

Linking imaging derived brain health to sex-associated plasma proteins in a large-scale aging cohort

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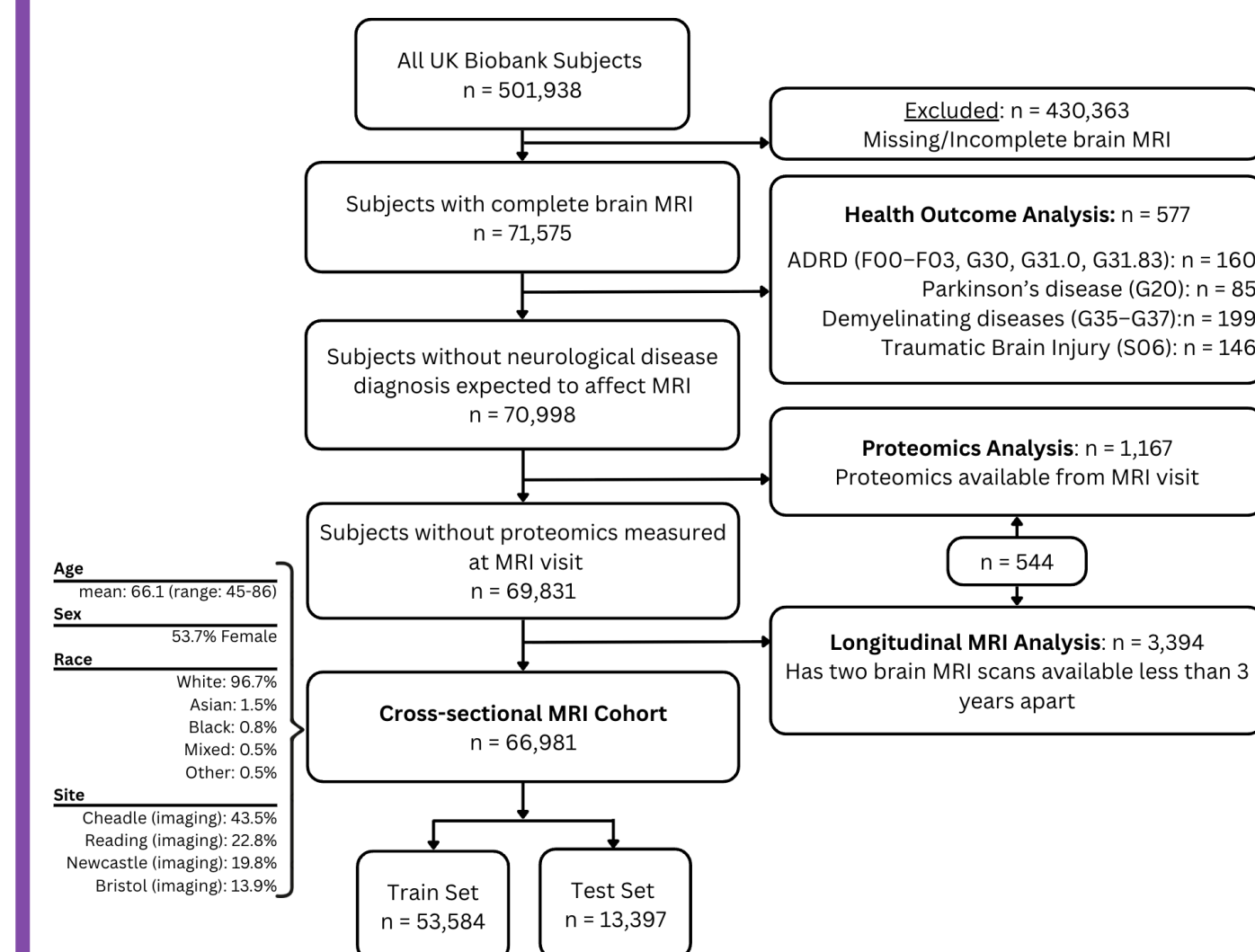
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Purpose

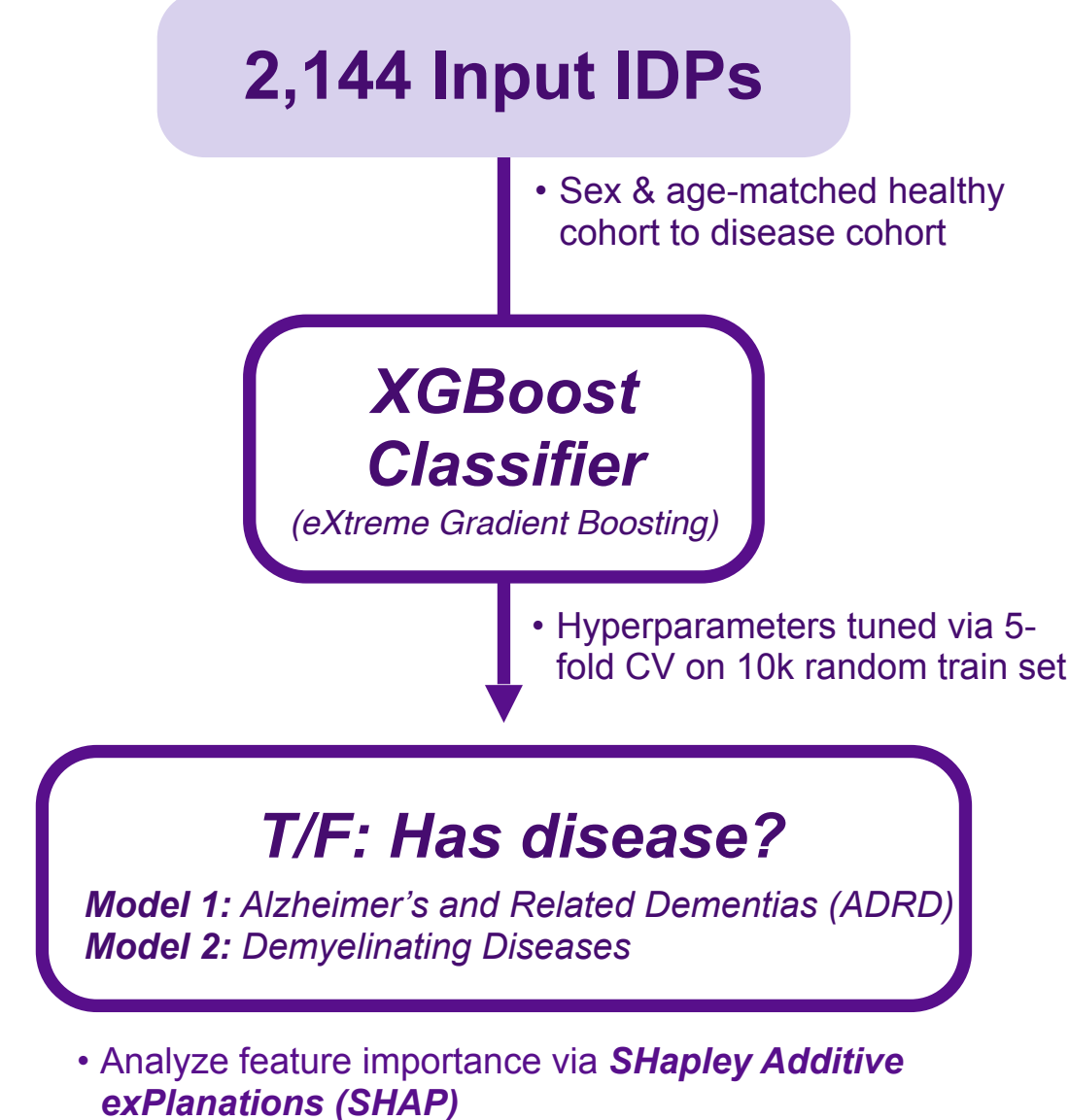
- (1) **Neurological and neurodegenerative diseases are collectively a major public health burden with sex-based disparities.¹**
- (2) **Predictive and diagnostic models of the aging brain that integrate blood- and brain markers will advance our understanding of the aging brain in health and disease**
- (3) **The high-dimensionality of multi-parametric MRI can reduce analytical sensitivity and highlight the need for latent biomarkers of brain health, such as brain age gap.**

Methods

A. UK Biobank² Cohort Selection



C. Binary Disease Classifier



B. Brain Age Gap Model Design

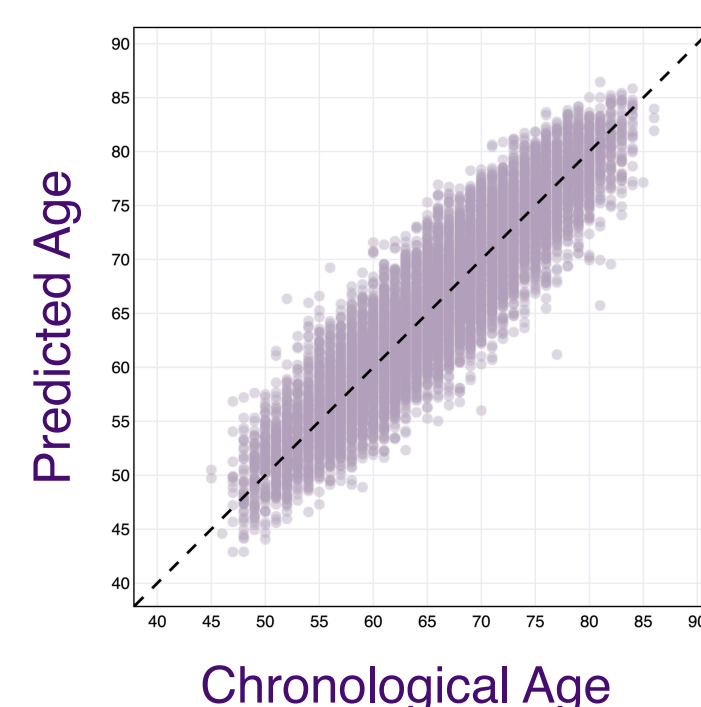
2,144 Imaging-Derived Phenotypes (IDPs)

- **T1-weighted structural MRI**
 - Volume, cortical thickness, surface area, grey-white contrast
- **T2 FLAIR**
 - White matter hyperintensities
- **Diffusion MRI**
 - FA, MD, MO, L1, L2, L3, ICVF, OD, ISOVF
- **T2* susceptibility-weighted imaging**
 - median T2*, median magnetic susceptibility

XGBoost Regressor
(eXtreme Gradient Boosting)

- Hyperparameters tuned via 5-fold CV on 10k random train set
- Age bias corrected using linear detrending

Brain Age Gap



- **All contrasts are segmented as described in ref³**
- **Repeated for subsets of input IDPs (white matter microstructure, cortical and subcortical)**
- **Performed one-sample Wilcoxon signed-rank tests on median BAG for clinical groups**

Results

D. Brain Age Gap Model Evaluation

	All IDPs	WM Microstructure IDPs	Cortical IDPs	Subcortical IDPs	State-of-the-art ^{4,5}
Number of IDPs	2,144	675	1,150	284	N/A
R ²	0.79	0.68	0.67	0.74	N/A
Adjusted R ²	0.75	0.66	0.63	0.74	N/A
MAE	2.50	2.87	2.92	2.69	3.65 - 3.70
TRV	1.26	1.43	1.33	1.29	N/A

Table 1. Performance was assessed across models. The full IDP model demonstrated superior fit (R², adjusted R²), the lowest MAE, and the highest test-retest reliability (lowest TRV). Models have comparable MAE to state-of-the-art feature⁴ and image-based⁵ brain age models.

	All IDPs	WM Microstructure IDPs	Cortical IDPs	Subcortical IDPs
No Prior Diagnosis (n = 13,397)	-0.05	-0.05	0.00	-0.04
ADRD (n = 160)	1.52	1.62	2.42	2.53
Demyelinating Diseases (n = 199)	2.26	3.50	1.98	2.54
Parkinson's Disease (n = 85)	1.42	1.12	0.62	1.39
Traumatic Brain Injury (n = 146)	1.01	2.09	0.59	1.26

Table 2. Median brain age gaps across neurological diagnoses in comparison to no prior diagnosis. A one-sample Wilcoxon signed-rank test was used to determine whether medians per clinical group were significantly different from zero (in bold).

E. Sex-Specific Proteomic Associations with Brain Age Gap

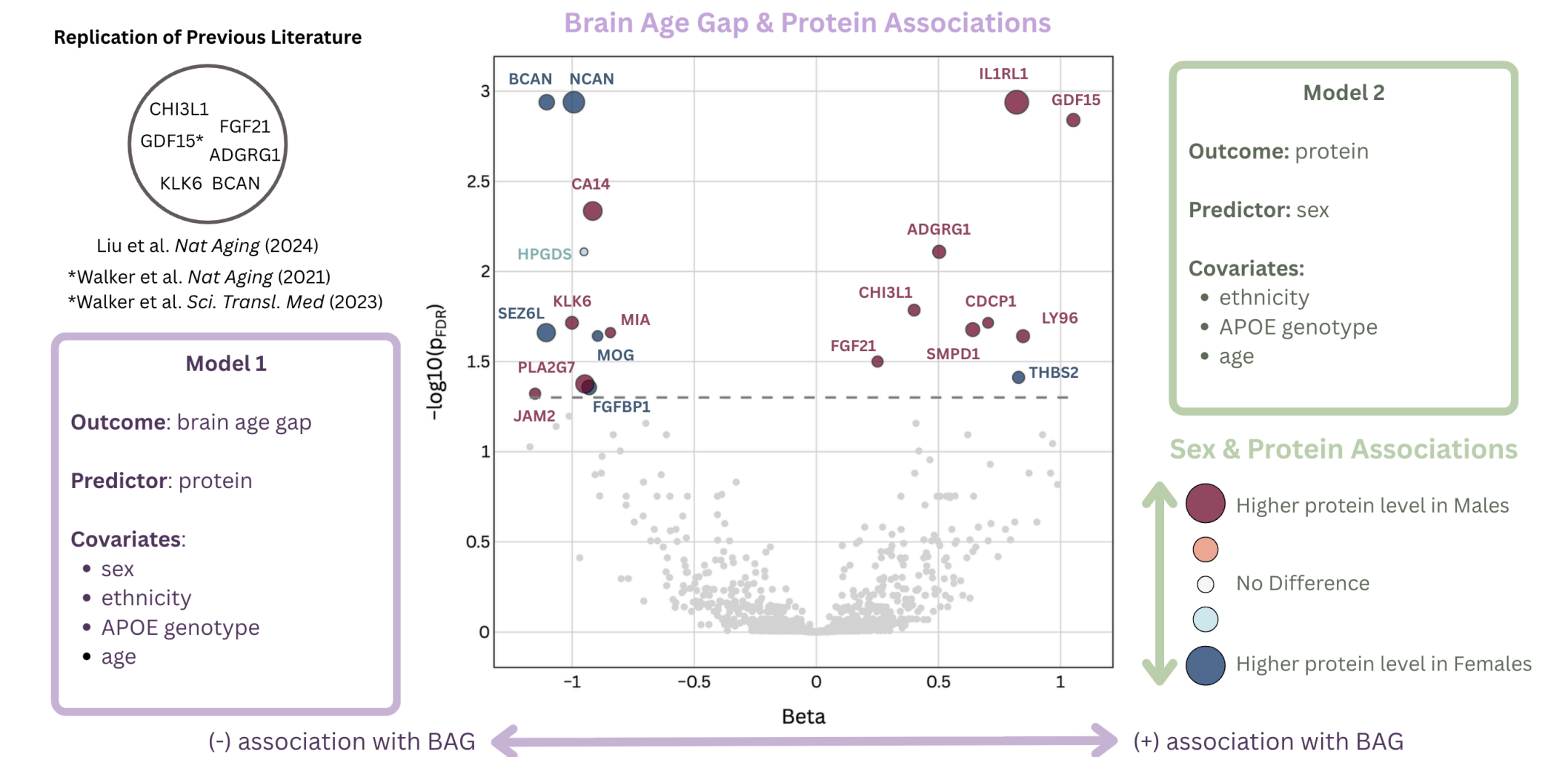
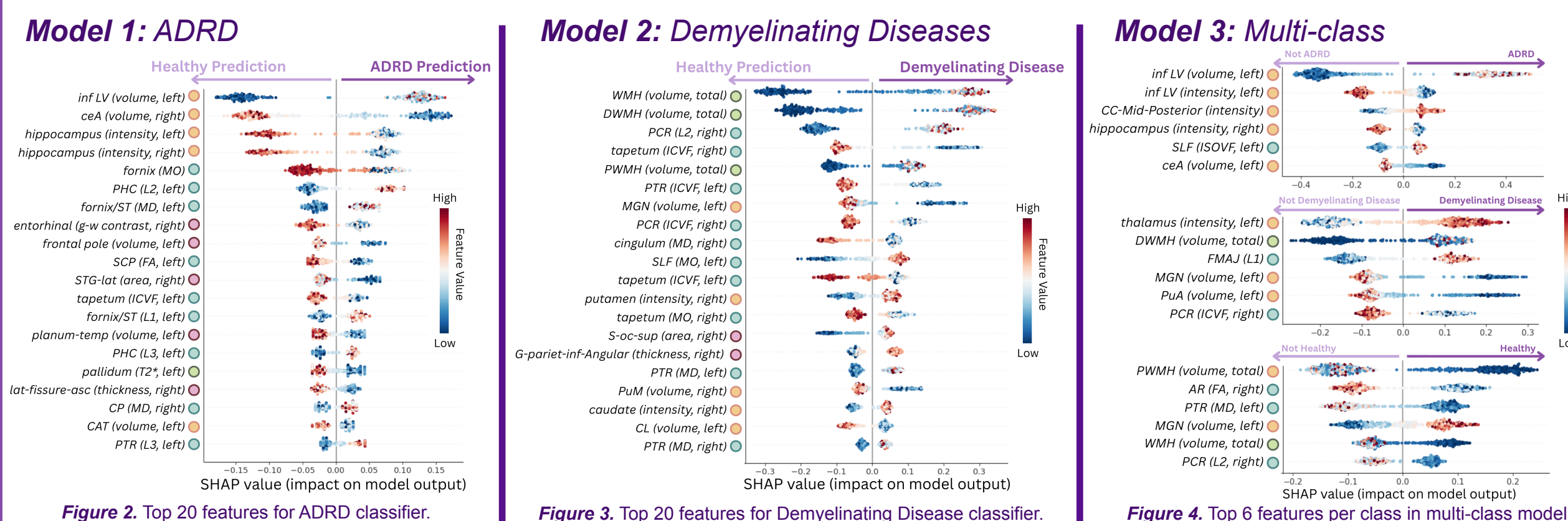


Figure 1. Model 1 identified 20 proteins significantly associated with BAG after adjusting for covariates (FDR). These 20 proteins were further evaluated in Model 2 for associations with sex using the full Olink Explore proteomics dataset (n=51,551). All 20 proteins demonstrated significant sex associations after FDR.

F. Feature Importance of Disease Classifier Models



	AUC	Precision	Recall	F1-score	Accuracy
Model 1: (ADRD)	0.78	0.71	0.74	0.72	70.8%
Model 2: (Demyelinating Diseases)	0.86	0.78	0.72	0.75	74.7%
Model 3: Multi-class (ADRD, Demyelinating, & Healthy)	0.80	0.70	0.69	0.67	68.9%

Table 3. Performance metrics of ADRD & demyelinating classification models, with macro-averaged statistics reported for the multi-class model.

References

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Conclusions

- Our Brain Age model **outperforms state-of-the-art approaches^{4,5}**, including image-based models, achieving a MAE of 2.50 while **remaining sensitive to different neurodegenerative disorders** across diagnostically relevant feature sets.
- Models that are inclusive of WM microstructural features, derived from diffusion MRI, are most sensitive in the detection of demyelinating diseases and traumatic brain injury.
- We demonstrate the association of BAG model predictions with plasma proteins, while also identifying **20 novel proteins** that may have a more **sex-specific effect on brain aging**.
- Alignment between SHAP feature importance and the underlying pathology of ADRD⁹ and demyelinating diseases¹⁰ suggests that the **models are capturing biologically relevant signals**
- **Together, this work highlights sex-specific blood-based targets to inform early, stratified brain health interventions.**

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