Longitudinal determinants of insomnia among patients with alcohol use disorder

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Abstract

Insomnia is common among patients with AUD and can impair quality of life and cognitive functioning, as well as cause psycho-social problems and increased risk of relapse. Nonetheless, determinants of insomnia in patients with AUD have scarcely been studied. We aimed to examine prevalence and development of self-perceived insomnia among inpatients in treatment for AUD, and to examine factors in this group known to be associated with sleep disturbance in the general population. We examined self-reported information about sleep from 94 AUD inpatients in long-term treatment (up to 9 months) using a questionnaire identifying probable insomnia. Potential predictors identified in bivariate tests were used in binomial logistic regressions to examine the effect on sleep at baseline and at 6-week follow-up. Longitudinal multilevel analyses were used to examine factors affecting development of sleep quality during the treatment stay. At baseline, 54% of the patients reported sleep problems indicating insomnia. This was reduced to 35% at 6-week follow-up. In a cross-sectional analysis of sleep at baseline, we found that being male (OR 0.18, $p = 0.042$) and engaging in physical activity (OR 0.09, $p < 0.001$) were negatively associated with insomnia, while a high level of depressive symptoms (OR 1.10, $p = 0.010$) was positively associated after adjustment for age, history of trauma, and severity of dependence. Multilevel analyses of data over a 6-month period showed time interactions with physical activity, such that sleep improvement was greater in patients who initially had a low level of physical activity. This longitudinal study corroborates findings of high prevalence of insomnia among AUD patients and identifies factors in this group associated with insomnia, such as sex, depression, and physical activity. Future longitudinal studies are needed to examine the causal directions between sleep, depression, and physical activity and how these might be targeted in clinical settings.

Highlights

- 54% of alcohol use disorder inpatients report insomnia in early abstinence.

- Female gender, depression, and low physical activity associate with insomnia.

- Sleep quality improves during the treatment stay.

Introduction

Insomnia is a prevalent complaint, affecting 15% to 30% of the general population (Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014; Roth, 2007) and as many as 36–91% of people with alcohol use disorder (AUD) (Brower, 2003; Brower, Aldrich, Robinson, Zucker, & Greden, 2001; Cohn, Foster, & Peters, 2003). Insomnia is defined in the DSM-5 as dissatisfaction with sleep quality or quantity caused by problems with initiation or maintenance of sleep, resulting in daytime distress or impaired functioning (American Psychiatric Association, 2013). For people in treatment for AUD, insomnia is found to vary over the course of treatment. During early withdrawal, i.e., the first two weeks of treatment, insomnia symptoms are found in 88% (Kolla, Mansukhani, Biernacka, Chakravorty, & Karpyak, 2020), and in the early recovery phase, i.e., up to about eight weeks, symptoms are reported in approximately 65% of patients (Brower et al., 2001). Longitudinal studies indicate that symptoms of insomnia may persist for months or years after detoxification and sustained sobriety, even if strong predictors of insomnia, such as depressive symptoms, are decreased (Currie, Clark, Rimac, & Malhotra, 2003; Kolla et al., 2020). Insomnia is also a robust predictor of relapse (Brower, 2003, 2015; Brower et al., 2001) and has been found to impair impulse control and induce conflicts and psychosocial problems among AUD patients (Chaudhary et al., 2015), factors that may lead to reduced quality of life and poorer outcomes for AUD treatment.

Comorbid AUD and insomnia are likely to have a bidirectional causal relationship where sleep problems predict future consumption of alcohol in adults (Ford & Kamerow, 1989) and adolescents (Wong, Robertson, & Dyson, 2015), and heavy and sustained consumption of alcohol may lead to persistent insomnia (Britton, Fat, & Neligan, 2020; Meyrel, Rolland, & Geoffroy, 2020). Alcohol has partly sedative properties, and intake at bedtime might improve sleep initiation and sleep during the first part of the night, but with more disrupted sleep at later stages (Ebrahim, Shapiro, Williams, & Fenwick, 2013; Thakkar,

Sharma, & Sahota, 2015). Struggling to fall asleep is common among AUD patients, and 44% to 60% of AUD patients report using alcohol to try to ease this problem (Brower, 2001). However, alcohol's positive effect on sleep initiation is limited and has been shown to wane after a few nights, ultimately resulting in reduced sleep quality, both in the general population (Dufour, Archer, & Gordis, 1992; Stein & Friedmann, 2005) and among AUD patients. In addition, studies have found that using alcohol to aid sleep initiation may increase sleep onset latencies and decrease total sleep time, alterations which may persist long after withdrawal (Brower, 2001; Currie et al., 2003). This is reflected in a study where severity of alcohol problems was related to severity of sleep problems, even after adjustment for known risk factors and predictors of insomnia such as mood disorders, demographics, and smoking (Hartwell, Bujarski, Glasner-Edwards, & Ray, 2015).

Studies demonstrate that insomnia is associated with mental health problems, such as depression, both in the general population (Sivertsen, Krokstad, Øverland, & Mykletun, 2009) and in clinical samples, where sleep problems have been reported in as many as 75% of depressed patients (Nutt, Wilson, & Paterson, 2008). This strong association is further emphasized by the fact that insomnia (or hypersomnia) is one of the criteria for depressive disorders in the DSM-5. AUD patients with insomnia have more severe depressive symptoms (Brower et al., 2001), and in a recent study among patients in early recovery, depressive symptoms were found to be one of the factors most strongly related to sleep disturbances (Kolla et al., 2020). One study among AUD patients has identified levels of psychiatric symptoms as an important mediating factor between alcohol use severity and insomnia, while psychosocial problems and current alcohol consumption levels were not found to be significant mediators (Chaudhary, Wong, Kolla, Kampman, & Chakravorty, 2020). Other psychiatric disorders and symptoms, such as ADHD, are also common among AUD patients, but it is not known how these influence sleep in this group.

Factors such as low physical activity, being overweight, smoking, and trauma background have been associated with impaired sleep in the general population but are less studied in people with AUD. While physical activity is well established as a promoter of healthy sleep in the general population (Kelley & Kelley, 2017), studies have found that people with AUD and hazardous drinking report being less physically active (Hallgren et al., 2021; Smothers & Bertolucci, 2001). Smoking, which is particularly frequent among people with AUD (Weinberger, Funk, & Goodwin, 2016), and being overweight are reported to be positively correlated with insomnia (Hu, Wang, Liao, Dai, & Cao, 2021; Traversy & Chaput, 2015). Finally, sleep disturbances after traumatizing experiences are common and can persist for many years (Babson & Feldner, 2010; Sinha, 2016). This is highly relevant for people with AUD, because trauma is a strong predictor of risk for developing AUD (Zaorska et al., 2020).

The purpose of this study was to examine insomnia among AUD inpatients in terms of prevalence, presentation, and development over time, and to investigate, in AUD patients, factors known to be associated with insomnia in the general population.

Materials and methods

Study participants

Data were collected in three treatment clinics in the Eastern region of Norway from January 2018 to August 2019. The material has been described in a previous publication (Bolstad, Lien, & Bramness, 2021). The clinics offer long-term residential treatment stays (from one to nine months duration) for people with substance use disorders (SUD), where the majority have a diagnosis of AUD. The patients receive individual psychological treatment and group therapy, and Activities of Daily Life (ADL) training is an integrated part of the treatment. Patients receive medical attention comprising somatic examination and treatment, and medications are prescribed by medical staff as required for somatic and psychiatric

diagnoses. People were considered for inclusion in the study if they had current AUD as

diagnosed according to the International Classification of Diseases 10th Revision (ICD-10)

and were not in an unsuitable condition to participate in the study, as assessed by the clinical

staff, because of severe somatic illness, psychosis, cognitive impairment, or inability to speak

a Scandinavian language. Of the 366 patients who were admitted to treatment in the clinics

during our inclusion period from January 2018 to March 2019, 224 (61%) were considered

eligible for participation in this study. Eligible participants were provided with information

about the study and of these, 114 (51%) patients signed written informed consent and were

enrolled in the study. Of the enrolled patients, 27 (24%) did not return a valid sleep quality

questionnaire form at baseline. Thus, 87 patients were included in the descriptive and

baseline analyses, whereas the longitudinal analyses included information from 94

participants, as some responded in follow-up questionnaires. The baseline data collection

took place when the patients had been in the treatment clinic for a median (1st, 3rd quartile:

Interquartile range, [IQR]) of 7 (5–12) days and when they had reported abstinence from

alcohol since 19 (IQR 12–30) days earlier. The study was approved by the Norwegian

Regional Ethics Committee before data collection commenced (ID no: 21505/2017/1314).

Measures
Sleep Condition Indicator (SCI)

To collect information about subjective sleep quality, we used the Sleep Condition

Indicator (SCI) questionnaire (Espie et al., 2014). The SCI has been developed to screen for

insomnia and consists of eight questions regarding the occurrence of the following issues in

the past month: 1) sleep onset delay, 2) night-time awakenings, 3) number of nights with

problematic sleep per week, 4) self-rate of sleep quality, 5) effect on mood, energy, and

relations, 6) effect on concentration, productivity, and staying awake, 7) overall effect of poor

sleep, and 8) duration of the sleep problem. All items have response alternatives ranging from

0 to 4, where 0 indicates a poor state and 4 indicates no/little problem, resulting in a total score ranging from 0–32. The SCI was used as a dichotomized variable according to Espie and co-workers, with a cut-off of ≤16 and >16, where a score ≤16 indicates probable insomnia and a score >16 indicates no insomnia (Espie et al., 2014). The instrument has shown convergent validity with the Insomnia Severity Index and the Pittsburgh Sleep Quality Index, and the original version had high internal consistency (Cronbach's alpha of 0.86) (Espie et al., 2014). The corresponding internal consistency in our study was similar (Chronach's alpha of 0.90). The current version was constructed by a forward-backward translation procedure where the original English version was first translated into Norwegian by a bilingual native Norwegian speaker and then back-translated into English by a native English-speaking translator. The original and back-translated versions were then compared, and only minor deviations not requiring further adjustments were found.

Background variables

Baseline data collection consisted of an interview, biometric measures (body mass index (BMI), waistline, blood pressure), blood sampling for CRP, structured interviews, and administration of questionnaires. During the structured interview, background information was collected, including information about daily cigarette smoking (yes/no). Selected modules of the Mini International Neuropsychiatric Interview (M.I.N.I) version 6.0 were conducted by trained staff, while all other information was collected using self-report forms.

Mini International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I. was used to diagnose AUD and SUD, as well as current anxiety disorders. Anxiety disorders included panic disorder, agoraphobia, social phobia, and generalized anxiety disorder.

Beck Depression Inventory 2 (BDI-II)

The level of depressive symptoms was measured using the BDI-II (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; McPherson & Martin, 2010). This self-report

questionnaire consists of 21 questions asking the respondents how they have been feeling the preceding two weeks, with responses given on a 4-point Likert scale ranging from 0 to 3. Reponses are added into a total score ranging from 0–63, where a higher score indicates a higher level of depressive symptoms.

Severity of dependence scale (SDS)

The SDS was used to measure the severity of alcohol dependence. The SDS was originally constructed to measure dependency on illicit drugs (Gossop, Best, Marsden, & Strang, 1997), but has later been shown to be a reliable and valid measure of alcohol dependence (Ferri, Marsden, Araugo, Laranjeira, & Gossop, 2000). It consists of five items that target subjective aspects of dependence during the preceding year, such as, "Did you think your alcohol use was out of control?" and, "Did you wish you could stop drinking?" The response alternatives range from 0) 'Never' to 3) 'Always' for each question. The responses are added into a total score ranging from 0–15, where a higher score indicates more severe dependence.

Traumatic experiences

Exposure to trauma was measured using a structured self-report form with five questions that have previously been used in a study of psychiatric inpatients (Toft et al., 2018). The first three questions ask whether the person has experienced the following in his or her childhood: sexual assault (1), physical abuse (2) and other traumatic events that have subsequently caused significant/considerable problems (3). The last two questions deal with experiences in adulthood: sexual assault or physical abuse (4) and other traumatic events that have subsequently caused significant/considerable problems (5). For each item, the response alternatives were: 0) '*No*', 1) '*Yes, once*' or 2) '*Yes, several times*'. Dichotomous variables (No/Yes, once or several times) for childhood and adulthood trauma, respectively, were constructed. The patients were advised to speak to a psychologist at the clinic if the questions evoked negative emotions.

International Physical Activity Questionnaire Short Version (IPAQ-S)

To identify levels of physical activity among the patients we used the IPAQ-S (Craig et al., 2003). The Norwegian version has been validated (Kurtze, Rangul, & Hustvedt, 2008). In the IPAQ-S the respondent specifies the time spent (number of days and minutes each time) doing vigorous exercise, moderate exercise, or walking during the preceding week. Activities during leisure time, work, domestic activities, and transport are reported. Hours of sitting are also reported. On the basis of this information, respondents are distributed into three levels of physical activity: low, moderate, and high (IPAQ web site, 2005). We collapsed the moderate and high categories and produced a binary variable that was used in the analyses.

Adult ADHD Self-Report Scale (ASRS)

To collect information about ADHD symptoms we used the ASRS (Kessler et al., 2005). The full version of this questionnaire consists of 18 items addressing inattentive or hyperactive-impulsive symptoms with five ordered response alternatives 0) 'Never', 1) 'Seldom', 2) 'Sometimes', 3) 'Often', and 4) 'Very often'. A 6-item screening version of the ASRS has demonstrated good specificity and sensitivity (Kessler et al., 2005). We calculated the total score of these six items (Kessler et al., 2007). Patients receiving ADHD medication were identified from clinical records.

Sleep aid medication

Clinical records of administered medical drugs were used to identify patients who were receiving sleep aid medication. Both routine and sporadic administration were included, and a dichotomous variable was constructed. Pharmaceuticals registered in patients' records with an effect on sleep were the antihistamines alimemazine (trimeprazine), promethazine, hydroxyzin; the sedative antidepressants mianserin, mirtazapine, amitriptyline; the benzodiazepines oxazepam and nitrazepam; the hypnotics zopiclone, zolpidem, melatonin; and the antipsychotic drug quetiapine (low dosage).

Withdrawal symptoms

Patients were asked during an interview whether they were having current withdrawal symptoms such as trembling, sweating, or restlessness. The responses were recorded as a binary variable (yes/no).

Treatment drop-out

Patients who discontinued the treatment program and left the clinic before planned discharge were regarded as dropped out, as opposed to patients who completed their stay or were still in treatment at 6-month follow-up.

Biological markers

Venous blood was drawn from the median cubital vein into serum tubes and ethylenediaminetetraacetic tubes for the analyses of C-reactive protein (CRP) and Phosphatidylethanol (PEth; 16:0/18:1), respectively. The tubes were turned slowly upside-down 8–10 times and left in a stand for 30 minutes. Then the serum tubes were centrifuged before all tubes were transferred to the laboratory for analysis.

Missing data

Missing items in the SCI questionnaire were imputed with each patient's mean score based on their available data (Hawthorne, Hawthorne, & Elliott, 2005). There were six patients with missing data in the SCI questionnaire at baseline. Four of these patients had missing data in four questions (50%), one patient had missing data in three questions (38%), while one patient had missing data in one question (13%). Four patients had missing data in one question (13%) at the 6-week follow-up, and one patient had missing data in three questions (38%) at the 6-month follow-up. In the BDI-II questionnaire, there was one patient with missing data in one question (5%) at baseline. Complete data were collected for 87 patients at baseline, 62 patients at 6-week follow-up, and 34 patients at 6-month follow-up.

Statistical analyses

Descriptive statistics were used to assess sociodemographic data at baseline. For continuous variables, medians and 25th and 75th percentiles were used to measure central

tendency and the Wilcoxon rank sum test was used to test group differences. Categorical variables were described with n (%), and group differences were tested using the Pearson chi-square test. Logistic regression was used to assess associations between various predictors on the binary dependent variable SCI at baseline and at 6-week follow-up. Initially, all available variables were analyzed independently with binary SCI as dependent variable to assess the p values and consider which variables to keep. Independent variables with p values less than 0.25 were kept and subsequently entered in the adjusted logistical models (Bursac, Gauss, Williams, & Hosmer, 2008). The age and sex variables were included despite non-significant p values. Two logistic regression models were constructed: a model with baseline independent and outcome variables and a model with baseline independent variables and 6-week follow-up outcome variable. The longitudinal part of this study included repeated measurements of the SCI, IPAQ-S, and BDI-II questionnaires. These were submitted three times during the treatment period, at baseline (one week after admittance), at 6 weeks, and at 6 months after enrollment. As our main outcome was the binary measure of insomnia vs. no insomnia (SCI), logistical multilevel models were used for analysis (Rabe-Hesketh & Skrondal, 2008). These measurements were repeated across the three time points, constituting a clustering of correlated measurements within each individual. The nested measurements within each patient created a 2-level structure with measurements at level 1 within patients at level 2. In multilevel models, all available data are used. Thus, a patient who submitted data for at least one measurement was still included and contributed to parameter estimation (Fitzmaurice, Laird, & Ware, 2011). A random intercept variation was included in the multilevel models. The random intercept allowed each patient's intercept to vary at baseline, thus accounting for the clustering and random variability of the initial scores. Allowing the patient's slope to vary across time was tested by including random slope, but this did not improve model fit. The models were compared using likelihood ratio tests, and all

comparisons came out non-significant. In conclusion, the simpler model was preferred. Thus, the logistical multilevel models took the form of:

$$logit[\Pr(y_{ij}|x_j, time, u_j)] = \beta_0 + \beta_1 x_j + \beta_2 time + \beta_3 x_j \times time + u_j$$

where i = 1,….,n; j = 0, 6, or 26 weeks of follow-up, β_0 = fixed intercept; β_1 = fixed slope for independent variable; β_2 = fixed slope for time; β_3 = interaction between time and independent variable; $u_j \sim N(0, \sigma^2)$, denoting the level 2 residual where σ^2 is the level 2 variance. The time variable took the values 0, 6, and 26 corresponding to baseline, 6 weeks and 6 months of follow-up.

In addition to the logistic multilevel analyses, equivalent linear models were constructed to explore associations between the exposure variables and the SCI score continuous variable (Supplementary material). Lastly, multilevel linear models stratified by insomnia were constructed with previously described exposure variables and the continuous SCI score outcome variable. The statistical package Stata was used for all analyses (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, Texas, United States: StataCorp LLC.).

Results

At baseline, 47 (54%) participants had SCI scores below cut-off, indicating insomnia. At 6-week and 6-month follow-ups, 24 (35%) and 15 (37%) participants reported insomnia, respectively. Relative to patients who reported satisfactory sleep, patients with insomnia scored significantly lower on all SCI items ($p < 0.001$), and the most significant findings were more problems related to sleep onset and time spent awake after awakenings during the night (Figure 1). The majority of patients with insomnia had experienced this for a long time; 87% reported having sleep problems for more than one year (not shown in Figure 1). When investigating the occurrence of insomnia in the course of the study period, we found that 21 (34%) had insomnia at both baseline and follow-up, 13 (21%) reported insomnia at baseline

but not at follow-up, indicating improved sleep, 1 (2%) did not report insomnia at baseline but at follow-up, indicating impaired sleep, while 27 (44%) did not have insomnia at either baseline or follow-up.

Background and health variables were examined in participants who scored below or above SCI cut-off (≤16 indicating insomnia) (Table 1). There were no group differences for age, educational level, marital status, BMI, waistline, blood pressure, or CRP. There were fewer men among the patients with insomnia than among the patients without insomnia (64% vs. 88%, $p = 0.011$), and patients with insomnia were less likely to engage in physical activity (21% vs. 70%, $p < 0.001$). When we examined psychiatric variables, there were no group differences regarding anxiety disorders, experience of trauma, or ASRS score, but patients with insomnia reported more depressive symptoms (BDI: Median 21 [IQR 13, 29] vs. 11 [IQR 4, 19], $p < 0.001$). When we looked at measures of dependence, patients with insomnia reported higher severity of dependence on alcohol (SDS: Median 11 [IQR 8, 13] vs. 10 [IQR 7, 11], $p = 0.040$). Furthermore, the rank sum test indicated a slightly higher age at first drink in patients with insomnia (Median 15 [IQR 14, 17] vs. 15 [IQR 13, 16], $p = 0.046$). There were, however, no differences in smoking, other SUD, time since last drink, blood PEth level, duration of drinking career, or having a parent with alcohol problems. Among the 15 patients that had other SUD, 2 (13%) reported heroin as the main drug, 6 (40%) reported illegal use of prescription drugs, 2 (13%) reported cocaine use, and 4 (27%) reported cannabis use. The information was missing for one patient. Drugs specifically prescribed for sleep disorder were more common in the insomnia group (35 [74%] vs. 18 [45%], $p = 0.005$), where 12 (26%) patients used antihistamines, and 24 (51%) used quetiapine prescribed to aid sleep, versus 4 (10%) and 16 (40%) in the group of patients without insomnia (not shown in table). One patient in the group with insomnia received methylphenidate. There was no difference

between groups in mean change of SCI score from baseline and 6 weeks or 6 months, and

finally, no difference in drop-out rate between the groups.

Logistic regression models with insomnia (SCI below vs. above cut-off) at baseline as

outcome variable (Table 2) were constructed using age and sex as predictors alongside

potential predictors of insomnia at baseline with p values below 0.25 (Table 1), excepting

sleep medication and age of first drink. The Hosmer and Lemeshow goodness-of-fit test was

non-significant ($\chi^2 = 69.70$, $p = 0.488$), which indicated an overall good model fit (Z. Zhang,

2016). The unadjusted models demonstrated significant associations with insomnia, where

being female, having higher dependence severity, having experienced trauma in adulthood,

having higher levels of depressive symptoms, and lower physical activity levels, increased

the odds for probable insomnia. In the model adjusted for age and sex, a high level of

depressive symptoms and low levels of physical activity were still significantly associated

with insomnia. The multivariable model that included all variables demonstrated that the

association with increased depressive symptoms (OR 1.11 [CI 1.02, 1.20], $p = 0.010$),

reduced physical activity (OR 0.09 [CI 0.02, 0.35], $p < 0.001$) as well as female sex (OR 0.18

[CI 0.03, 0.94], $p = 0.042$), remained statistically significant. In equivalent regression models

with insomnia at 6-week follow-up as outcome variable, younger age (OR 0.95 [CI 0.90,

1.00], $p = 0.038$), low levels of physical activity (OR 0.31 [CI 0.12, 0.81], $p = 0.017$), and

higher levels of depressive symptoms (OR 1.06 [CI 1.01, 1.11], $p = 0.023$) were associated

with insomnia in the unadjusted models. In the full multivariable model, adjusting for all

covariates, only age (OR 0.89 [CI 0.82, 0.97], $p = 0.007$) and physical activity (OR 0.18 [CI

0.05, 0.63], $p = 0.007$) remained statistically significant. Linear regression models, with the

same set of predictors but SCI score as continuous outcome variable, were also constructed

(Supplementary Table S1). There were no substantial differences compared to the results

from the logistic regression, but the effect of SDS was statistically significant when adjusted for age and sex, but attenuated to non-significant in the fully adjusted model.

Longitudinal effects on sleep over a 6-month period (Table 3) were examined using a logistical multilevel model. For sex, there was a borderline significant interaction between time and sex, where women improved their sleep more during the treatment stay than men (OR 1.18 [CI 1.00, 1.40], $p = 0.048$). However, a variance inflation factor (VIF) analysis gave a value of 5.06 for the interaction estimate of sex × time, indicating possible multicollinearity between these variables. For depressive symptoms, there was a statistically significant main effect of BDI-II score (OR 1.16 [CI 1.06, 1.27], $p = 0.002$), indicating that those with high levels of depressive symptoms had poor sleep overall during their treatment stay, but there was no interaction with time. For level of exercise, the patients who had a moderate or high level of physical activity had less risk of insomnia during their stay (OR 0.06 [CI 0.01, 0.32], $p < 0.001$). In this model there was a significant effect of time, indicating that the risk of insomnia diminished over time for all patients (0.95 [CI 0.89, 1.00], $p = 0.046$), and a significant interaction between time and IPAQ, indicating that those who had a low level of physical activity at baseline improved their sleep more throughout the treatment stay (OR 1.17 [CI 0.32, 1.34], $p = 0.028$). Linear multilevel models with a continuous SCI score outcome variable demonstrated statistically significant effects of sex and SDS in addition to the predictors identified in Table 3, but no interaction effects (Supplementary Table S2).

In linear multilevel models stratified by insomnia there was a significant main effect for BDI-II (OR −0.10 [CI −0.18/−0.02], $p = 0.012$) among patients with insomnia. For the patients without insomnia there was an effect for SDS (OR −0.38 [CI −0.74/−0.02], $p = 0.037$). There were no other main effects, effect of time, or interaction effects.

As sensitivity analyses, the logistic regression models and the logistic multilevel models were also tested with exclusion of five individuals where more than one item of the SCI had been imputed. After excluding the five subjects, there were no substantial changes except that the effect of sex changed from borderline significant to non-significant (OR 0.22 [CI 0.04/1.14], $p = 0.072$) in Step 3 of the logistic regression of insomnia at baseline, and that the borderline significant interaction effect of sex × time changed slightly to OR 1.17 (CI 1.0/1.38), $p = 0.068$.

Figure 2 illustrates development of sleep quality from baseline to 6-month follow-up in relation to depressive symptoms and physical activity, in patients with complete longitudinal data (n = 34). Stratified by categories of low, moderate, or high levels of depressive symptoms, there were differences in sleep quality at baseline but not at follow-up (panel A). However, stratified by SCI cut-off, patients with probable insomnia had statistically higher levels of depressive symptoms at all time points (panel C). Depressive symptoms diminished from baseline to 6-week follow-up for both groups, but not from 6-week to 6-month follow-up. Stratified by level of physical activity, it was apparent that those who were physically active had better sleep, but this was only statistically significant at baseline. The development of sleep quality was similar in both physical-activity groups with an increase from baseline to 6 weeks, but not from 6 weeks to 6 months (panel B). When patients were stratified by SCI cut-off, there was a significant difference in physical activity level at baseline but not at follow-ups (panel D). Those with insomnia increased their activity level throughout the treatment stay, whereas those without insomnia decreased their level of physical activity from baseline to 6 weeks but increased from 6 weeks to 6 months.

Discussion

In this study of insomnia in AUD inpatients, we found that more than half of the patients admitted to treatment for AUD had probable insomnia. The majority reported

insomnia for more than a year, with sleep initiation being the major complaint. Predictors of insomnia at baseline were female sex, high levels of depressive symptoms, and low levels of physical activity, significant after adjustment for severity of dependence and history of trauma. Insomnia after 6 weeks of treatment was associated with younger age, higher levels of depressive symptoms, and lower levels of physical activity at baseline. Longitudinal analyses of data over a 6-month period showed sleep improvements in all patients, which was greatest among patients with lower levels of physical activity at baseline.

Compared to previous estimates of 35% to 91%, our sample's prevalence rate of 54% is thus at an intermediate level (Brower, 2001, 2003; Cohn et al., 2003; Kolla et al., 2020). Variation in prevalence estimates could be explained by heterogeneity in patient samples and sleep quality measurement instruments, as well as factors like time of abstinence and alcohol-related cognitive deficits, which may influence the ability for self-reporting of sleep quality (Laniepce et al., 2019). All these issues make comparisons between studies a challenge. Nonetheless, these findings demonstrate the magnitude of insomnia as a particular treatment challenge for AUD patients.

Sleep onset latency was reported as more problematic than nightly awakenings, in line with previous findings, showing that up to 60% of AUD patients use alcohol to initiate sleep (Brower, 2001), which often, in fact, results in longer sleep onset latencies (Brower, 2001; Currie et al., 2003). Previous studies have indicated that the propensity to use alcohol to alleviate sleep initiation problems among abstinent AUD patients may result in relapse (Kolla et al., 2020; Vitiello, 1997). In our study there was no statistically significant difference in treatment drop-out between insomnia and non-insomnia groups. Patients with insomnia reported having had sleep problems for a long time, most of them for more than one year. Previous studies have shown that sleep problems caused by high levels of alcohol

consumption may last for a long time after withdrawal from drinking (Currie et al., 2003; Kolla et al., 2020).

Our study found that being female was associated with poorer sleep. In general, it is estimated that women are 40% more likely to develop sleep problems than men (B. Zhang & Wing, 2006), but very few studies have addressed sex differences associated with sleep problems among AUD patients, partly because AUD is more prevalent among men and most research on AUD has been conducted in samples with a majority of males. A review by Inkelis and colleagues indicates several factors that could be relevant to sex-specific associations between alcohol use and sleep problems, such as alcohol pharmacokinetics, sleep physiology, and psychiatric symptoms (Inkelis, Hasler, & Baker, 2020). In our study, being female still predicted insomnia after adjustment for depressive symptoms. Some studies on general population samples find that women seem to get more sleep on average than men, but it has been suggested that this increased sleep quantity in women is a result of compensating for poorer sleep quality (Burgard & Ailshire, 2013), and this has been reflected in findings of lower sleep quality and more fragmented sleep in women (Burgard, 2011; Burgard & Ailshire, 2013).

Higher levels of depressive symptoms were also associated with insomnia. This is in line with previous research that has reported more severe depressive symptoms in AUD patients with insomnia than those without insomnia (Brower et al., 2001). Insomnia is considered a hallmark symptom of depression in the general population (Nutt et al., 2008), and in a study among AUD patients in treatment, depressive symptoms, together with a propensity to drink because of physical discomfort, were identified as the strongest predictors of insomnia (Kolla et al., 2020). As depressive symptoms are more common among women than men, this association could be attributed to a confounding effect by sex. However, after adjustment for age and sex, high levels of depressive symptoms remained a significant

predictor for insomnia, which was still significant after adjustment for trauma background, severity of alcohol dependence, and physical activity. This supports a clinically important connection between insomnia and depression, including in patients with AUD (Nutt et al., 2008).

Insomnia was strongly associated with low physical activity after adjustment for trauma background, alcohol dependence severity, and even depressive symptoms. Research shows that levels of physical activity among patients with AUD are too low (Hallgren, Andersson, Ekblom, & Andréasson, 2018), and contribute to higher risk of somatic co-morbidities, such as cardiovascular disease, type 2 diabetes, and metabolic syndrome (Vancampfort et al., 2016), leading to increased mortality rates (Roerecke & Rehm, 2013). However, BMI and waistline were not found to be associated with insomnia, despite this being a known association in the general public (Vorona et al., 2005). The association between exercise and sleep is well established in the general population (Kelley & Kelley, 2017), and evidence that increased physical activity might improve sleep among AUD patients could have important clinical implications.

There was an overall improvement in sleep over time, which was greatest during the first 6 weeks of treatment. This improvement during the initial phase may have several explanations. First, initial sleep problems could have been worse than normal, because of being in a novel environment, and sleep may then return to habitual levels by 6 weeks. Also, at admission, patients were closer to alcohol withdrawal, which is known to impair sleep (Thakkar et al., 2015). Severity of withdrawal symptoms has been related to impaired sleep, reduced gray matter volume, and cognitive deficits, without being directly related to duration of abstinence before inclusion (Laniepce et al., 2020). However, the majority of patients reported insomnia for more than a year, indicating that the sleep score at admission might resemble the sleep score before admission, and therefore suggesting a positive effect on sleep

related to the inpatient stay. This could be related to unmeasured parameters such as stable environment, improved diet, and treatment progress, as well as measured parameters detected in our study, such as alcohol abstinence, increased physical activity, and improvement of depressive symptoms. Specifically, when examining time interactions across 6 months in a multilevel model, we found that female patients and patients with a low initial physical activity level were more likely to improve their sleep than their peers. Because of poor sleep at baseline, these groups had greater potential for improvement, where the time interactions could be interpreted as a regression to the mean. However, it could also imply that increasing physical activity could be helpful for improving sleep, as there was an overall increase in physical activity during the treatment stay. The association between depressive symptoms and insomnia at baseline revealed no interaction with time, possibly arguing against a general regression to the mean. However, the lack of a statistically significant effect of time could also be due to a corresponding improvement of BDI score over time.

One strength of this study was the longitudinal data material that enabled analyses of development. Having longitudinal data also diminished the risk of confounding from possible withdrawal symptoms. There was a considerable amount of missing data in the follow-up material, in particular at 6 months, limiting the power in the longitudinal analyses and possibly introducing a bias toward better sleep. Although it was a strength having information about trauma background, the questionnaire did not address emotional abuse or neglect, which could act as confounders to sleep problems. Those patients who did not return a valid sleep questionnaire were excluded, so there is potential risk of bias toward higher functioning level in the included patients. This could imply that participants with insomnia were less likely to be included, as insomnia is associated with reduced cognitive functioning. Lastly, information about specific treatment targets and progress at the clinic was not available for direct comparison to the different measurements included in the study.

This study confirms that insomnia is highly prevalent among AUD patients, with the greatest sleep problem being sleep initiation. This study also shows that for these patients, as for the general population, insomnia is associated with female gender, high levels of depressive symptoms, and a low level of physical activity, even after adjustment for severity of dependence and trauma background. Future longitudinal and larger studies are needed to examine the causal directions between insomnia, alcohol consumption/abstinence, depression, and physical activity, and how these associations might be targeted in clinical settings.

Author note

Declarations of interest: none.

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Figure legends

Figure 1. Scores for the eight individual SCI items at baseline. Patients are stratified by not having or having insomnia (based on SCI total score >16 / ≤16).

Figure 2. Development of sleep quality, depressive symptoms, and level of physical activity over a 6-week time period. Sleep quality (SCI score) in patients stratified by **A**) level of depressive symptoms (BDI-II score categories), and by **B**) level of physical activity (IPAQ categories low vs. moderate/high). Lower panels depict **C**) level of depressive symptoms (BDI-II score) and **D**) level of physical activity (IPAQ total score) in patients with insomnia and without insomnia. Only cases with complete data at baseline and 6-week follow-up are included (n = 62). Given in medians and upper or lower quartile. Group differences tested using Kruskal-Wallis equality of populations' rank test (**A**) or Wilcoxon rank sum test (**B–D**).

Table 1. Sociodemographic characteristics of patient sample categorized by Sleep Condition Indicator (SCI) score at baseline measure. A low SCI score (≤16) indicates probable insomnia, while a high SCI score (SCI >16) indicates absence of insomnia.

		SCI >16 n=40 (46%)	SCI ≤16 n=47 (54%)	p-value
Demographics				
Age (years)	Median (IQR)	54.1 (46.6, 59.0)	54.3 (47.6, 58.6)	0.844
Sex (male)	n (%)	35 (88)	30 (64)	**0.011**
Educational level >upper secondary school	n (%)	15 (38)	20 (47)	0.462
Marital status (living with a partner)	n (%)	11 (26)	10 (26)	0.955
Lifestyle and physiology				
Smoking	n (%)	29 (73)	36 (77)	0.661
Level of physical activity (≥moderate)	n (%)	26 (70)	9 (21)	**<0.001**
Waistline (cm)	Median (IQR)	102 (88, 110)	101 (93, 111.5)	0.578
BMI (kg/m^2)	Median (IQR)	25.7 (22.5, 29.4)	26.8 (24.7, 29.3)	0.495
Systolic blood pressure	Median (IQR)	127.5 (118, 136)	128 (120, 143)	0.419
Diastolic blood pressure	Median (IQR)	79 (71, 88)	82 (75, 87)	0.414
CRP	Median (IQR)	1 (1, 3.5)	2 (1, 5)	0.193
Pulse	Median (IQR)	77 (62, 87)	77 (69, 88)	0.498
Psychiatric comorbidities				
BDI-II score	Median (IQR)	10.5 (4, 19)	21 (13, 29)	**<0.001**
Anxiety disorder	n (%)	24 (62)	31 (66)	0.671
ASRS score	Median (IQR)	11 (9, 16)	15 (9, 16)	0.240
Childhood trauma experience	n (%)	28 (70)	33 (72)	0.859
Adulthood trauma experience	n (%)	21 (53)	32 (71)	0.077
Substance use related measures				
Severity of Dependence score	Median (IQR)	10 (7, 11)	11 (8, 13)	**0.040**
Days since last drink	Median (IQR)	17 (12.5, 27.5)	20 (12, 30)	0.559
Subjective withdrawal symptoms (yes/no)	n (%)	3 (7)	9 (17)	0.130
Phosphatidylethanol	Median (IQR)	0.18 (0.06, 0.55)	0.22 (0.07, 0.59)	0.980
Age of first drink	Median (IQR)	15 (13, 15.5)	15 (14, 17)	**0.046**
Drinking career duration (years)	Median (IQR)	15 (7, 21.5)	16 (10, 25)	0.589
Family history of alcohol problems	n (%)	27 (68)	34 (74)	0.514
Other substance use disorder	n (%)	8 (20)	7 (15)	0.530
Development of sleep quality				
Baseline to six weeks (n=62)	Median (IQR)	1 (0, 5)	3 (-1, 10)	0.226
Baseline to six months (n=34)	Median (IQR)	2 (-3, 6)	3.5 (0, 10)	0.180
Dropped out of treatment	n (%)	10 (24)	15 (38)	0.175

IPAQ-S: International Physical Activity Questionnaire Short version. BDI-II: Beck depression Inventory 2. ASRS: Adult ADHD symptom Rating scale. Descriptive statistics given as medians (IQR (Interquartile range): 25th and 75th percentile) and group differences tested with Wilcoxon rank sum test for continuous variables and given as frequencies and percent and tested with Pearson´s chi-square test for categorical variables.

Table 2. Binary logistic regression for predictors of insomnia (SCI ≤ 16) compared to absence of insomnia (SCI > 16) at baseline as outcome variable and with baseline exposure variables.

		Baseline (n=87)				Six-week follow-up (n=62)			
		95% CI				95% CI			
	Ref.	OR	LL	UL	p-value	OR	LL	UL	p-value
Step 1, unadjusted									
Sex	Female	0.25	0.08	0.76	**0.015**	0.71	0.23	2.21	0.559
Age[a]	Cont.	1.01	0.97	1.05	0.678	0.95	0.90	1.00	**0.038**
SDS[b]	Cont.	1.19	1.01	1.39	**0.033**	1.16	0.95	1.40	0.138
Trauma experience[c]	No	2.23	0.91	5.45	0.079	2.83	0.80	9.98	0.105
BDI-II[d]	Cont.	1.10	1.05	1.16	**<0.001**	1.06	1.01	1.11	**0.023**
IPAQ-S[e]	Low	0.12	0.04	0.32	**<0.001**	0.31	0.12	0.81	**0.017**
Step2, adjustment for age and sex									
SDS[b]	Cont.	1.15	0.98	1.36	0.090	1.14	0.92	1.41	0.246
Trauma experience[c]	No	1.37	0.51	3.73	0.533	2.48	0.62	9.95	0.200
BDI-II[d]	Cont.	1.10	1.04	1.16	**0.001**	1.05	0.99	1.11	0.079
IPAQ-S[e]	Low	0.10	0.03	0.30	**<0.001**	0.17	0.05	0.56	**0.003**
Step 3, multivariable model including all listed predictors									
Sex	Female	0.18	0.03	0.94	**0.042**	1.42	0.26	7.70	0.684
Age[a]	Cont.	1.01	0.94	1.07	0.877	0.89	0.82	0.97	**0.007**
SDS[b]	Cont.	0.92	0.72	1.16	0.472	0.93	0.70	1.23	0.593
Trauma experience[c]	No	0.37	0.08	1.61	0.183	1.15	0.19	6.80	0.877
BDI-II[d]	Cont.	1.11	1.02	1.20	**0.010**	1.02	0.95	1.10	0.595
IPAQ-S[e]	Low	0.09	0.02	0.35	**<0.001**	0.18	0.05	0.63	**0.007**

[a]Per one-year increase of age. [b]Per one-point increase of Severity of dependence scale (SDS). [c]Has experienced traumatic event in adulthood (yes/no). [d]Per one-unit increase of Beck depression inventory-2 (BDI-II). [e]International physical activity questionnaire short version (IPAQ-S), low vs moderate/high level of physical activity. OR=Odds ratio. CI=Confidence interval. LL=lower limit. UL=Upper limit.

Table 3. Multilevel logistic regression for predictors of insomnia (SCI ≤ 16) over a six-month period.

	Ref.	Main effect models 95% CI OR	LL	UL	p-value	Models with interaction term 95% CI OR	LL	UL	p-value
Sex									
Sex	Female	0.22	0.04	1.31	0.097	0.08	0.01	0.73	0.025
Time	Continuous	0.96	0.91	1.01	0.142	0.84	0.72	0.98	0.027
Sex x Time						1.18	1.00	1.40	**0.048**
Age at baseline									
Age[a]	Continuous	0.98	0.91	1.05	0.525	1.00	0.92	1.08	0.897
Time	Continuous	0.96	0.91	1.01	0.139	1.11	0.86	1.44	0.412
Age x Time						1.00	1.00	1.00	0.260
SDS score									
SDS[b]	Continuous	1.28	0.96	1.70	0.098	1.45	1.02	2.06	0.038
Time	Continuous	0.96	0.91	1.01	0.092	1.13	0.93	1.36	0.219
SDS x Time						0.98	0.97	1.00	0.083
Age at first drink									
Age[a]	Continuous	1.30	0.96	1.77	0.087	1.27	0.93	1.73	0.133
Time	Continuous	0.96	0.91	1.01	0.139	0.89	0.66	1.19	0.423
Age x Time						1.01	0.99	1.02	0.576
Trauma experience									
Trauma[c]	No	4.80	0.88	26.21	0.071	4.68	0.78	28.12	0.092
Time	Continuous	0.95	0.90	1.01	0.083	0.95	0.86	1.05	0.302
Trauma x Time						1.00	0.90	1.13	0.935
BDI-II									
BDI-II[d]	Continuous	1.16	1.06	1.27	**0.002**	1.18	1.07	1.31	0.001
Time	Continuous	0.96	0.91	1.01	0.137	1.01	0.91	1.13	0.814
BDI-II x Time						1.00	1.00	1.01	0.288
IPAQ-S									
IPAQ-S[e]	Low	0.06	0.01	0.32	**0.001**	0.02	0.00	0.19	0.001
Time	Continuous	0.95	0.89	1.00	**0.046**	0.89	0.82	0.97	0.008
IPAQ-S x Time						1.17	1.02	1.34	**0.028**

[a]Per one-year increase of age. [b]Per one-point increase of Severity of dependence questionnaire (SDS). [c]Has experienced traumatic event in adulthood (yes/no). [d]Per one-unit increase of Beck depression inventory-2 (BDI-II). [e]International physical activity questionnaire short version (IPAQ-S), low vs moderate/high level of physical activity. OR=Odds ratio. CI=Confidence interval. LL=lower limit. UL=Upper limit.

Figure 1. Scores for the eight individual SCI items at baseline. Patients are stratified by not having or having insomnia (based on SCI total score >16 / ≤16).
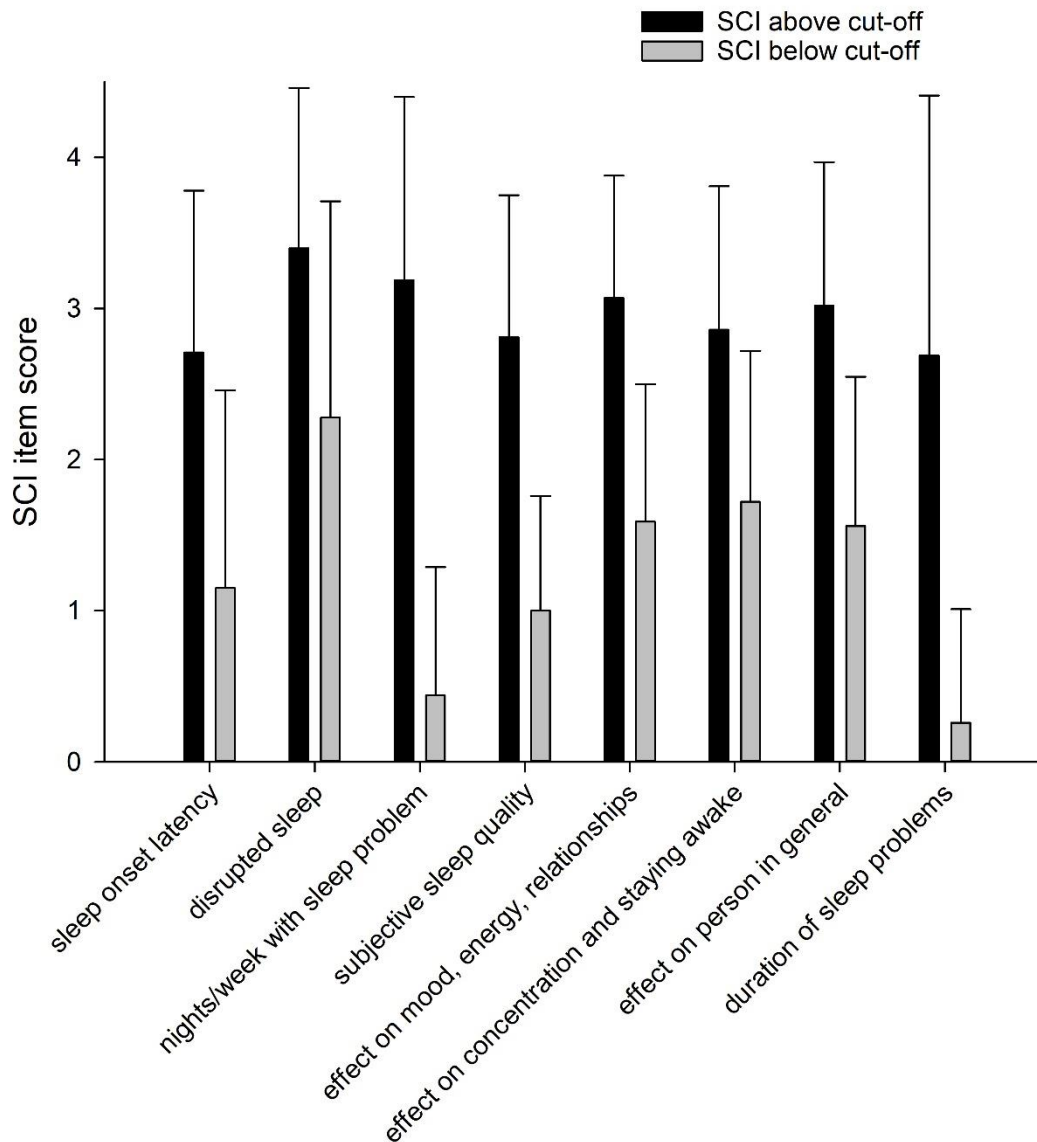

Figure 2. Development of sleep quality, depressive symptoms and level of physical activity over a six-week time period. Sleep quality (SCI score) in patients stratified by a) level of depressive symptoms (BDI-II score categories), and by b) level of physical activity (IPAQ categories low vs moderate/high). Lower panels depict c) level of depressive symptoms (BDI-II score) and d) level of physical activity (IPAQ total score) in patients with insomnia and without insomnia. Only cases with complete data at baseline and six-week follow-up are included (n=62). Given in medians and upper or lower quartile. Group differences tested using Kruskal-Wallis equality of populations' rank test (a) or Wilcoxon rank sum test (b-d).