

Impact of Heterogeneity on MRI-based Alzheimer's Disease Classification Accuracy

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Background

- Reproducing MRI-based Alzheimer's disease (AD) classifiers across cohorts is essential for clinical translation, but **heterogeneity** in clinical features and cohort composition is a key challenge for classification.
- Research cohorts often apply stringent inclusion criteria which may not reflect the heterogeneity of clinical populations. The impact of their underlying clustering geometry on classifier performance remains underexplored.

Aim: To examine how **inter-** and **intra-cluster geometry** differ between a research and memory clinic cohort, and how manipulations of this heterogeneity can affect machine learning classification accuracy.

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI) research cohort:
n = 1385 (603 AD, 792 controls)

generated 10 randomly subsampled cohorts, matched to QMIN-MC sample size for AD and control groups

Quantitative MRI in NHS Memory Clinics (QMIN-MC) clinically recruited cohort:
n = 428 (281 AD, 147 controls)

Structural MRI features (Freesurfer parcellation) adjusted for age, sex and estimated total intracranial volume

Cluster geometry manipulations

- Inter-cluster:** features shifted toward or away from control group means (by range of percentages)
- Intra-cluster:** spread of features scaled around group centroids

Between-centroid and within-cluster distances (Euclidean) computed on original and PCA-transformed data.

Classification

Linear support vector machine (SVM) with class-weighted penalties, 10-fold cross-validation.

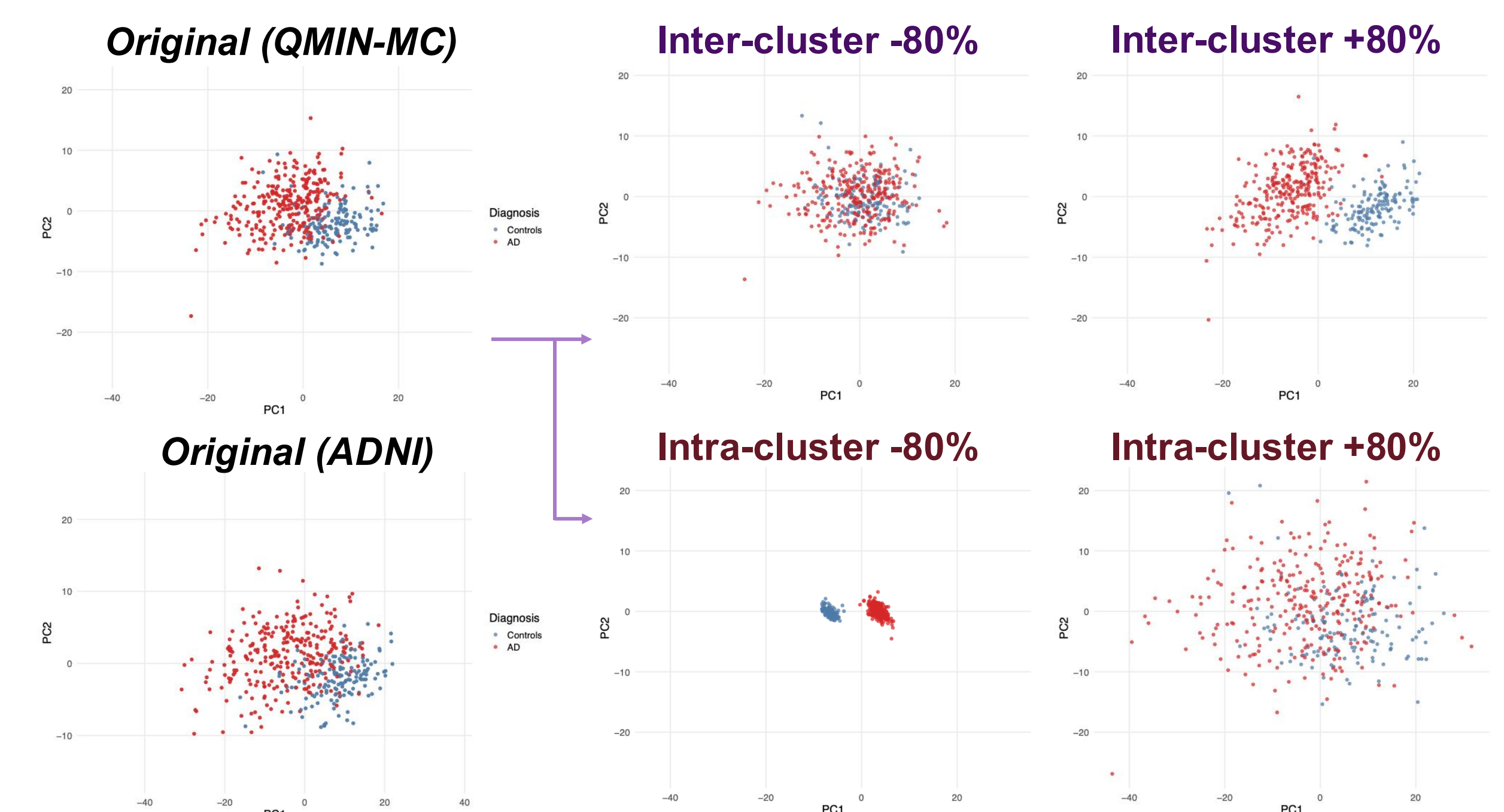
Classification (AD vs non-AD) accuracy correlated with clustering metrics

Results

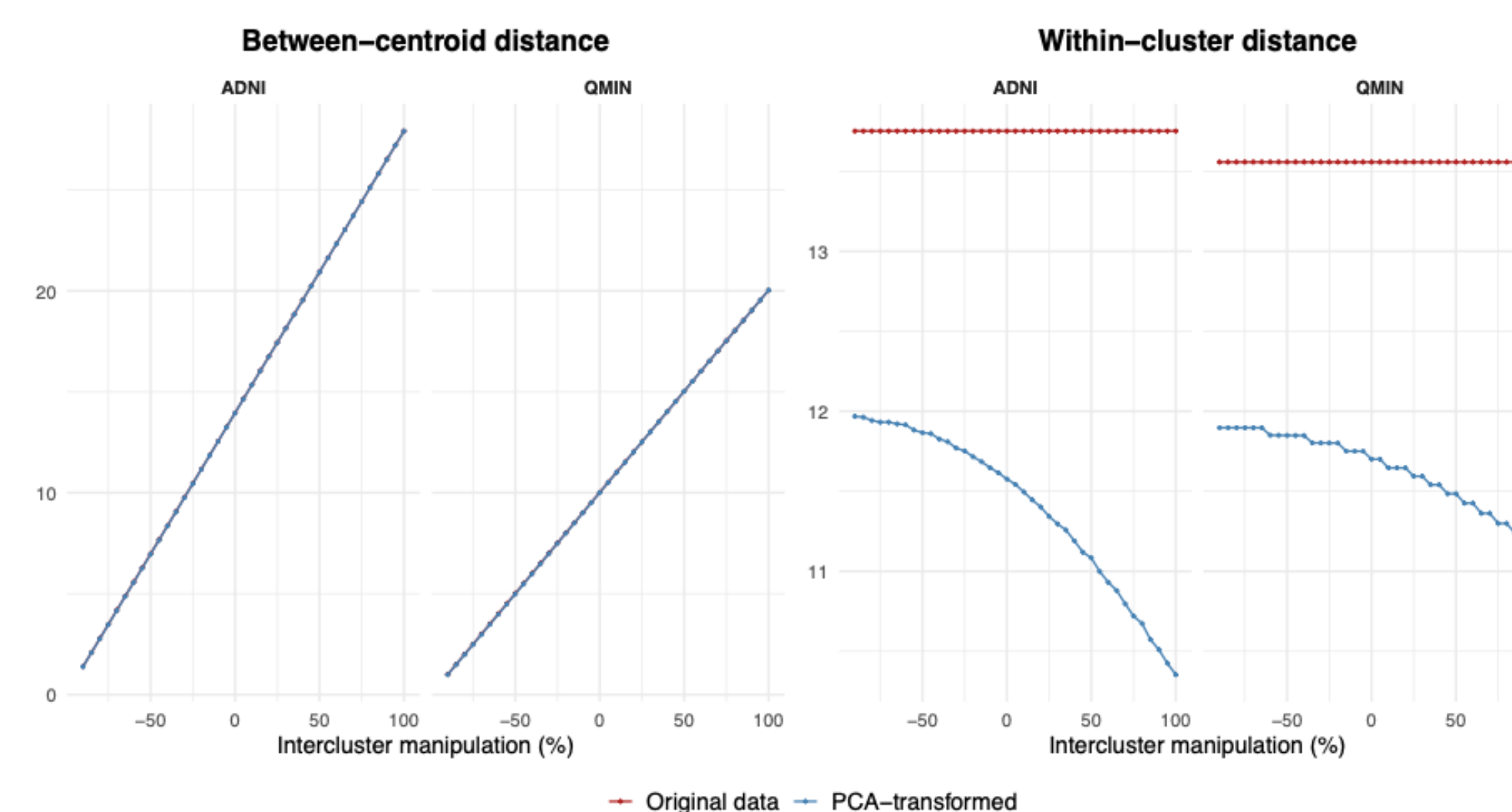
Baseline cohort comparison

	ADNI (subsets)	QMIN-MC
Variance (total)	252.68	230.21
Variance (AD)	245.40	233.54
Variance (controls)	148.24	159.07
Within-cluster distance	13.75	13.56
Between-centroid distance	13.96	10.02

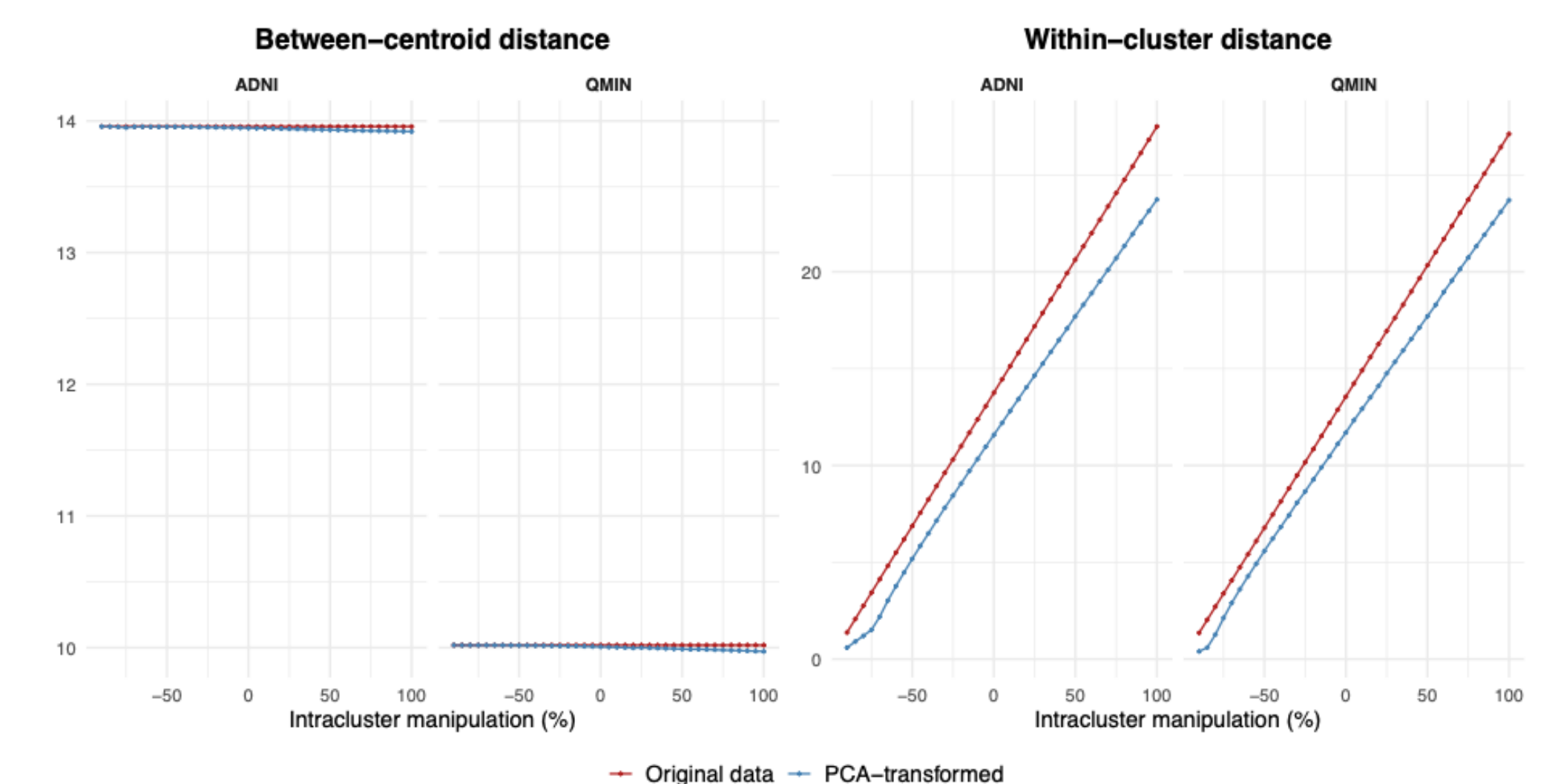
PCA plots showing cluster manipulations (QMIN-MC)



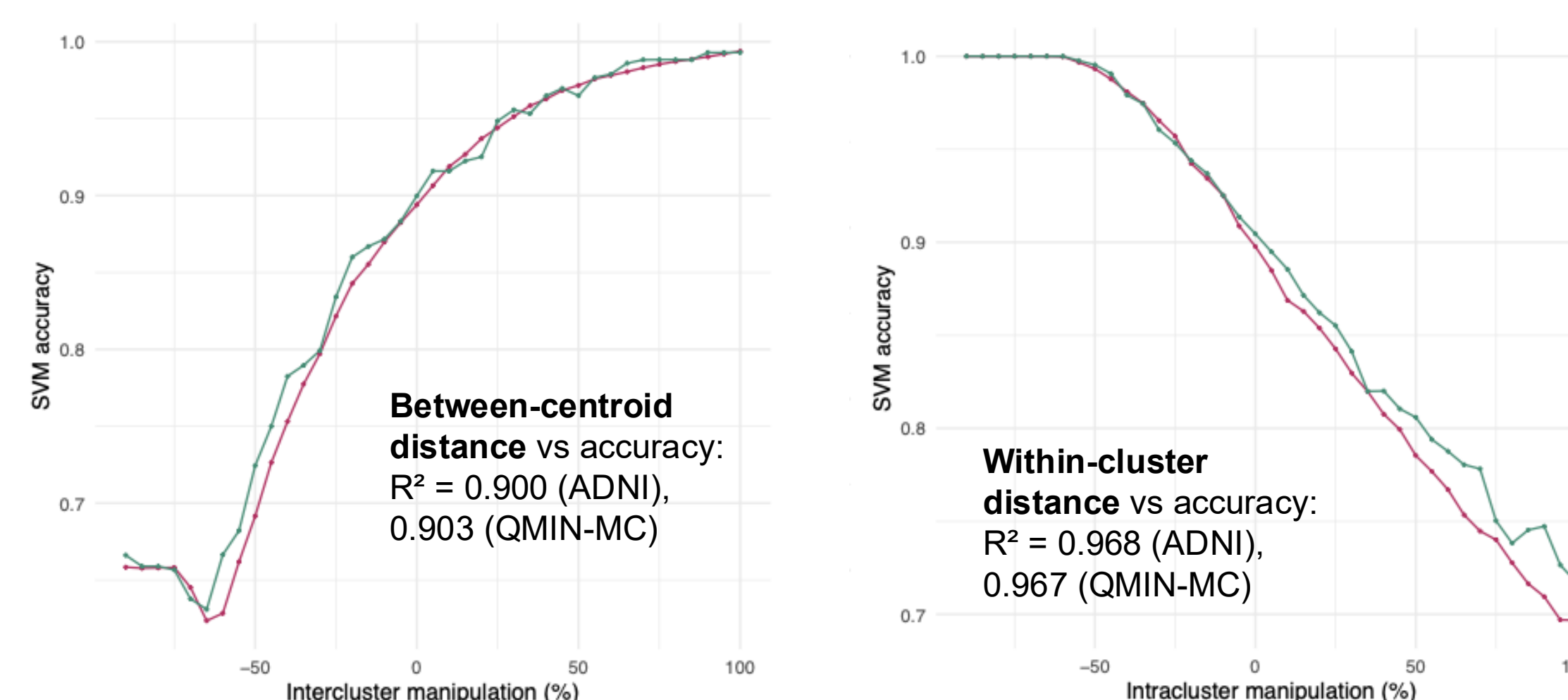
Clustering metrics: inter-cluster manipulations



Clustering metrics: intra-cluster manipulations



SVM classification accuracy



Conclusion

- A real-world cohort QMIN-MC showed reduced cluster separation and greater AD-control overlap than research cohort ADNI.
- Classification performance was more sensitive to changes in clustering geometry in QMIN-MC compared to ADNI.
- Clustering metrics may provide a useful benchmark for classifier performance across heterogeneous AD cohorts.**