematic alcohol use and the standard deviation of accelerometer-derived sleep duration.

### 3.3 LCV analysis

We used LCV analysis to assess each of the 31 substance use and sleep/activity measure genetic correlations that survived Bonferroni correction. Of the 31 LCV models, one LCV model survived further Bonferroni correction (.05/31 = .0016), with evidence of OUD being genetically causal for self-report long sleep duration (gcp = 0.50, corrected p = 0.01). Several models reached nominally significant p-values before Bonferroni correction, including CUD being causal for...
self-report short sleep duration ($gcp = -0.23$, nominal $p = 0.04$), CUD being causal for insomnia ($gcp = -0.29$, nominal $p = 0.05$) and OUD being causal for insomnia ($gcp = -0.35$, nominal $p = 0.05$). A majority of the models lacked significance before correction, indicating a general lack of support for genetic causality between substance use/misuse and sleep measures (Table S4). Thus, there was scarce evidence of genetic causality once pleiotropy, polygenicity and sample overlap were appropriately accounted for.

We conducted Mendelian Randomisation to corroborate evidence from LCV on the causal effect of OUD on long sleep (Table S5). There was no significant evidence for a causal association between OUD and long sleep duration using MR.

### TABLE 1 Significant genetic associations between substance use and sleep/activity traits that survived Bonferroni correction ($N$ tests = 231), demonstrating shared genetic liability between these domains

| Sleep and activity trait | Substance use trait | $r_G$ | P-values before correction | Bonferroni-corrected P-value |
|--------------------------|---------------------|-------|----------------------------|-----------------------------|
| Self-report sleep duration | Lifetime tobacco use | -0.11 | 4.6E-07 | 0.001 |
| Short sleep | Lifetime tobacco use | 0.23 | 2.77E-24 | 6.37E-22 |
| Long sleep | Lifetime tobacco use | 0.13 | 6.59E-06 | 0.001 |
| Insomnia | Lifetime tobacco use | 0.29 | 6.44E-20 | 1.48E-17 |
| Diurnal | Lifetime tobacco use | 0.14 | 9.68E-07 | 0.001 |
| Chronotype | Lifetime tobacco use | -0.08 | 2.00E-04 | 0.046 |
| Short sleep | Age of first becoming a regular smoker | -0.32 | 4.41E-22 | 1.01E-19 |
| Long sleep | Age of first becoming a regular smoker | -0.27 | 7.63E-12 | 1.75E-09 |
| Insomnia | Age of first becoming a regular smoker | -0.36 | 1.25E-24 | 2.88E-22 |
| Diurnal | Age of first becoming a regular smoker | -0.15 | 5.61E-05 | 0.013 |
| Short sleep | Cigarettes per day | 0.23 | 8.86E-13 | 2.04E-10 |
| Long sleep | Cigarettes per day | 0.27 | 2.44E-12 | 5.61E-10 |
| Insomnia | Cigarettes per day | 0.29 | 4.34E-15 | 9.98E-13 |
| Diurnal | Cigarettes per day | 0.18 | 4.96E-09 | 1.14E-06 |
| Short sleep | Smoking cessation | -0.25 | 6.51E-13 | 1.50E-10 |
| Long sleep | Smoking cessation | -0.26 | 5.95E-09 | 1.37E-06 |
| Insomnia | Smoking cessation | -0.28 | 2.72E-13 | 6.26E-11 |
| Sleep midpoint | Drinks per week | 0.24 | 9.14E-09 | 2.10E-06 |
| Insomnia | Drinks per week | 0.11 | 3.07E-05 | 0.007061 |
| Diurnal | Drinks per week | -0.12 | 2.00E-04 | 0.046 |
| M10 | Drinks per week | 0.24 | 6.70E-09 | 1.54E-06 |
| Chronotype | Drinks per week | -0.12 | 4.26E-10 | 9.80E-08 |
| Long sleep | Problematic alcohol use | 0.16 | 1.20E-06 | 0.001 |
| Insomnia | Problematic alcohol use | 0.21 | 2.43E-13 | 5.59E-11 |
| Sleep midpoint | Lifetime cannabis use | 0.26 | 4.03E-06 | 0.001 |
| Accelerometer sleep duration | Lifetime cannabis use | -0.17 | 3.72E-05 | 0.008 |
| Chronotype | Lifetime cannabis use | -0.25 | 3.90E-21 | 8.97E-19 |
| Short sleep | CUD | 0.27 | 2.89E-14 | 6.65E-12 |
| Insomnia | CUD | 0.31 | 5.21E-12 | 1.20E-09 |
| Long sleep | OUD | 0.29 | 2.00E-04 | 0.046 |
| Insomnia | OUD | 0.25 | 1.35E-05 | 0.003 |

Abbreviations: CUD, cannabis use disorder; OUD, opioid use disorder.

### DISCUSSION

Using summary data from the largest publicly available GWAS of both sleep/circadian-related activity and substance use measures to date, we found 31 significant genetic correlations between traits in these domains that survived Bonferroni correction. Clustering analysis uncovered two principal genetic clusters: (1) tobacco use severity and sleep health and (2) substance consumption/problematic use and sleep problems. LCV analyses confirmed that the associations between sleep/activity measures and substance use behaviours were driven primarily by common or shared genetic influences, with one exception, a model which implied that OUD may plausibly exert a
alcohol that reflects negative reinforcement-related drug intake, and it is speculated that the relationship could be centred on sleep elements such as sleep duration, efficiency and M10. We also found novel relationships between drinking frequency (drinks per week) and sleep midpoint, diurnal inactivity and M10 are the first reports of a genetic relationship between alcohol use and objective measures of sleep and circadian-related activity. Interestingly, increased drinks per week being genetically correlated with less diurnal inactivity, later midpoint (proxy for evening chronotype) and increased M10 (more active later in the day) imply that genetic predisposition to increased drinking might also be associated with increased activity throughout the day and being more active later in the day or evening.

These genetic correlations formed two distinguishable well-delineated clusters. The first cluster, the “tobacco use severity and sleep health” cluster, suggests that genes associated with aspects of tobacco use severity (a younger age of regular smoking initiation and smoking cessation) also contribute to elements of sleep health such as sleep duration (self-report long sleep duration, shorter self-report sleep duration and shorter accelerometer-derived sleep duration), sleep efficiency and self-report chronotype. Tobacco use is highly comorbid with insufficient sleep, and it is speculated that the relationship could be centred on potential nicotine withdrawal during the night, the strong stimulant effects of nicotine and an increased prevalence of sleep disordered breathing in smokers relative to nonsmokers. Exploration of sleep deficits during tobacco withdrawal may benefit from understanding shared genetic vulnerabilities to poor sleep health.

The second cluster, “substance consumption/problematic use and sleep problems”, suggests that substance use behaviours, such as consumption (lifetime tobacco use, lifetime cannabis use, drinks per week and cigarettes per day) and problematic use (CUD, OUD and problematic alcohol use) share genetic overlap with measures of problematic sleep (insomnia, self-report short sleep duration, increased number of sleep episodes, increased standard deviation of accelerometer-derived sleep duration and diurnal inactivity) as well as measures of circadian-related activity (L5, M10 and sleep midpoint). Insomnia-related deficits are thought to be part of the “dark side” of substance use disorder that reflects negative reinforcement-related drug intake and, based on this cluster, is co-inherited with heavy substance use and problematic substance use. Interestingly, recent drug targets for these

![Image](https://example.com/image.png)

**FIGURE 2** Silhouette coefficients from K-means clustering algorithm. A silhouette coefficient determined that a two-cluster solution was optimal to characterise the relationships between sleep/activity and substance use dimensions.
negative affect/withdrawal-related symptomology of substance use disorders have been shown to improve insomnia symptoms as well. For instance, Acamprosate that is used to treat alcohol use disorder targets withdrawal symptoms and thus improves sleep symptoms during treatment.

Though some previous work argues that the association between insomnia and substance use is causal (via Mendelian Randomisation),

based on results herein, these findings are likely confounded by pleiotropy or polygenicity. Our approach accounted for pleiotropy and involved SNPs across the genome. The LCV approach is also known to outperform Mendelian Randomisation, particularly in the case of genetic correlations.

Additionally, we did find one novel association. Specifically, our LCV analyses provided novel evidence that liability to OUD may be genetically causal for self-reported long sleep duration, even after accounting for pleiotropy between these traits. Over 80% of individuals with OUD report poor sleep quality and sleep problems, which likely impede opioid maintenance and other pharmacological treatments.

Opioid therapy for pain and related conditions has been well-documented to disrupt sleep and due to its respiratory depressant effects, exacerbate risk for sleep-disordered breathing. While this is the first finding of a significant relationship between OUD and long sleep duration, long sleep duration has been found to be phenotypically correlated with depression, antidepressant use, benzodiazepine use, and heavy drinking, as well as genetically correlated with depression. Thus, the causal genetic relationship demonstrated could reflect more of the genetic factors associated with a general maladaptive behavioural profile in comparison to specific opioid use genetics. While three other LCV models were nominally significant before correcting for multiple tests, the lack of significance in these models ultimately implies pleotropic inferences as the more supportive explanation of the associations. Further, our one result that did survive correction was not corroborated by Mendelian Randomisation. Taken together, our results suggest that genetic pleiotropy may underlie sleep problems in substance use, but we find less evidence for causal relationships.

4.1 Limitations

There are several limitations of this study that would influence LDSC and LCV analyses and the generalisability of our findings. First, GWAS results are comprised of mostly common variants; therefore, no rare variation would be included in our analyses, but rare variants may be an additional source of genetic overlap or provide stronger instruments for causality. Second, the GWAS summary statistics used in our analyses assume that the genomic liability to a trait is a good instrument for manifesting the phenotype (e.g., genomic liability for...
insomnia is a good predictor of having insomnia), but this may not necessarily be true for all traits. Third, LCV and LDSC are best when used in one ancestral population, and all GWAS used in our analyses included only individuals of European ancestry. There is a need to include more ancestrally diverse samples in genetics research. Fourth, Mendelian Randomisation and LCV found differing results for causality. This is likely due to the difference in marginal SNP effects that LCV uses, which has considerably more power and can account for sample overlap and minor deviations from population stratification due to the LD score intercept. Further, Mendelian Randomisation has potentially lower power given few GWAS significant hits. Fifth, LCV cannot establish bidirectional causality. Finally, the objectively measured sleep/activity phenotypes (the accelerometer-derived traits) had much smaller samples than the self-report sleep measures; this difference in statistical power may mean that genetic correlations with the accelerometer traits were less likely to be statistically significant than those for self-report sleep measures and therefore less likely to be carried forward in the causal analyses. This may also influence the causal variable analysis, as these analyses require very large sample sizes.

5 | CONCLUSIONS

While substances such as cannabis and alcohol are often used as sleep aids, individuals with substance use disorders also struggle with sleep difficulties, and poor sleep complicates pathways to sustained remission from substance use disorders. Our study documents the role of shared genetic influences on substance use disorders and both sleep and circadian-related measures. For OUD in particular, mechanisms of association could extend beyond pleiotropy into potential causality. Together, these results imply a strong shared genetic relationship between the domains of common substance use behaviours and sleep traits.

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CONFLICT OF INTEREST
We have no conflicts of interest to report.

AUTHOR CONTRIBUTION
AH and EW conceptualized and designed the study, performed the analyses, drafted the initial manuscript, and reviewed and revised the manuscript. CM aided in data analysis and and reviewed and revised the manuscript, EJ and AA reviewed and revised the manuscript.

DATA AVAILABILITY STATEMENT
All data are available through their original authors. Citations for each dataset are included in the Section 2 and in Table 1.

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REFERENCES
1. Teplin D, Raz B, Daiter J, Varenbut M, Tyrrell M. Screening for substance use patterns among patients referred for a variety of sleep complaints. *Am J Drug Alcohol Abuse*. 2006;32:111-120. doi:10.1080/00952990500328695
2. Hasler BP, Martin CS, Wood DS, Rosario B, Clark DB. A Longitudinal Study of Insomnia and Other Sleep Complaints in Adolescents With and Without Alcohol Use Disorders. *Alcohol Clin Exp Res*. 2014;38(8):2225-2233. doi:10.1111/acer.12474
3. Chakravorty S, Vandreng RA, He S, Stein MD. Sleep Management Among Patients with Substance Use Disorders. *Med Clin North Am*. 2018;102(4):733-743. doi:10.1016/j.mcn.2018.02.012
4. Diep C, Tian C, Vachhani K, et al. Recent cannabis use and nightly sleep duration in adults: a population analysis of the NHANES from 2005 to 2018. *Reg Anesth Pain Med*. 2021:rapm-2021-103161;47(2):100-104. doi:10.1136/rapm-2021-103161
5. Angarita GA, Emad N, Hodges S, Morgan PT. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: A comprehensive review. *Addict Sci Clin Pract*. 2016;11(1):1-17. doi:10.1186/s13722-016-0056-7
6. APA. American Psychiatric Association. 2013 *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. 2013. doi:10.1176/app.books.9780890425596
7. Altman BR, Mian MN, Slavin M, Earleywine M. Cannabis Expectancies for Sleep. *J Psychoactive Drugs*. 2019;51(5):405-412. doi:10.1080/02791072.2019.1643053
8. Goodhines PA, Gellis LA, Kim J, Fucito LM, Park A. Self-Medication for Sleep in College Students: Concurrent and Prospective Associations With Sleep and Alcohol Behavior. *Behav Sleep Med*. 2019;17(3):327-341. doi:10.1080/15402002.2017.1357119
9. Goodhines PA, Gellis LA, Ansell EB, Park A. Cannabis and Alcohol Use for Sleep Aid: A Daily Diary Investigation. *Health Psychol*. 2019;38(11):1036-1047. doi:10.1037/heawe0000765
10. Taylor DJ, Bramoweth AD. Patterns and Consequences of Inadequate Sleep in College Students: Substance Use and Motor Vehicle Accidents. *J Adolesc Health*. 2010;46(6):610-612. doi:10.1016/j.jadohealth.2009.12.010
11. Roehrs T, Pappensky N, Rosenthal L, Roth T. Ethanol as a hypnotic in insomnia is a good predictor of having insomnia, but this may not necessarily be true for all traits. Third, LCV and LDSC are best when used in one ancestral population, and all GWAS used in our analyses included only individuals of European ancestry. There is a need to include more ancestrally diverse samples in genetics research. Fourth, Mendelian Randomisation and LCV found differing results for causality. This is likely due to the difference in marginal SNP effects that LCV uses, which has considerably more power and can account for sample overlap and minor deviations from population stratification due to the LD score intercept. Further, Mendelian Randomisation has potentially lower power given few GWAS significant hits. Fifth, LCV cannot establish bidirectional causality. Finally, the objectively measured sleep/activity phenotypes (the accelerometer-derived traits) had much smaller samples than the self-report sleep measures; this difference in statistical power may mean that genetic correlations with the accelerometer traits were less likely to be statistically significant than those for self-report sleep measures and therefore less likely to be carried forward in the causal analyses. This may also influence the causal variable analysis, as these analyses require very large sample sizes.

While substances such as cannabis and alcohol are often used as sleep aids, individuals with substance use disorders also struggle with sleep difficulties, and poor sleep complicates pathways to sustained remission from substance use disorders. Our study documents the role of shared genetic influences on substance use disorders and both sleep and circadian-related measures. For OUD in particular, mechanisms of association could extend beyond pleiotropy into potential causality. Together, these results imply a strong shared genetic relationship between the domains of common substance use behaviours and sleep traits.

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CONFLICT OF INTEREST
We have no conflicts of interest to report.

AUTHOR CONTRIBUTION
AH and EW conceptualized and designed the study, performed the analyses, drafted the initial manuscript, and reviewed and revised the manuscript. CM aided in data analysis and and reviewed and revised the manuscript, EJ and AA reviewed and revised the manuscript.
15. Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. Sleep Med Rev. 2012;16(1):67-81. doi:10.1016/j.smrv.2011.03.004

16. Kerkhof GA. Inter-individual differences in the human circadian system: A review. Biol Psychol. 1985;20(2):83-112. doi:10.1016/0301-0511(85)90019-5

17. Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. Addiction. 1994;89(4):455-462.

18. Fernández-mendoza J, Ilioudi C, Montes MI, et al. Circadian preference, nighttime sleep and daytime functioning in young adulthood. Sleep Biol Rhythms. 2010;8(1):52-62. doi:10.1111/j.1479-8425.2010.00430.x

19. Hasler BP, Franzen PL, de Zambotti M, et al. Evenness and Later Sleep Timing Are Associated with Greater Risk for Alcohol and Marijuana Use in Adolescence: Initial Findings from the National Consortium on Alcohol and Neurodevelopment in Adolescence Study. Alcohol Clin Exp Res. 2017;41(6):1154-1165. doi:10.1111/acer.13401

20. Prat G, Adan A. Influence of circadian typology on drug consumption, hazardous alcohol use, and hangover symptoms. Chronobiol Int. 2011;28(3):248-257. doi:10.1080/07420528.2011.553018

21. Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, Sleep, Behavior, and Diet Associated with Habitual Sleep Duration and Chronotype: Data from the UK Biobank. Ann Behav Med. 2016;50(5):715-726. doi:10.1016/j.amebhm.2015.05.026

22. Kervan C, Fatséas M, Serre F, et al. Association between morningness/eveningness, addiction severity and psychiatric disorders among individuals with addictions. Psychiatry Res. 2015;229(3):1024-1030. doi:10.1016/j.psychres.2015.05.004

23. Mitchell JA, Quante M, Godbole S, et al. Variation in actigraphy-estimated rest-activity patterns by demographic factors. Chronobiol Int. 2017;34(8):1042-1056. doi:10.1080/07420528.2017.1337032

24. Saito Y, Kume Y, Kodama A, Sato K, Yasuba M. The association between circadian rest-activity patterns and the behavioral and psychological symptoms depending on the cognitive status in Japanese nursing-home residents. Chronobiol Int. 2018;35(12):1670-1679. doi:10.1080/07420528.2018.1505752

25. Tsanas A, Woodward E, Ehlers A. Objective characterization of activity, sleep, and circadian rhythm patterns: insights into posttraumatic stress disorder. JMMR. M heapslate Sleep. 2020;8(4):14306. doi:10.2196/14306

26. Santiesteban JA, Brown TG, Gruber B, et al. Association between the Munich Chronotype Questionnaire and Wrist Actigraphy. Sleep Disord. 2018;2018:1-7. doi:10.1155/2018/5646848

27. Gross G, Maruani J, Vorspan F, et al. Association between coffee, tobacco, and alcohol daily consumption and sleep/day wake cycle: an actigraphy study in euthymic patients with bipolar disorders. Chronobiol Int. 2020;37(5):712-722. doi:10.1080/07420528.2020.1725542

28. Pieters S, Burk WI, Van der Vorst H, Dahl RE, Wiers RW, Engels RCME. Prospective Relationships Between Sleep Problems and Substance Use, Internalizing and Externalizing Problems. J Youth Adolesc. 2014;44(2):379-388. doi:10.1007/s10964-014-0213-9

29. Pasch KE, Latimer LA, Cance JD, Moe SG, Lytle LA. Longitudinal Bidirectional Relationships Between Sleep and Youth Substance Use. J Youth Adolesc. 2012;41(9):1184-1196. doi:10.1007/s10964-012-9784-5

30. Wong MM, Brower KJ, Nigg JT, Zucker RA. Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. Alcohol Clin Exp Res. 2010;34(6):1033-1044. doi:10.1111/j.1530-2277.2010.01178.x

31. Wong MM, Brower KJ, Zucker RA. Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. Sleep Med. 2009;10(7):787-796. doi:10.1016/j.sleep.2008.06.015

32. Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. Sleep. 2008;31(10):1351-1356. doi:10.5665/sleep/31.10.1351

33. Wong MM, Brower KJ, Fitzgerald HE, Zucker RA. Sleep Problems in Early Childhood and Early Onset of Alcohol and Other Drug Use in Adolescence. Alcohol Clin Exp Res. 2004;28(4):578-587. doi:10.1111/j.1530-0277.2003.tb08916.x

34. Miller MB, Janssen T, Jackson KM. The Prospective Association Between Sleep and Initiation of Substance Use in Young Adolescents. J Adolesc Health. 2017;60(2):154-160. doi:10.1016/j.jadohealth.2016.08.019

35. Nguyen-Louie TT, Brumback T, Worley MJ, et al. Effects of sleep on substance use in adolescents: a longitudinal perspective. Addict Biol. 2018;23(2):750-760. doi:10.1111/adb.12519

36. Brook JS, Zhang C, Rubenstein E, Brook DW. Insomnia in adults: the impact of earlier cigarette smoking from adolescence to adulthood. J Addict Med. 2015;9(1):40-45. doi:10.1097/ADM.0000000000000883

37. Rognmo K, Bergvik S, Rosenvinge JH, Bratlid KL, Friborg O. Gender differences in the bidirectional relationship between alcohol consumption and sleeplessness: The Tromsø study. BMC Public Health. 2019;19(1):1-8.44. doi:10.1186/s12889-018-6801-6

38. Haynie DL, Lewin D, Luk JW, et al. Beyond sleep duration: Bidirectional associations among chronotype, social jetlag, and drinking behaviors in a longitudinal sample of US high school students. Sleep. 2018;41(2). doi:10.1093/sleep/zsz202

39. Ogeil RP, Phillips JG, Rajaratnam SMW, Broadbear JH. Risky drug use and effects on sleep quality and daytime sleepiness. Hum Psychopharmacol. 2015;30(5):356-363. doi:10.1002/hup.2483

40. Haario P, Rahkonen O, Laaksonen M, Lallukka T. Bidirectional associations between insomnia symptoms and unhealthy behaviours. J Sleep Res. 2013;22(1):89-95. doi:10.1111/j.1365-2869.2012.01043.x

41. Winiger EA, Huggett SB, Hatoum AS, Stallings MC, Hewitt JK. Onset of regular cannabis use and adult sleep duration: Genetic variation and the implications of a predictive relationship. Drug Alcohol Depend. 2019;204:107517. doi:10.1016/j.drugalcdep.2019.06.019

42. Winiger EA, Huggett SB, Hatoum AS, et al. Onset of regular cannabis use and young adult insomnia: an analysis of shared genetic liability. Sleep. 2019;43(5). doi:10.1093/sleep/zsz293

43. Deak JD, Johnson EC. Genetics of substance use disorders: a review. Psychosom Med. 2021;51(13):1-12. doi:10.1016/S0033-2917(21)00096-9

44. Madrid-Valero JJ, Rubio-Aparicio M, Gregory AM, Sánchez-Meca J, Ordoñana JR. The heritability of insomnia: Systematic review and meta-analysis of twin studies. Sleep Med Rev. 2021;51:1-12. doi:10.1016/j.smrv.2021.101437

45. Kocevska D, Barclay NL, Bramer WM, Gehman PR, Van Someren EJW. Heritability of sleep duration and quality: A systematic review and meta-analysis. Sleep Med Rev. 2021;59:101448. doi:10.1016/j.smrv.2021.101448

46. Short NA, Mathes BM, Gibby B, Oglesby ME, Zvolensky MJ, Schmidt NB. Insomnia symptoms as a risk factor for cessation failure following smoking cessation treatment. Addict Res Theory. 2016;24(1):17-23. doi:10.1080/16666359.2016.1190342

47. Hatoum AS, Colbert SMC, Johnson EC, et al. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. medRxiv. January 2022;2022.01.06.22268753. doi:10.1101/2021.01.06.22268753
48. Watson NF, Buchwald D, Harden KP. A twin study of genetic influences on diurnal preference and risk for alcohol use outcomes. J Clin Sleep Med. 2013;9(12):1333-1339. doi:10.5664/jcsm.3282

49. Hammerschlag AR, Stringer S, De Leeuw CA, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. Nat Genet. 2017;49(11):1584-1592. doi:10.1038/ng.3888

50. Gibson M, Munafò MR, Taylor AE, Treur JL. Evidence for Genetic Correlations and Bidirectional, Causal Effects Between Smoking and Sleep Behaviors. Nicotine Tob Res. 2019;21(6):731-738. doi:10.1093/ncr/nty230

51. Kranzer HR, Zhou H, Kember RL, et al. Genome-wide association study of multiple alcohol consumption and use disorder in 274,442 individuals from multiple populations. Nat Commun. 2019;10(1):1499. doi:10.1038/s41467-019-09480-8

52. Zhou H, Rentsch CT, Cheng Z, et al. Association of OPRM1 Functional Coding Variant with Opioid Use Disorder: A Genome-Wide Association Study. JAMA Psychiat. 2020;77(10):1072-1080. doi:10.1001/jamapsychiatry.2020.1206

53. Winiger EA, Ellingson JM, Morrison CL, et al. Sleep deficits and cannabis use behaviors: an analysis of shared genetics using linkage disequilibrium score regression and polygenic risk prediction. Sleep. 2020;44(3). doi:10.1093/sleep/zsa188

54. Smith GD, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? Br Med J. 2005;330(7499):1076-1079. doi:10.1136/bmj.330.7499.1076

55. Pasman JA, Smit DJA, Kingma L, Vink JM, Treur JL, Verweij KJH. Causal relationships between substance use and insomnia. Drug Alcohol Depend. 2020;214:108151. doi:10.1016/j.drugalcdep.2020.108151

56. Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. Med Hypotheses. 2010;74(5):928-933. doi:10.1016/j.mehy.2009.10.020

57. Conroy DA, Arnett JT. Sleep and substance use disorders: An update. Curr Psychiatry Rep. 2014;16(10):1-9. doi:10.1007/s11920-014-0487-3/TABLES/1

58. Jansen PR, Watanabe K, Stringer S, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet. 2019;51(3):394-403.

59. Jones SE, Lane JM, Wood AR, et al. Genome-wide association analysis of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun. 2019;10(1):1-11, 343. doi:10.1038/s41467-018-08259-7

60. Dashi HS, Jones SE, Wood AR, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun. 2019;10(1):1-12, 1100. doi:10.1038/s41467-019-08917-4

61. Jansen PR, Watanabe K, Stringer S, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet. 2019;51(3):394-403. doi:10.1038/s41467-018-0333-3

62. Kaufmann CN, Gershon A, Depp CA, Miller S, Zeitzer JM, Ketter TA. Daytime midpoint as a digital biomarker for chronotype in bipolar disorder. J Affect Disord. 2018;241:586-591. doi:10.1016/j.jad.2018.08.032

63. Fekedulegn D, Andrew ME, Shi M, Violanti JM, Knox S, Innes KE. Actigraphy-based assessment of sleep parameters. Ann Work Expo Heal. 2020;64(4):350-367. doi:10.1093/ANNWEH/WXAA007

64. Jones SE, van Hees VT, Mazzotti DR, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. Nat Commun. 2019;10(1):1-12, 1585. doi:10.1038/s41467-019-09576-1

65. Häusler N, Marques-Vidal P, Haba-Rubio J, Heinzer R. Does sleep predict next-day napping or does napping influence same-day nocturnal sleep? Results of a population-based ecological momentary assessment study. Sleep Med. 2019;61:31-36. doi:10.1016/j.sleep.2019.04.014

66. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet. 2019;51(2):237-244. doi:10.1038/s41588-018-0307-5

67. Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci. 2018;21(9):1161-1170. doi:10.1038/s41593-018-0206-1

68. Johnson EC, Demontis D, Thorgeirsson TE, et al. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry. 2020;7(12):1032-1045. doi:10.1016/S2215-0366(20)30339-4

69. Bulik-Sullivan B, Loh PR, Finucane HK, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291-295. doi:10.1038/ng.3211

70. Duan S, Zhang W, Cox NJ, Dolan ME. FstSNP-HapMap3: a database of SNPs with high population differentiation for HapMap3. Bioinformation. 2008;3(3):139-141. doi:10.1026/97320630003139

71. Gibbs RA, Boerwinkle E, Dzauvapani H, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68-74. doi:10.1038/nature15393

72. Bonferroni CE. Il Calcolo delle Assicurazioni su Gruppi di Teste. In: Studi in Onore Del Professore Salvatore Ortu Carboni; 1935.

73. Wagstaff K, Cardie C, Rogers S, Schrödl S. Constrained K-means clustering with background knowledge. In: International Conference on Machine Learning ICML; 2001.

74. Kanungo T, Mount DM, Netanyahu NS, Piatko CD, Silverman R, Wu AY. An efficient k-means clustering algorithm: Analysis and implementation. IEEE Trans Pattern Anal Mach Intell. 2002;24(7):881-892. doi:10.1109/TPAMI.2002.1017616

75. Grotzinger AD, Rhemtulla M, de Vlaming R, et al. Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav. 2019;3(5):513-525. doi:10.1038/s41562-019-0566-x

76. OConnor LJ, Price AL. Distinguishing genetic correlation from causal influence of schizophrenia. Nat Neurosci. 2017;20(12):1728-1734. doi:10.1038/nn.4518-018-0255-0

77. Heman G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018;7. doi:10.7554/eLife.34408

78. Hammerschlag AR, Stringer S, de Leeuw CA, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. Nat Genet. 2017;49(11):1584-1592. doi:10.1038/ng.3888

79. Gibson M, Munafò MR, Taylor AE, Treur JL. Evidence for genetic correlations and bidirectional, causal effects between smoking and sleep behaviors. Nicotine Tob Res. 2018;21(6):731-738. doi:10.1093/nty230

80. Buyse DJ. Sleep health: can we define it? Does it matter? Sleep. 2014;37(1):9-17. doi:10.5665/sleep.3298

81. Sabanayagam C, Shankar A. The association between active smoking, smokeless tobacco, second-hand smoke exposure and insufficient sleep. Sleep Med. 2011;12(1):7-11. doi:10.1016/j.sleep.2010.09.002

82. Wetter DW, Young TB. The relation between cigarette smoking and sleep disturbance. Prev Med (Baltim). 1994;23(3):328-334. doi:10.1006/ypmed.1994.1046

83. Koob GF. The dark side of addiction the horsley gantt to joseph brady connection. J Nerv Ment Dis. 2017;205(4):270-272. doi:10.1097/NMD.0000000000000551
84. Luc S, Peter B, Thierry D, et al. Effects of Acamprosate on Sleep During Alcohol Withdrawal: A Double-Blind Placebo-Controlled Polysomnographic Study in Alcohol-Dependent Subjects. *Alcohol Clin Exp Res.* 2006;30(9):1492-1499. doi:10.1111/j.1530-0277.2006.00180.x

85. Dunn KE, Finan PH, Andrew Tompkins D, Strain EC. Frequency and correlates of sleep disturbance in methadone and buprenorphine-maintained patients. *Addict Behav.* 2018;76:8-14. doi:10.1016/j.addbeh.2017.07.016

86. Wilkerson AK, McRae-Clark AL. A review of sleep disturbance in adults prescribed medications for opioid use disorder: potential treatment targets for a highly prevalent, chronic problem. *Sleep Med.* 2021;84:142-153. doi:10.1016/j.sleep.2021.05.021

87. Rosen IM, Aurora RN, Kirsch DB, et al. Chronic opioid therapy and sleep: An American academy of sleep medicine position statement. *J Clin Sleep Med.* 2019;15(11):1671-1673. doi:10.5664/jcsm.8062

88. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. *Sleep.* 2006;29(7):881-889. doi:10.1093/sleep/29.7.881

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