Incidence of Treatment Resistant Schizophrenia in a Community Sample Using the TRRIP Consensus

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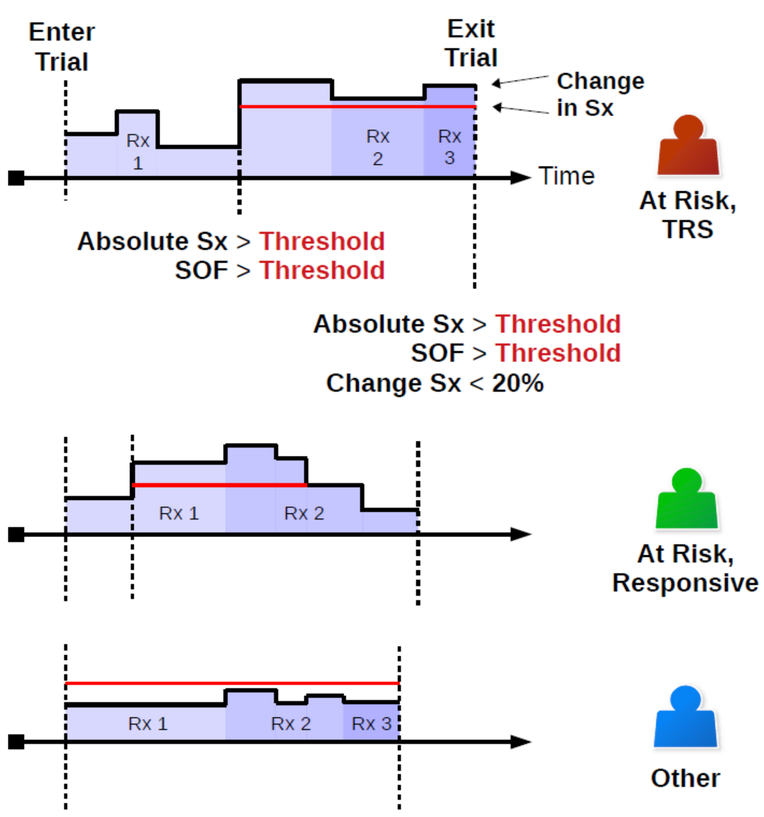
Background

Estimates of treatment resistant schizophrenia (**TRS**) vary due to lack of consensus definition. The Treatment Response and Resistance in Psychosis (**TRRIP**) consensus provides a rigorous prospective definition for TRS (Howes, *et al* 2016). We provide a **prospective estimate of the incidence of TRS** in a large community cohort using TRRIP by repurposing the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) dataset (Lieberman, *et al* 2005). In CATIE, an **exclusion** criterion was "clinical evidence" of treatment resistance.

Methods

- CATIE data retrieved for all available participants
- Pre-processed using custom scripts to extract trajectories for:
  - Social and Occupational Functioning (SOF)
  - PANSS symptoms scores (Sx)
  - Adequate Treatment Trials (Rx)

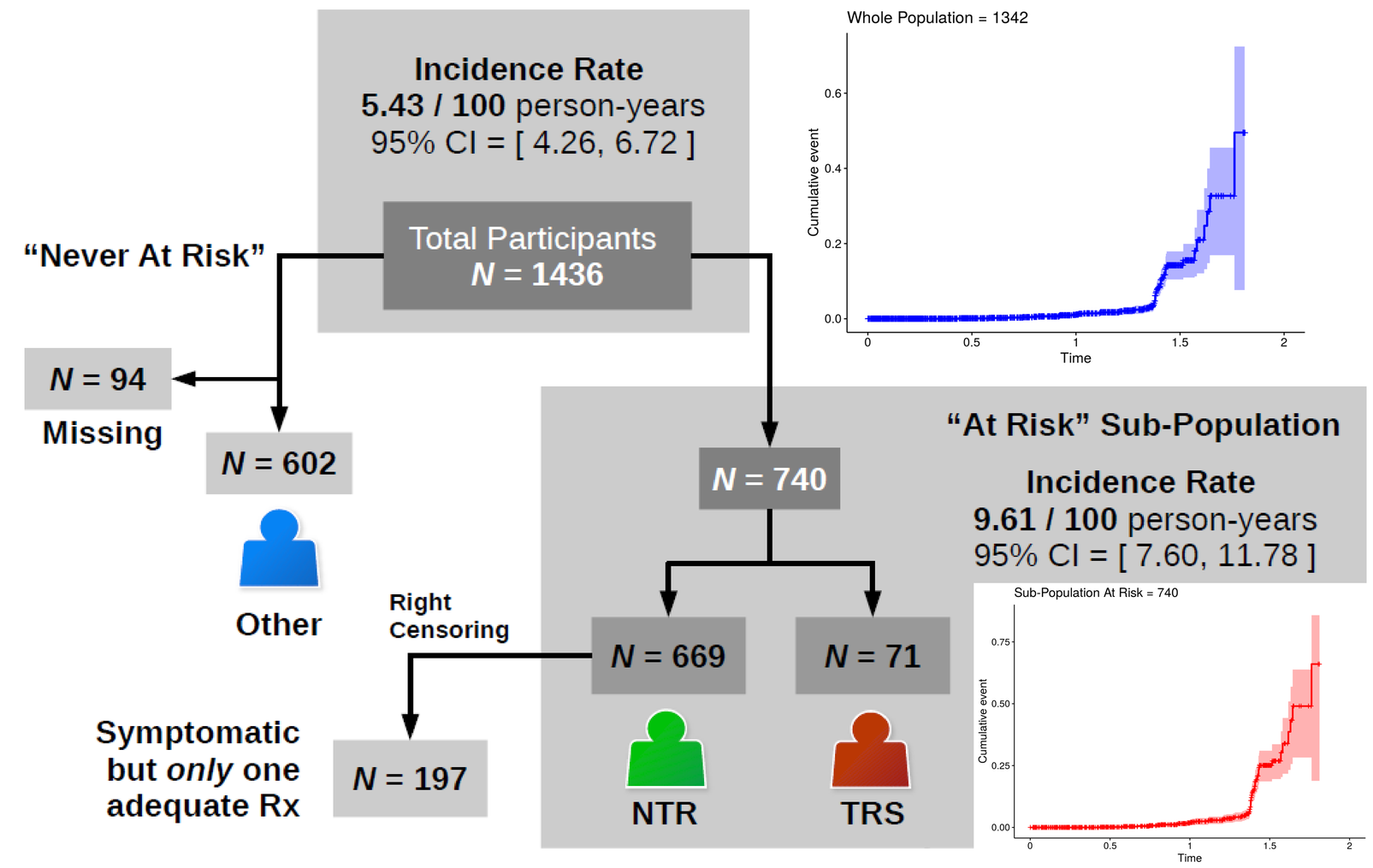
Each participant assessed and classified using an **event model** to ascertain TRS state throughout trial



Participants deemed to have TRS must

- "Trigger" absolute **Sx and SOF** TRRIP threshold at some time
- Then, have **at least 2 adequate trials** of different medications
- With Sx and SOF remaining above threshold **and** < 20% response in PANSS

Results Summary



Group Properties for TRS

TRS (*N* = 71) *versus* **remaining population (*N* = 1271)**

- Multiple, univariate analyses showed **no significant differences** on demographic and baseline clinical state variables (see Lieberman *et al* 2005 for variables used).

Resistant Domains for TRS participants:

- **Positive** domain only = 17
- **Negative** domain only = 8
- **Both** positive and negative domains = 46

Predictive Modelling

Using complete cases, from the **whole population,** with all variables from the inferential analyses, plus the full PANSS scale and baseline neurocognitive performance, we trained a tree-boosting classifier. Using 10,000 replications of 2-fold training / validation splits, we compared classifier performance to a null distribution generated similarly, but with random permutations of the TRS / NTR class labels. The actual classifiers performed **no better than random** - under the null distribution, $p > 0.05$ for all of sensitivity, specificity and misclassification error.

Inferential Analyses

Whole Population:

- Multiple logistic regression – probability of TRS given baseline data/demographics
- Stabilised inverse probability weighting for missing cases
- Only **higher PANSS negative** domain score yields very small increase in probability of TRS; OR = 1.06, 95% Confidence Interval = [1.01, 1.11]

At Risk Sub-Population:

- Same method as for whole population
- Only **younger age** showed very small reduction in probability of TRS; OR = 0.96, 95% CI = [0.92, 1.00]

Missing Data

N = 1436 In total, 94 participants were missing one or more items on demographic and baseline data used in (Lieberman, *et al* 2005).

	Missing Data Group	Complete Data Group	p-Value
Time in Trial (Yrs) †	0.178 (0.25)	1.381 (0.586)	< 0.001
Demographics †			
Years Education	12 (2)	12 (1)	0.035
Race	All Levels	All Levels	0.002
Baseline Medication *			
Olanzapine	21.37	27.83	0.039
Other (not CATIE Rx)	3.44	9.39	0.002
Past Medical Hx *			
Raised Lipids	9.54	15.14	0.024
STI	1.91	0.42	0.027
Past Psyhiatric Hx: *			
Exacerbation in Past 3 months	35.11	25.8	0.003
Alcohol Past 5 yrs *			
Dependency	19.47	13.03	0.009
Misuse	22.9	16.92	0.028
Drugs Past 5 yrs *			
Dependency	24.43	15.06	< 0.001

Race Levels: Black, Hispanic, White, Other

* = Percentage cases; Chi-square Test

† = Median (IQR); Kolmogorov-Smirnov Test

Conclusion

In a population of participants with chronic schizophrenia:

- treated with antipsychotic medications for a median of 13 years (IQR = 18)
- median age 42 (IQR = 17)
- where clinical history of treatment resistance was **excluded**

Applying a **prospective** algorithm for TRS revealed a population crude incidence rate of 5.42 per 100 person years. A majority of the 71 TRS participants were resistant in both positive and negative symptom domains.

Limitations

- Right censored cases (*N* = 197) **only** had 1 adequate trial, but a proportion may have converted to TRS
- SOF was approximated from available CATIE variables which map to PSP / SOFAS scales
- Maximum concordance recorded in CATIE was 75% (TRRIP specifies 80%)

Reproducibility

Code and derived data used in these analyses will be made available via `www.danwjoyce.com`

We gratefully acknowledge the NIMH Trial Datasets, which are available from `https://data-archive.nimh.nih.gov/ndct/`

References

Howes, *et al* (2017) **Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology**, *American Journal of Psychiatry*, 174(3), pp. 216–229.

Lieberman, *et al* (2005). **Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia**, *New England Journal of Medicine*, 353(12), 1209–1223