

Background

- Clinical and cognitive endpoints routinely deployed in Alzheimer’s disease (AD) clinical trials are vulnerable to administration and scoring errors.
- Scoring errors can impact data reliability and validity, potentially reducing ability to detect treatment effects.
- Risk-based approaches are recommended for data quality monitoring^{1,2}
- Statistical approaches to data monitoring offer an objective approach to detect anomalous scores across large scale clinical trial datasets and identify opportunities for data quality improvement interventions^{3,4}

Aim

- To develop a scalable data quality monitoring process for AD clinical trials.

Method

Sample

- Data were drawn from several multi-national AD clinical trials.
- A total of 41,245 visits with a combined 746,726 outcome scores across scales were examined.

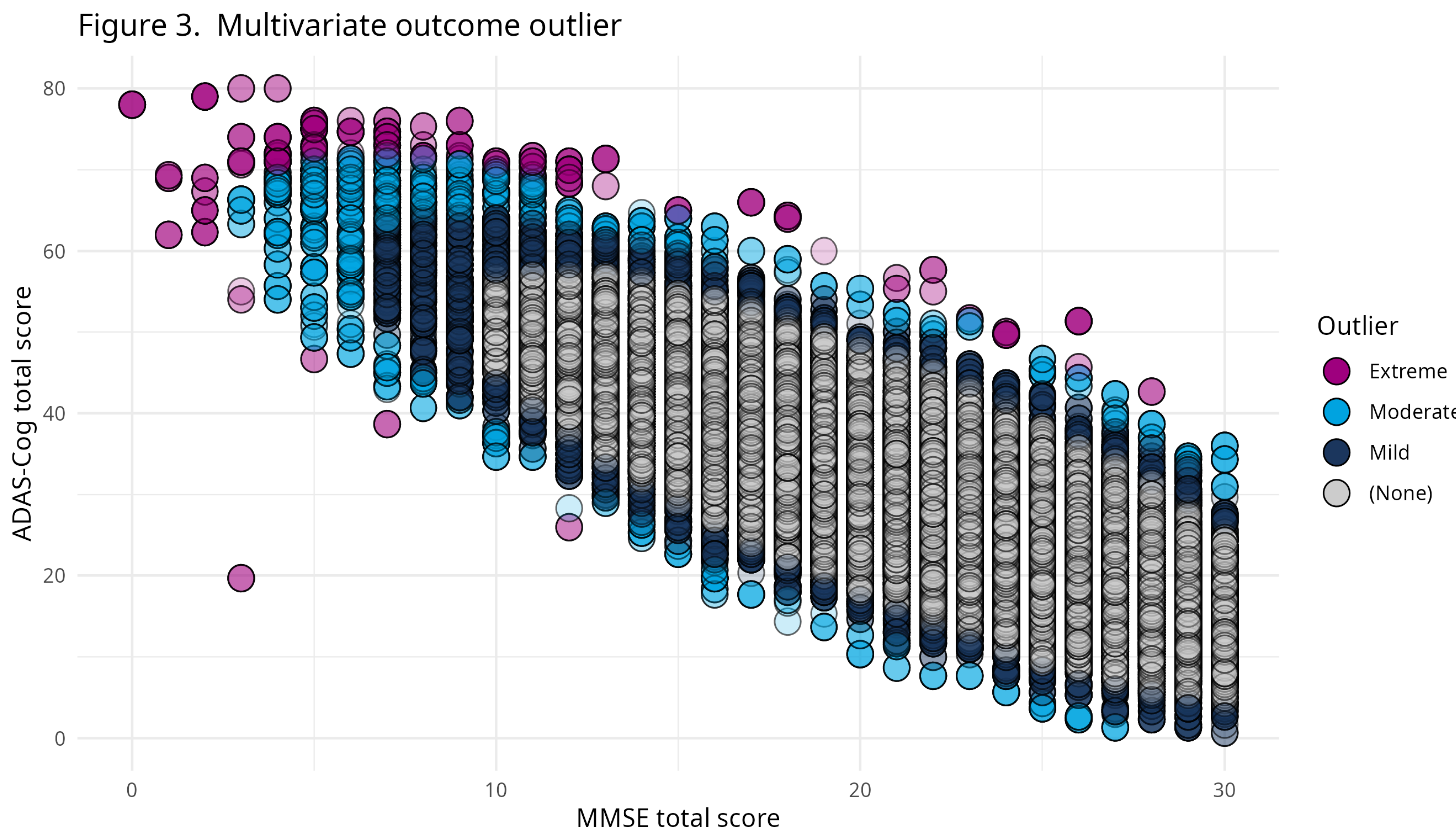
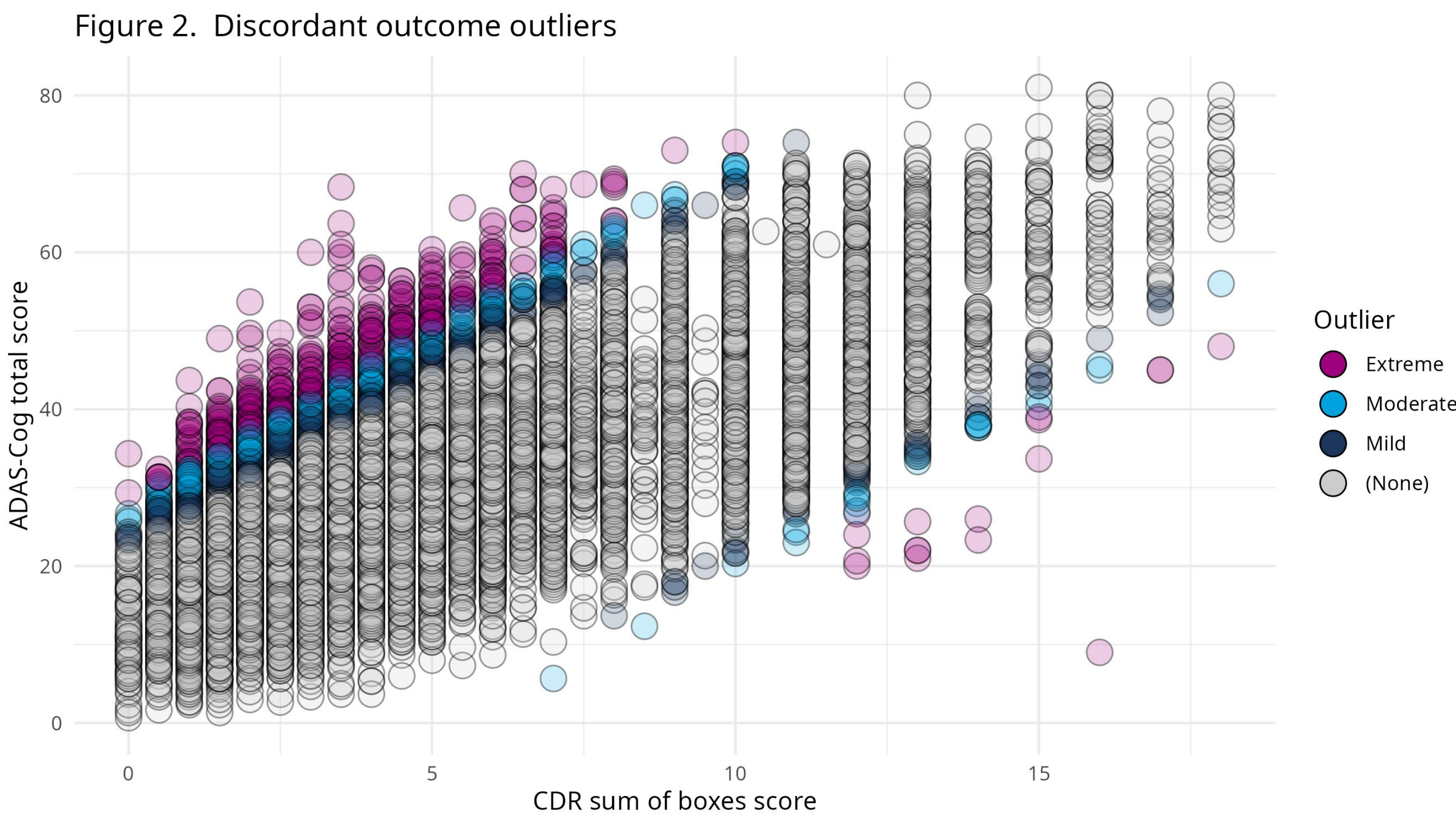
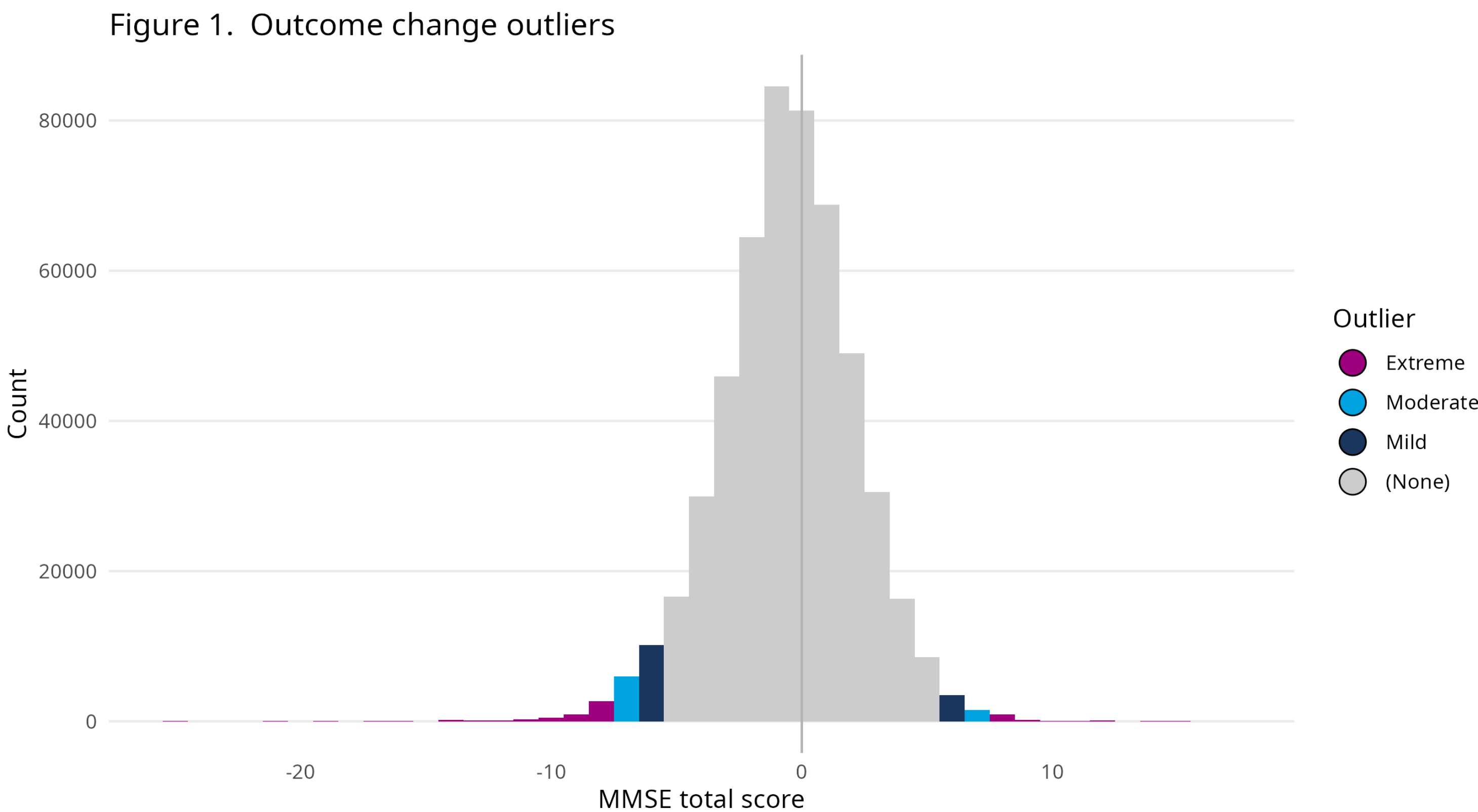
Procedure

- Anomaly detection analyses were developed for each study, configured for the set of scales and outcome scores included in the study.

Analyses

- Analyses compared individual outcome scores within a scale, as well as combinations of outcome scores across one or multiple scales.
- **Statistically large changes:** Changes in a single outcome that are greater in magnitude than other changes.
- **Discordance between outcomes:** Differences in pairs of normalized outcomes that are greater in magnitude than other differences.
- **Detection of multivariate outliers:** Multivariate outlier analysis based on the Mahalanobis distance measure.
- Distributional fitting after extreme quantile trimming were applied to generator metrics from each analysis. Threshold cutoffs were used to identify mild, moderate, and extreme outlier.

Results*



Results

Analyses across all visits from all studies showed:

- 6% contained at least one extreme outlier;
- 12% contained at least one moderate outlier;
- 24% contained at least one mild outlier.

Extreme outliers were most common in:

1. Discordance between outcomes measuring related constructs in 8% of visits
2. Statistically large change in a single outcome in 5% of visits
3. Multivariate outlier detection across outcomes in 2.5% of visits

Conclusion

- Statistical data monitoring offers a **scalable and efficient** approach to identifying anomalous scores and potential errors in Alzheimer's Disease and other dementia clinical trials.
- Approaches can be generalized to clinical trials within other populations, including psychiatric disorders, pediatrics, rare diseases, etc.
- This approach creates opportunities for **early detection of data quality issues** that can be remedied by interventions, such as supplemental rater training and specific feedback on scale administration and scoring procedures.
- Statistical data monitoring can be integrated as an additional tool for maintaining data quality of cognitive endpoints in AD clinical trials.
- Integration with centralized data and reporting systems enables statistical monitoring to become part of a broader, continuous clinical quality management strategy.
- These methodologies can be used to support small and large Phase 2 and Phase 3 clinical trials for anomaly detection and resolution.

References & Footnotes

1. US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring [Internet]. 2013 Available from: <https://www.fda.gov/media/116754/download>

2. EMA Guidance. Reflection paper on risk based quality management in clinical trials [Internet]. 2013. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

3. de Viron, S., Trotta, L., Steijn, W. et al. Does Central Statistical Monitoring Improve Data Quality? An Analysis of 1,111 Sites in 159 Clinical Trials. Ther Innov Regul Sci 58, 483–494 (2024). <https://doi.org/10.1007/s43441-024-00613-w>

4. Karas, S.M., Barbone, J.M., DeBonis, D. and Solomon, T.M. (2018), P1-064: THE USE OF STATISTICAL MODELING TO COMPLEMENT DATA QUALITY PROGRAMS. Alzheimer's & Dementia, 14: P295-P295. <https://doi.org/10.1016/j.jalz.2018.06.066>

* Data displayed are simulations of mock data

Figure 1. Outcome change outliers

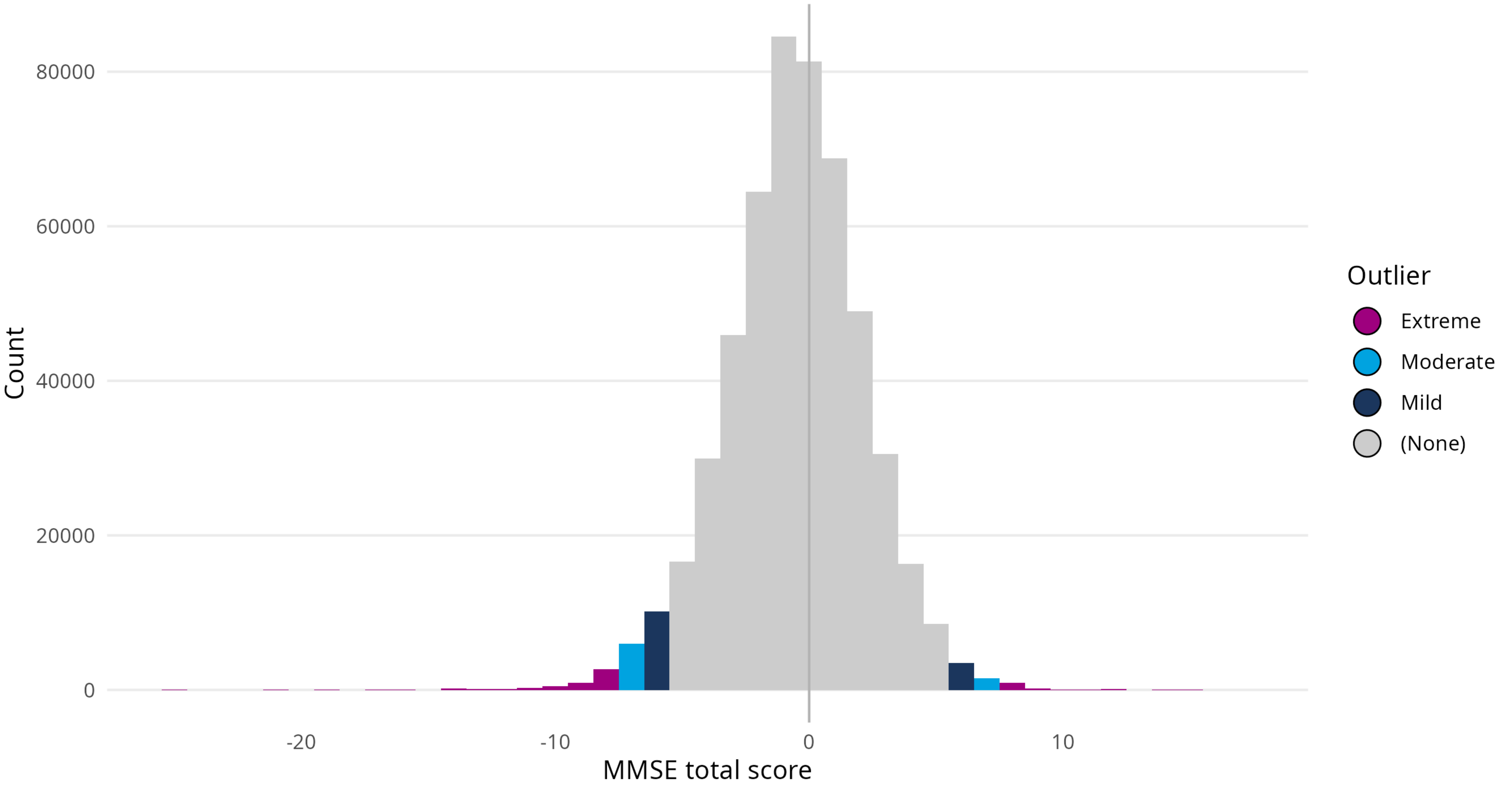


Figure 2. Discordant outcome outliers

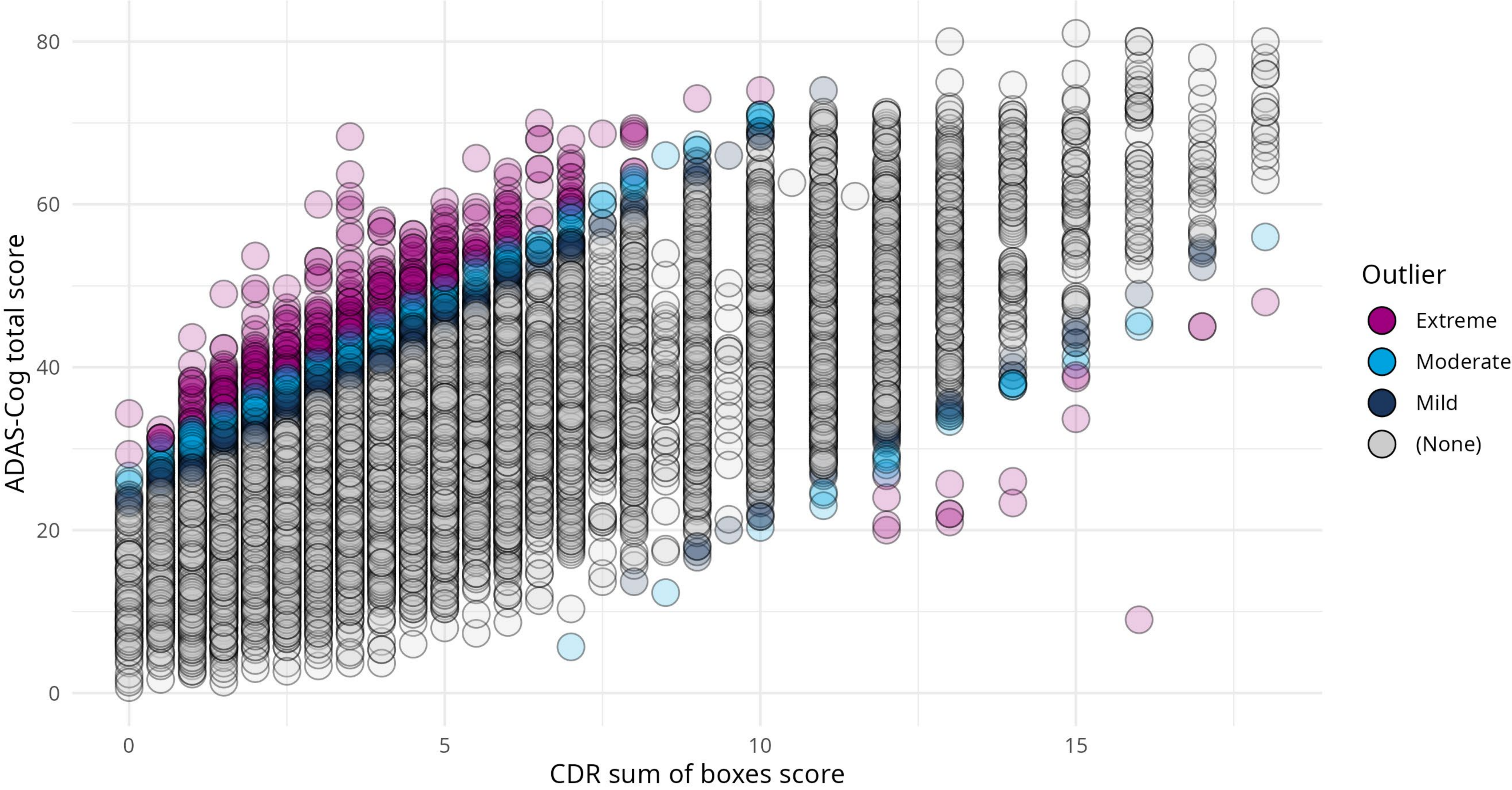


Figure 3. Multivariate outcome outlier

