European Neuropsychopharmacology 112 (2026) 112886

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Reconsidering regression-based predictors in adults with attention-deficit/hyperactivity disorder and substance use disorders

ARTICLE INFO

Keywords:
Attention-deficit/hyperactivity disorder
Substance use disorders
Logistic regression
Nonlinear associations
Parametric assumptions

Letter to the Editor

Brynte et al. (2026) provide a valuable contribution by characterizing adults with attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUD) in a large international cohort. The International Naturalistic Cohort Study of ADHD and SUD (INCAS), including 578 patients across nine countries, offers important insight into treatment outcomes in clinical settings. Their observation that ADHD medication at baseline, higher baseline health status (EQ-5D scores), and employment status predict treatment success offers clinical insight for treatment planning in this complex population. However, the reliance on multivariable logistic regression and the least absolute shrinkage and selection operator (LASSO) for identifying predictors of binary outcomes warrants further discussion.

In this clinical context, many predictors are unlikely to represent fully independent contributors. Baseline functioning, psychological distress, ADHD symptom burden, substance use severity, and psychiatric comorbidities often covary in ways that reflect shared clinical vulnerabilities rather than discrete constructs. Although logistic regression remains widely used, its additive logit-based framework can oversimplify these interrelated features when treated as separate effects (Pinheiro-Guedes et al., 2024). Under such conditions, odds ratios may partly reflect shared variance among correlated predictors rather than distinct clinical signals, limiting interpretability and obscuring underlying clinical structure.

Moreover, the assumption of logit-linearity is difficult to justify for behavioral and psychiatric phenomena. They note findings suggestive of nonmonotonic dynamics, stating that "there seems to be a U-shaped relationship for males, severe AUD and higher age," while also reporting relatively low explanatory power in several models. These patterns raise the possibility that important predictors may follow threshold or saturation patterns rather than monotonic trends. Symptom severity, age, and psychological distress may exhibit nonlinear relationships that logistic regression may inadequately capture. When these complex dependencies are not modeled explicitly, estimated associations are mischaracterized and heterogeneity obscured. These correlated and potentially nonlinear dependencies also complicate variable selection approaches such as LASSO.

Reliance on LASSO for variable selection further complicates interpretation of predictor importance. While LASSO is effective for regularization, it tends to select only one variable from a set of highly correlated predictors while shrinking others toward zero (Wüthrich and Zhu, 2023). In the INCAS dataset, where symptom measures and psychiatric comorbidities are inherently interrelated, this pattern may highlight a single variable that represents a broader clinical phenomenon, while excluding others that are equally reflective of the same underlying construct. As a result, retained predictors may appear uniquely important even though they capture shared variance, whereas excluded variables may be viewed as less relevant to the clinical presentation or treatment response.

To address these limitations, future research should consider analytic strategies beyond conventional parametric regression frameworks. Unsupervised feature-structuring approaches, such as Feature Agglomeration or Highly Valuable Gene Selection, can reduce dimensionality and identify coherent groupings before modeling (Xie et al., 2025; Zhang et al., 2020). Additionally, complementing regression analyses with nonparametric association measures, including Spearman's rho or Kendall's tau, may help determine whether reported associations reflect underlying relationships rather than model-driven artifacts. These approaches may improve interpretability and robustness in analyses of complex psychiatric populations.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

Data availability: No new data were created or analyzed in this study.

CRediT authorship contribution statement

Souichi Oka: Writing – original draft, Conceptualization. **Maito Suzuki:** Investigation. **Yoshiyasu Takefuji:** Writing – review & editing,

https://doi.org/10.1016/j.euroneuro.2026.112886
Received 8 May 2026; Accepted 27 May 2026
0924-977X/© 2026 Elsevier B.V. and ECNP. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Brynte, C., Schellekens, A., Konstenius, M., Begeman, A.H.A., Crunelle, C.L., Demetrovics, Z., Dom, G., Icick, R., Johnson, B., Kapitány-Fövény, M., Levin, F.R., Luderer, M., Matthys, F., Moggi, F., Palma-Álvarez, R.F., Ramos-Quiroga, J.A., Reif, A., van Kernebeek, M.W., Vélez-Pastrana, M.C., van den Brink, W., Franck, J., 2026. Predictors of treatment success in patients with substance use disorder (SUD) and co-morbid attention deficit/hyperactivity disorder (ADHD): results from the International Naturalistic Cohort Study of ADHD and SUD (INCAS). Eur. Neuropsychopharmacol. 106, 112783.

Pinheiro-Guedes, L., Martinho, C., Martins, M.R., 2024. Logistic regression: limitations in the estimation of measures of association with binary health outcomes. Acta Med. Port. 37, 697–705.

Wüthrich, K., Zhu, Y., 2023. Omitted variable bias of Lasso-based inference methods: a finite sample analysis. Rev. Econ. Stat. 105, 982–997.

Xie, Y., Jing, Z., Pan, H., Xu, X., Fang, Q., 2025. Redefining the high variable genes by optimized LOESS regression with positive ratio. BMC Bioinformat. 26, 104.

Zhang, J., Wu, X., Hoi, S.C.H., Zhu, J., 2020. Feature agglomeration networks for single stage face detection. Neurocomputing 380, 180–189.

Souichi Oka[a,*], Maito Suzuki[b], Yoshiyasu Takefuji[b]

[a] *Faculty of Data Science, Musashino University, 3-3-3 Ariake, Koto-ku, Tokyo 135-8181, Japan*

[b] *Science Park Corporation, 3-24-9 Iriya-Nishi, Zama-shi, Kanagawa 252-0029, Japan*

[*] Corresponding author.

E-mail addresses: s-oka@musashino-u.ac.jp (S. Oka), msuzuki@sciencepark.co.jp (M. Suzuki), takefuji@keio.jp (Y. Takefuji).