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Poor Response Inhibition and Symptoms of Inattentiveness Are Core Characteristics of Lifetime Illicit Substance Use among Young Adults in the General Norwegian Population: The HUNT Study

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ABSTRACT
Background: Impairments in neurocognitive functioning are associated with substance use behavior. Previous studies in neurocognitive predictors of substance use typically use self-report measures rather than neuropsychological performance measures and suffer from low sample sizes and use of clinical diagnostic cut offs. *Methods:* Crossectional data from the HUNT4 Study (Helseundersøkelsen i Trøndelag) was used to study executive neuropsychological performance and self-reported measures of neurocognitive function associated with a history of illicit substance use in a general **population** sample of young adults in Norway. We performed both between group comparisons and logistic regression modeling and controlled for mental health symptomatology. *Results:* Subjects in our cohort with a self-reported use of illicit substances had significantly higher self-reported mental health and neurocognitive symptom load. A logistic regression model with substance use as response included sex, commission errors and self-reported inattentiveness and anxiety as significant predictors. After 10-fold cross-validation this model achieved a moderate area under the receiver-operator curve of 0.63. To handle the class imbalance typically found in such population data, we also calculated balanced accuracy with a optimal model cut off of 0.234 with a sensitivity of 0.50 and specificity of 0.76 as well as precision recall—area under the curve of 0.28. *Conclusions:* Subtle cognitive dysfunction differentiates subjects with and without a history of illicit substance use. Neurocognitive factors outperformed the effects of depressive symptoms on substance use behavior in this cohort. We highlight the need for using adequate statistical tools for evaluating the performance of models in unbalanced datasets.

KEYWORDS
Substance use; neuropsychology; population study;young adults

Introduction

Impairments in neurocognitive functioning in general, and executive functions in particular, are strongly associated with substance use (Kwako et al., 2016; Vassileva & Conrod, 2019). This relationship has been demonstrated for most substances (Barker et al., 2004; Biernacki et al., 2016; Crean et al., 2011; Ellis et al., 2016).

Executive dysfunction can lead to impaired cognitive and behavioral control, which, combined with heightened substance-related incentive salience, may contribute to developing and maintaining substance use problems (Kwako et al., 2016; Robinson, Robinson, & Berridge). Executive functions, such as working memory, behavioral response inhibition, attention, impulse control, and set-shifting, are essential to control behavior (Friedman & Miyake, 2017). Executive functions may be both stable (trait) and dynamic (state) (Vassileva & Conrod, 2019). Environmental factors (e.g., stress) and internal individual states (mental health) can influence state executive function (McKinney et al., 2020; Vassileva & Conrod, 2019), making it likely that executive functioning moderates the effects of internalizing symptoms on substance use behavior (Brand et al., 2008; Brand et al., 2019; Felton, Shadur, Havewala, Gonçalves, & Lejuez, 2020) (Figure 1).

Executive dysfunctions, such as disinhibition and impulsivity, are hallmarks of hyperkinetic disorders (ADHD). Continuous load of ADHD symptoms is also associated with the degree of executive dysfunction (Molitor et al., 2019) and substance abuse. However, the causality remains unclear (Treur et al., 2021). The associations are robust across diversities in age, gender, socioeconomic status, ethnicity, and a range of mental health disorders or symptoms, even without

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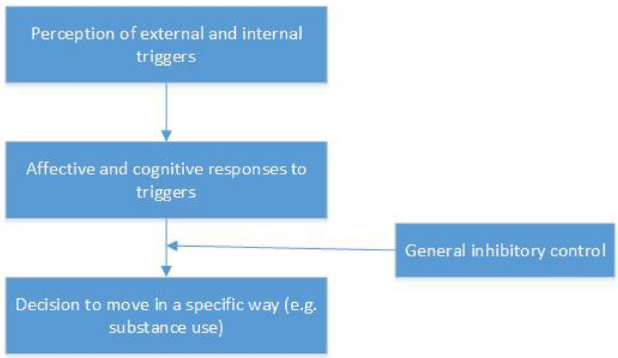

Figure 1. Theoretical model of the role of the executive function inhibitory control in the relationship between affective state and substance use behavior.

reaching the diagnostic threshold for ADHD (Capusan et al., 2019; De Alwis et al., 2014).

Neurocognitive functioning may be assessed both using self-report scales and performance measures. Self-report measures are easy to deploy and commonly used in population-based research and with larger, nonclinical groups due to their low cost and easy distribution. In contrast, performance-based measures are typically deployed in smaller clinical samples. Performance-based measures may not capture people's perceptions of their cognitive problems typically assessed by self-report scales and more personality-related domains (Buchanan, 2016).

Earlier studies on neurocognitive predictors of substance use are often limited by sample size, poor control of confounding mental health symptoms (Carbia et al., 2018) and primarily use of self-report measurement tools (Toledo-Fernández et al., 2020). Consequently, there is limited knowledge about the relationship between performance-based neurocognitive factors assessed with performance-based measures and substance use behavior in the general population, and if these objective executive performance measures add to our understanding of substance use trajectories (Verdejo-Garcia & Albein-Urios, 2021). This limits the progress in risk modeling and preventive work in the general population. In this study, we aimed to study both continuous neuropsychological performance-based and self-reported measures of executive cognitive function associated with illicit substance use in a large general population sample of young adults (19-30 years old) in Norway. Including neuropsychological data of executive functions in addition to the traditional self-report measures in a general population setting is highly needed and will expand our understanding of the role of executive cognitive functions in substance use (Verdejo-Garcia & Albein-Urios, 2021). We will enter self-reported symptomatology as continuous data rather than use clinical diagnostic cutoffs in line with the work of Capusan et al. (2019).

Methods

Participants

We used crossectional data from the 4th survey of the HUNT Study (Helseundersøkelsen i Trøndelag, HUNT4), an extensive population database consisting of questionnaires, physical examination results, and biological specimens. The entire population of Nord-Trøndelag County in Norway was invited to participate. For further details, the reader is referred to https://www.ntnu.edu/hunt.

Each wave of the HUNT Study consisted of 2 questionnaires and sub-studies, all carried out at the same time. For the purpose of cross-sectional analyses in the current paper, we used data from the general questionnaire (Q1) and the age cohort-specific questionnaire 2 (Q2) in addition to the web-based neuropsychological assessment (Memoro) substudy. The current data set included an age cohort ranging from 19 to 30 years old at the time of participation

Self-reported cognition

ASRS-6: Adult ADHD self report scale:screener

Variables corresponding to part A Screener of the ASRS version 1.1 (ASRS-6) were included in the Q2 of HUNT4 and were used as a proxy measure of self-reported executive dysfunction. The six-question ASRS-6 Screener is a brief self-report instrument that has demonstrated the ability to discriminate DSM-IV cases of ADHD from non-cases (Kessler et al., 2007). The ASRS symptom score is also significantly correlated with general impulsivity measures such as the Short form Barrat Impulsiveness Scale, BIS-11 (Bozkurt et al., 2016). The ASRS-6 has been validated both in general and treatment-seeking substance use populations (Bozkurt et al., 2016). Furthermore, the six-item version has been validated for Norwegian substance use populations as part of the complete instrument (Bu et al., 2012; Kornør & Hysing, 2011). The ASRS-6 typically loads onto the factors inattentiveness (ASRS IA, items 1-4) and hyperactivity/impulsivity (ASRS H/I, items 5 and 6) (Hesse, 2013).

Neuropsychological measures

Memoro assessment battery

The neuropsychological assessments were administrated using the web-based Memoro neuropsychological assessment platform. Memoro is developed to assess neuropsychological functions in large scale cohorts. The battery is self-administered, and all tests have written and oral instructions. The battery is based on traditional neuropsychological tests (resembles well-known clinical instruments) and has been validated against such instruments with good concurrent validity ((r = .49–.63) (Hansen et al., 2015) and test-retest reliability (Hansen et al., 2016). We used two tests assessing working memory capacity and response inhibition in this study. Working memory was assessed by "Digit Span forwards" and 'Digit Span backwards'. These tasks were presented as series of digits presented for two seconds on the screen, and the subjects were required to repeat them either forwards or backwards. The task difficulty level increased progressively, starting with three digits in the first trial and ending when a participant either completed 18 trials or made three consecutive errors. The performance score was the maximal number of correctly recalled digits (maximum digit span) (Hansen et al., 2016). Complex Reaction Time (CRT) was measured using a continuous performance type test with a Go/No-Go paradigm. Poor performance on this type of task is strongly associated with the lifetime use of cannabinoids in a recent mega-analysis (Liu et al., 2019). During the administrated 40 trials (ISI = 1000 ms, 2000 ms, 4000 ms. 20% No-Go trials. Performance was measured as the number of valid responses (GO), correct inhibition of response to non-targets (correct-NOGO), omissions (failure to respond) and commissions (failure to inhibit response). In this study, we used the number of CRT omission and commission errors as continuous candidate input variables.

Mental health and substance use assessments

Illicit drug use

The participants were asked if they had ever used illicit substances. A total of 406 out of the original 480 subjects responded to this question of which 86 answered Yes and 320 No (74 did not answer). Substance use was defined as any use of illicit substances prior to answering the questionnaires, and such confirmation of history of illicit drugs was used as the binary primary response variable.

HADS: hospital anxiety and depression scale

The HADS questionnaire has seven questions about anxiety and seven questions about depression, each with a possible total score of 21 (Zigmond & Snaith, 1983). It has previously been validated for use in alcohol-dependent populations (McPherson & Martin, 2011) and the Norwegian language form (Mykletun et al., 2001). A composite score for each of anxiety and depression were used in the statistical analyses.

Statistical analyses

We performed correlational analyses with between-group comparisons and classifications. The R statistical tool version 3.6.3 (R Core Team, 2020) was used for all statistical analyses.

Analyses of attrition

Attrition from Q1 to Q2 was analyzed using between-group comparisons for use of illicit substances or not. Chi-square, t- and Wilcoxon tests were implemented to investigate differences in proportions of biological sex and symptom load between Q1-, Q2- and Memoro participants.

Between-group comparisons

We used Wilcoxon tests to compare the scores on all predictor variables for subjects answering Yes, No or NA to the question of use of illicit substances.

Model selection

Sex, age, HADS, ASRS-6 and the cognitive test scores from the Digit span forward/backwards and complex reaction time test were used as candidate predictors in binary logistic regression with use of illicit substances as the response variable. Only main effects were considered. Cronbach's alpha scores for the two ASRS factors in our sample were moderate and low, ranging from 0.63-0.72 (95% CI) for factor 1 and 0.24-0.47 (95% CI) for factor 2. 145 subjects with one or more missing values within the predictor variables, including 20 subjects out of the original 86 with use of substances were removed, since stepwise model selection requires the same number of observations in each step. This left 335 subjects with 66 positives for substance use. Then we implemented stepwise selection based on the Akaike Information Criterion using the step-AIC function in the 'MASS'-package in R (Ripley et al., 2013) with both forward and backward selections, to arrive at the final model.

Evaluating the model

To evaluate model performance, we used the pROC R-package (Robin et al., 2011) to calculate the Receiver Operating Characteristics (ROC) curve and the area under the ROC curve (ROC-AUC) for the selected model. When there is a large difference in the distribution of classes (e.g., drug use vs. non-drug-use), ROC plots may provide a too optimistic view of the performance of an algorithm. Precision-recall curves may be used as an alternative in such cases. As the dataset is unbalanced with only about 15-20% positive cases, we also calculated the area under the precision-recall curve using the PRROC package (Grau et al., 2015). The ROC-AUC metric uses sensitivity and specificity as input, whereas precision-recall uses the positive predictive value (precision) of the outcome and the sensitivity. The latter's advantage is that it does not use correctly classified non-cases and, therefore, will not exaggerate model performance when analyzing unbalanced datasets (Sofaer et al., 2019). The authors are not aware of any methods to compare different PR-curves.

Ethics and data protection

As part of the original inclusion process, participants in the HUNT4 Survey signed an informed consent allowing the use of the data for future medical research. The research has been approved by the Regional Committee of Medical Research Ethics (REC project 43144) and the HUNT publication board.

Results

Attrition

Q1 could be completed physically or online. Of the 6510 individuals that completed and returned Q1, 6123 participants were invited for Q2, of which 3917 provided data. Attrition beyond Q1 (n = 2593) occurred as subjects either

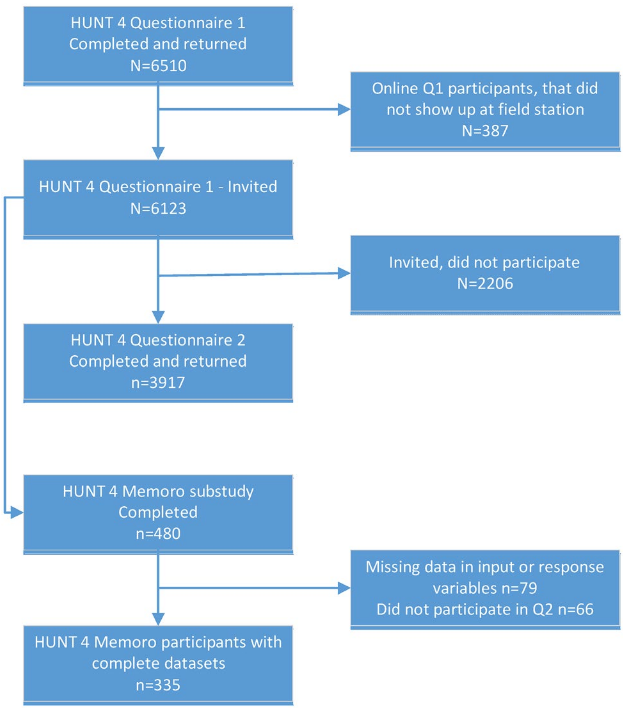

Figure 2. Flowchart of attrition in the HUNT4 population study.

did not complete Q2 despite being asked to do so after completing the physical Q1 (n = 2206) or did not show up at the field station after being invited after the online completion of Q1 (n = 387). A total of 480 participated in HUNT4 Memoro. Of these, 406 answered the question about history of use of illicit drugs in Q2, serving as the response variable in this study and finally, 335 had complete datasets. All data was collected as part of the same data collection, and data was considered cross-sectional (Figure 2).

Full datasets for all variables were available for 335 subjects. The proportion of female respondents changed significantly from Q1 to Q2 from 56.5% women in Q1 to 63.5% in Q2 ($\chi2 = 55.417$, df = 1, $p < 0.001$). The same pattern was evident from Q1 participation to participation in the Memoro sub-study, with the share of women in Memoro significantly increasing to 71.9% ($\chi2 = 34.325$ df = 1, $p < 0.001$). Compared to the estimated total population in this age cohort (N = 68832), the proportions were significantly different with 47% women in the full population compared to 71.9% in our sample ($\chi2 = 80.625$, df = 1, $p < 0.001$), indicating a lack of representativity concerning sex. The subjects who both participated in Q2 and the Memoro sub-study did not have significantly different HADS scores than those who did not continue. The proportion of subjects reporting substance abuse was not significantly different from Q2 participants (where that question was included) to Memoro participants with full datasets (n = 335, $\chi2 = 0.39$, df = 1, $p > 0.05$). The subjects in the Memoro subset did have a significantly higher symptom load on ASRS items 4 and 5 and significantly less on item 2 ($p < 0.05$). No significant differences were found for the other input variables.

Multi-collinearity

We performed correlational analyses between all variables (prior to model selection). This revealed limited correlations between the self-reported and neuropsychological test of cognition, and small to moderate correlations within instruments and between self-reported mental health and cognitive variables, as well as between mental health and the neurocognitive candidate variables. We evaluated multicollinearity in the final model using the variance inflation factor (VIF), calculated with the vif() function in the caret package (Kuhn, 2015). This revealed modest scores (range 1.01-1.24). VIF score >10 is typically considered worrysome (Finch et al., 2019), our results thus indicate low collinearity in the final model.

Between-group comparisons

Descriptive data and group comparisons for the participants reporting use of illicit substances (Yes), no use (NO) or did not respond (NA) on/for ASRS, HADS, and neuropsychological assessments are shown in Table 1. The groups differed significantly on the ASRS inattentiveness items 2, 3 and 4, the HADS anxiety and depression subscales, and CRT omission and commission errors. The subjects with a history of illicit substance use consistently had a higher symptom load combined with lower response inhibition scores.

We performed between-group comparisons for sex, the only variable that significantly differed was ASRS item 4 (Delay or avoid starting tasks that require a lot of thought) ($p < 0.05$).

Modeling

Stepwise AIC selection resulted in a model including five predictor variables, of which four were significant or marginally significant for use of illicit substances (Table 2).

The significant predictors were ASRS factor 1 and ex, while CRT Commission errors and HADS Anxiety were marginaly significant. Although part of the model with lowest AIC score, Digit Span Forward was not a significant predictor ($p = 0.127$) and was removed from the final model.

This means that more symptoms of inattentiveness, being male, more commission errors and higher levels of anxiety predicted a self-reported history of illicit substance use. To illustrate this with an example, being male, having 1 SD over mean score on ASRS Factor 1 (i.e., a score of 2.14), HADS Anxiety (i.e., a score of 9.52) and commission errors (i.e., 2.48 errors), gives a predicted probability of 0.16 of having a self-reported history of use of illicit substances. 2 SD over mean yields a predicted probability of 0.28. Further out the other end of the risk spectrum, females with 1 SD below the mean score on CRT (0.04), HADS Anxiety (1.9), and ASRS Factor 1 (0.61) only give a predicted probability of about 0.026.

The final model showed an overall moderate ability to identify subjects with self-reported use of illicit drugs considering an AUC of 0.68; after 10-fold Cross-Validation, we

Table 1. Between-group comparisons for subjects with and without history of illicit substance use ($N = 335$).

	Life time use of Illicit Substances			
	n	YES	NO	
Male	94	24 (27 %)	70 (73 %)	
Female	241	42 (17 %)	199 (83 %)	
Adult ADHD Self-report Scale - Screener	n	Mean (SD)	Mean (SD)	p-value
ASRS Factor 1: Inattentiveness	335	1.63(0.72)	1.31(0.76)	**0.0009346**
ASRS Factor 2: Hyperactivity/Impulsivity	335	2.03(0.98)	1.82(0.86)	0.1164
Hospital Anxiety and Depression Scale (HADS)				
Anxiety	335	7.0 (4.0)	5.39 (3.7)	0.001961
Depression	335	4.14 (3.4)	3.28 (3.01)	0.04495
Memoro: Complex Reaction Time (CRT)				
Ommision errors	335	0.56 (1.36)	0.42 (2.2)	0.03497
Commission errors	335	1.61 (1.26)	1.18 (1.2)	0.006757
Memoro: Digit Span				
Forwards	335	7.41 (1.81)	7.11 (1.42)	0.385
Backwards	335	6.82 (1.86)	6.93 (2.03)	0.8343
Age	335	25.2 (2.7)	25.2 (3.0)	0.9046

Table 2. Final model with Odds ratios after stepwise AIC model selection in the substance group with complete data set, $n = 335$).

	Coefficient	SE	z value	Pr(>|z|)	OR	95% CI (OR)
(Intercept)	−3.90	0.793	−4.928	$8.32{*}10^{-7}$	0.020	0.004-0.09
CRT Commission errors	0.206	0.111	1.86	*0.0632*	1.23	0.99-1.53
ASRS Factor 1: Inattentiveness	0.394	0.196	2.01	**0.0446**	1.48	1.01-2.19
Digit Span Forwards	0.139	0.091	1.528	0.127	1.15	0.96-1.38
HADS Anxiety	0.07	0.0402	1.808	*0.0705*	1.08	0.99-1.63
Sex (Male)	0.605	0.307	1.973	**0.0485**	1.83	1.00-3.33

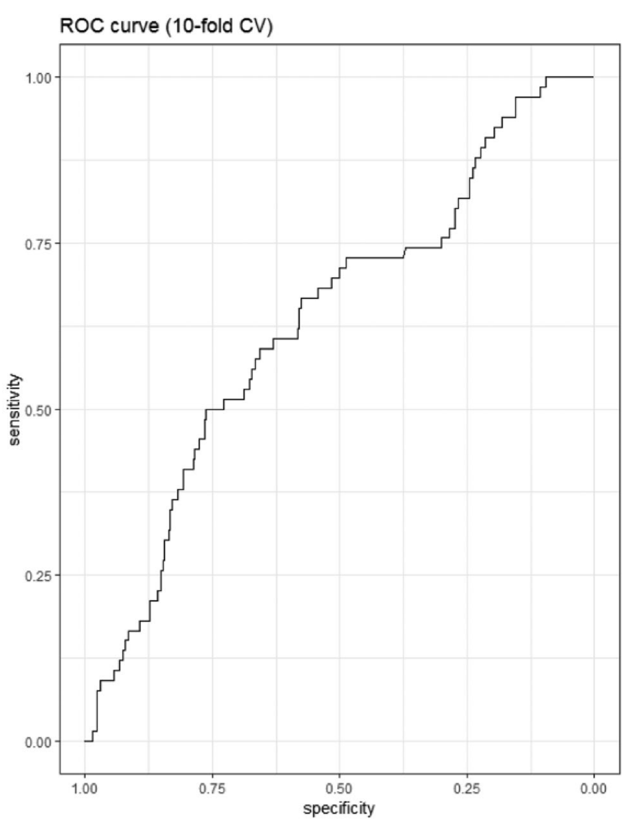

Figure 3. ROC-curve for the final model showing an AUC of 0.64 after 10-fold cross validation.

achieved an AUC of 0.64 We thus ran a 10-fold cross Validation for a final AUC of 0.63. In Figure 1, the AUC curve for the fitted model without Digit Span Forward is shown (Figure 3).

As our data was unbalanced with only about 19.7% (n = 66) answering Yes on history of use of illicit drugs we also performed a precision-recall estimation giving a PR-AUC of 0.28 in the final model after cross-validation. A balanced accuracy curve may also be more informative in selecting optimal sensitivity and specificity values. A balanced accuracy calculation indicated that the optimally balanced accuracy was 0.234 with a sensitivity of 0.50 and specificity of 0.76.

Discussion

In this study, we found that a group of young adults from the general population in Norway with a self-reported history of use of illicit substances differed significantly from their peers without such substance use history on several self-reported variables of executive dysfunction and mental health neuropsychologically measured response inhibition as well as objective test of neuropsychological functioning. Subjects with illicit substance use had higher anxiety or depression symptom loads than subjects without such substance use history. However, only anxiety was left in the final models predicting which subjects had a substance use history when controlling for neurocognitive functioning.

As presented, the final model achieved an area under the receiver operating characteristics curve of 0.63, which indicates that this model has a borderline acceptable classification capability in this sample. As our dataset was unbalanced, the AUC metric may give an overly optimistic prediction accuracy and precision recall estimate. Therefore, precision-recall AUC was used as an alternative performance metric as this is often considered a better approach when using imbalanced datasets (Sofaer et al., 2019). This resulted in a precision-recall AUC score of 0.28. This highlights the importance of considering alternative performance metrics when modeling imbalanced datasets, such as balanced accuracy, precision recall-AUC, and techniques for resampling and harmonization of data. This indicates that our model may be good at correctly classifying negative cases, but not as good at classifying the positives.

Our study expanded on the existing literature by including neuropsychological assessments of working memory (digit-span forward and backwards) and response inhibition (Go-NoGo), in addition to self-reported mental health (anxiety and depression) and continuous measures of ADHD symptoms (the ASRS-6) in a general population. Using a logistic regression model selection method based on AIC, we arrived at a model with sex, response inhibition (commission errors), anxiety (HADS Anxiety) and inattentiveness (ASRS-6 factor 1) as significant or marginally significant predictors of the self-reported history of illicit drug substance use. Inhibitory difficulties have been known to predict alcohol and substance abuse in adolescents (Lees et al., 2021; Liu et al., 2019), Self-reported motor impulsivity as represented by ASRS factor 2 was not in the final model, which is in line with the findings of Verdejo-Garcia and Albein-Urios (2021) who reported hyperactivity/impulsivity traits to be inconsistently associated with substance use.

Questionnaire-based measures of depression were no longer significant in a logistic regression model when controlling for both self-reported and performance based neurocognitive functioning, and measures of anxiety were only marginally significant. This may confirm the previous finding that executive neurocognitive factors as moderators of mental health effects in general, and depression specifically on substance abuse in clinical populations (Bozkurt et al., 2016; Felton et al., 2020). Both subjective and objective measures of neuropsychological functioning contributed to the prediction of which subjects had a history of substance use. These measures obtained weak intercorrelations suggesting that they are independent state and trait predictors in line with the findings of Toledo-Fernández et al. (2020). Our analyses showed several significant correlations among predictor variables which may also create multicollinearity among input data and influence the final model selection, however analysis of multicollinearity in the final model only showed very modest variability inflation due to multicolinearity.

The significant attrition from the full population sample in the current study may limit the generalizability of our findings. We have acknowledged systematic attrition based on Sex from the entire population to the group studied in our sample. Since we have previously reported significant differences between male and female participants on some of the predictor variables in Q2 (Lauvsnes et al., 2021), we suspected that the final data would consist of individuals with a lower general symptom load. However, this was not the case, and we conclude that symptom load was not an essential explanation of the attrition beyond Q2. Another limitation of the current work is that the outcome measure of history of use of illicit substances is retrospective in nature, which may hamper it's validity. Also there may be a big difference in the actual amount used and for how long.

Conclusions

Our study shows that even in a general population of young adults in Norway, subtle cognitive dysfunction differentiates young adults with and without a history of illicit substance use. Such neurocognitive factors also likely moderate the effects of mental health on substance use behavior in this cohort, as neurocognitive variables outperform mental health measures in predicting substance use. Our findings inform colleagues in clinical and preventive work that poor response inhibition and inattentiveness are important for understanding the risks of substance use. Moreover, future research may benefit from looking at the identified neurocognitive variables as continuous measures rather than categorical clinical classes. Our work adds to the existing literature by combining self-reported cognition and neuropsychological measures in a general population cohort of young adults. Our findings also highlight the critical need for using more adequate statistical tools to evaluate the performance of analyses in unbalanced datasets.

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