Supplementary Materials for: *Underrepresentation of key demographic groups in opioid use disorder trials*

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A1 Statistical Analysis

The stacked trial and TEDS-A data can be written: $O = (S, W)$, where S is a binary indicator such that $S = 1$ indicates membership in one of the trials and $S = 0$ indicates membership in the TEDS-A MOUD population, and where W denotes a vector of baseline individual-level demographic and clinical covariates listed in Patient Characteristics subsection.

Each individual, i, has some observed vector (i.e., realization) of W values, denoted w_i. We denote the space of all observed covariate combinations as w. There is a set of w values present among those with $S = 1$, which we denote $w^{S=1}$, and a set of w values present among those with $S = 0$, which we denote $w^{S=0}$. The intersection, or "overlap", of these two sets, denoted $w^{S=0} \cap w^{S=1}$ represents the characteristics of those who are both treated with MOUD in TEDS-A and who were represented in one of the three OUD trials. We are interested in characterizing those who were treated with MOUD in TEDS-A but who were not represented in any of the three trials, characterized by $w^{S=0} \notin w^{S=1}$. To that end, we use another binary indicator, R, to denote lack of representation such that each individual in the TEDS-A MOUD population with $w^{S=0} \notin w^{S=1}$ is assigned $R = 1$ and $R = 0$ otherwise. We describe the largest subgroups with $R = 1$ in terms of these characteristics and also calculate the proportion of those treated with MOUD in TEDS-A who are not represented in any of the trials.

We then fit a simple classification tree[1,2] with R as the dependent variable to be classified and with all observed $w^{S=0}$ covariate combinations as the predictor variables. A classification tree is well-suited to summarize non-represented subgroups multi-dimensionally, because each split in the tree represents an interaction between dichotomous variables, and these interactions represent relevant intersections of demographic and clinical characteristics. We used 10-fold cross-validation in fitting the tree and used a threshold complexity parameter of 0.03 to mitigate risk of over-fitting.

Nearly all of the covariates had missingness (Table A1 in the appendix). We used multiple imputation by chained equations[3] to address missing data in the covariates, resulting in 5 imputed datasets.

For each imputed dataset, we defined $w^{S=0} \notin w^{S=1}$ (and consequently the R indicator variable) as the subset not represented across any of the imputations for all TEDS-A MOUD individuals. We identified this subset using all W listed in the Patient Characteristics subsection. In a secondary analysis, we identified this subset excluding pregnancy, as there has been at least one trial comparing buprenorphine to methadone treatment in pregnant women,[4] with another CTN trial ongoing.[5] In another secondary analysis, we identified the non-represented subset further excluding educational attainment and marital status characteristics, due to their large amount of missing data. We then fit the simple classification tree described above for the subset identified in the primary analysis and the subset identified without pregnancy in the secondary analysis.

A2 Additional Results

Table A1: Missing data in patient characteristics by dataset.

Characteristic	Trials % Missing	TEDS-A % Missing
Sex	0	0.02
Age	0	0
Race/ethnicity	0	1.77
Education	50.30	4.99
Marital status	50.39	25.83
Pregnancy status	0	1.60
Amphetamine use	0.09	0
Benzodiazapine use	0.09	0
Cannabis use	0.09	0
IV drug use	4.32	0

Figure A1: Classification tree of patients receiving MOUD treatment in TEDS-A who are not represented in MOUD trials, excluding pregnancy status. Numbers at the end of each branch indicate the number of TEDS-A patients in the represented subgroup (pink) or non-represented subgroup (green).

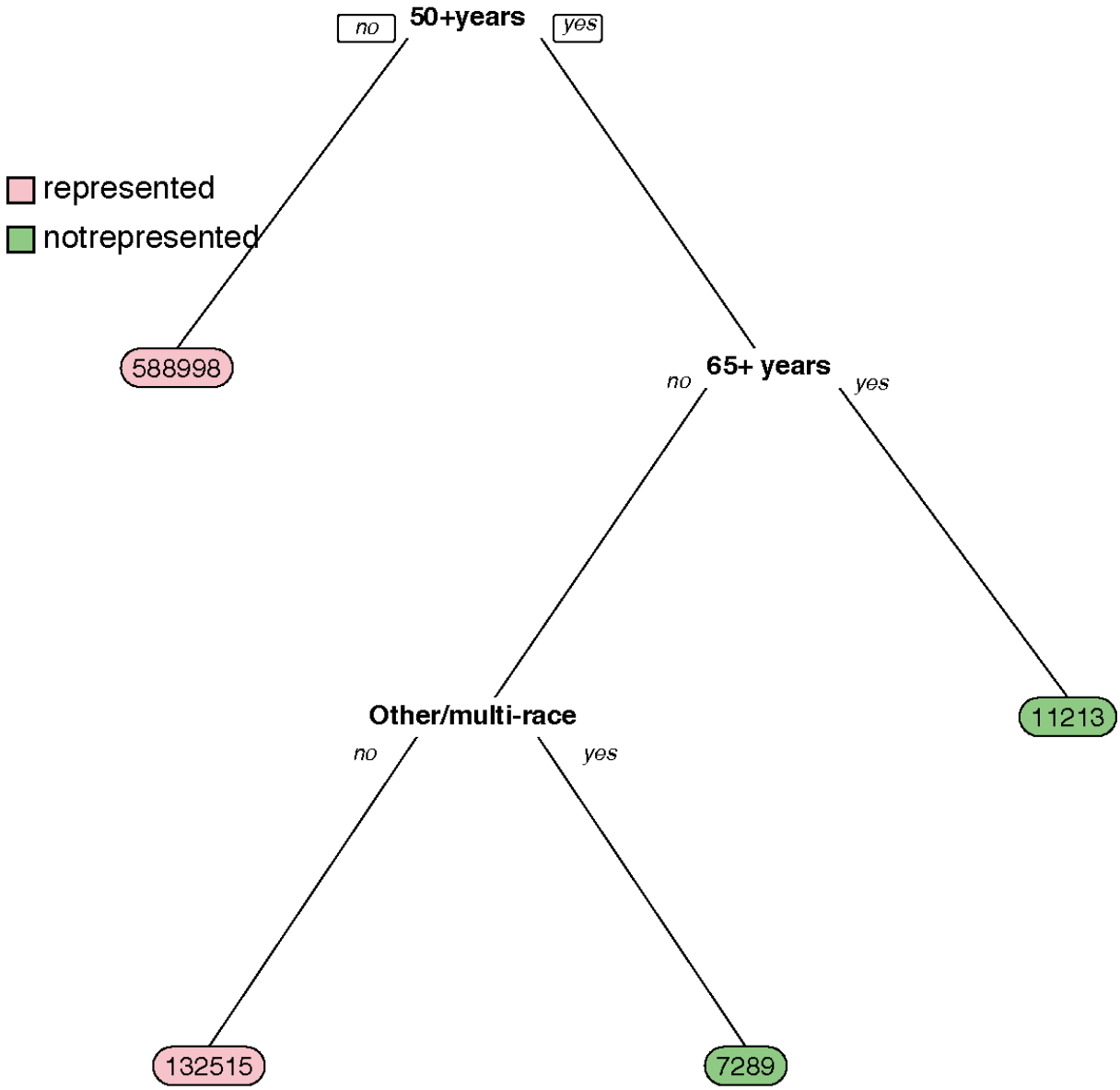
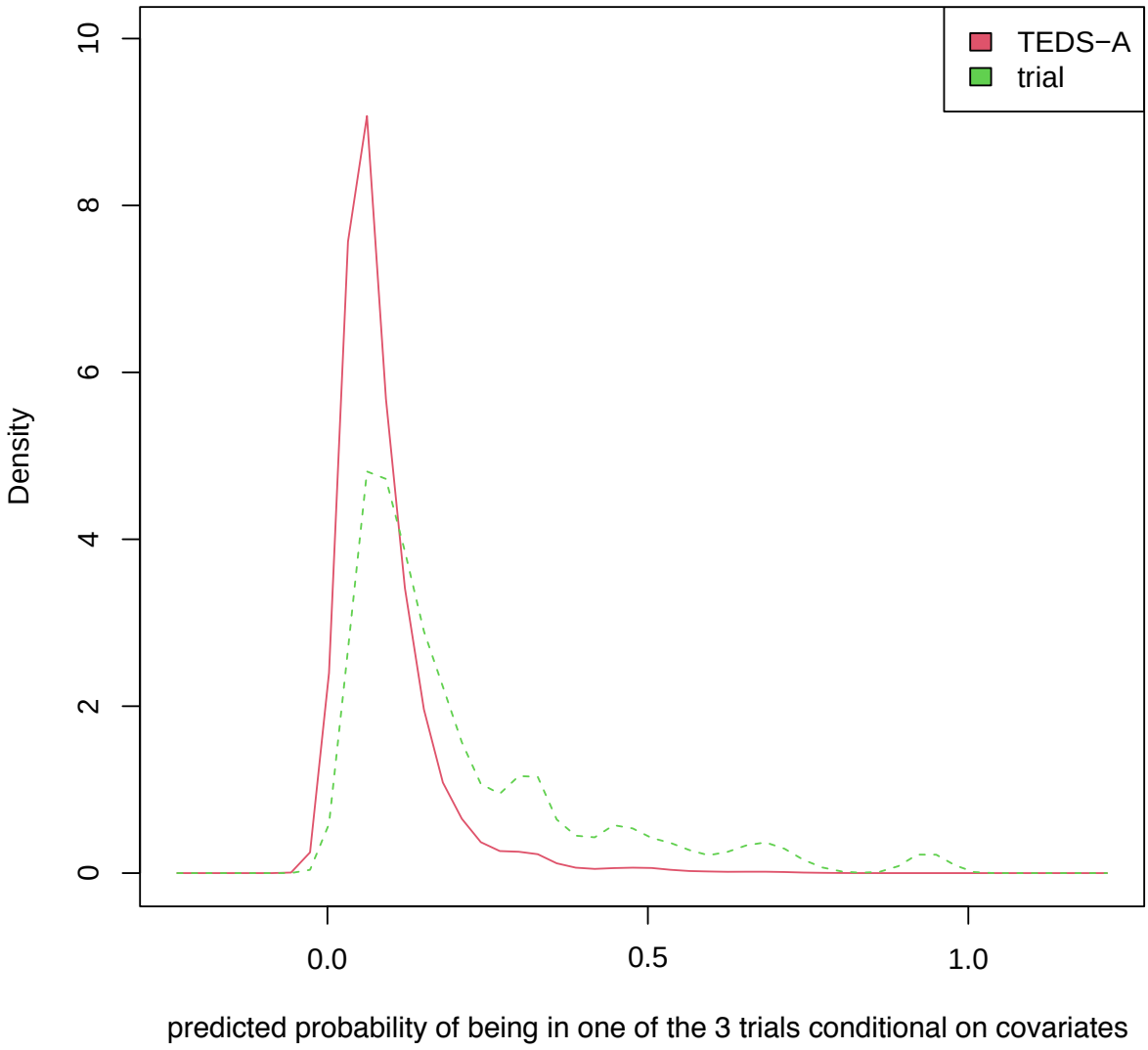


Figure A2: Distributions of sample propensity scores for the TEDS-A population (in red) and the trial participants (in green). The sample propensity score is the predicted probability of being in one of the 3 trials conditional on covariates.



References

[1] Leo Breiman, Jerome Friedman, Charles J Stone, and Richard A Olshen. *Classification and regression trees*. CRC press, 1984.

[2] Terry Therneau, Beth Atkinson, Brian Ripley, and Maintainer Brian Ripley. Package 'rpart'. *Available online:* `cran.ma.ic.ac.uk/web/packages/rpart/rpart.pdf` *(accessed on 20 April 2022)*, 2015.

[3] Stef Buuren and Karin Groothuis-Oudshoorn. mice: Multivariate imputation by chained equations in r. *Journal of Statistical Software*, 45(3), 2011.

[4] Hendrée E Jones, Karol Kaltenbach, Sarah H Heil, Susan M Stine, Mara G Coyle, Amelia M Arria, Kevin E O'grady, Peter Selby, Peter R Martin, and Gabriele Fischer. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine*, 363(24):2320–2331, 2010.

[5] Theresa Winhusen, Michelle Lofwall, Hendrée E Jones, Christine Wilder, Robert Lindblad, Davida M Schiff, Scott Wexelblatt, Stephanie Merhar, Sean M Murphy, Shelly F Greenfield, et al. Medication treatment for opioid use disorder in expectant mothers (moms): Design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemporary Clinical Trials*, 93:106014, 2020.