

Data-driven subgrouping of individuals on Alzheimer's continuum based on amyloid-β aggregation

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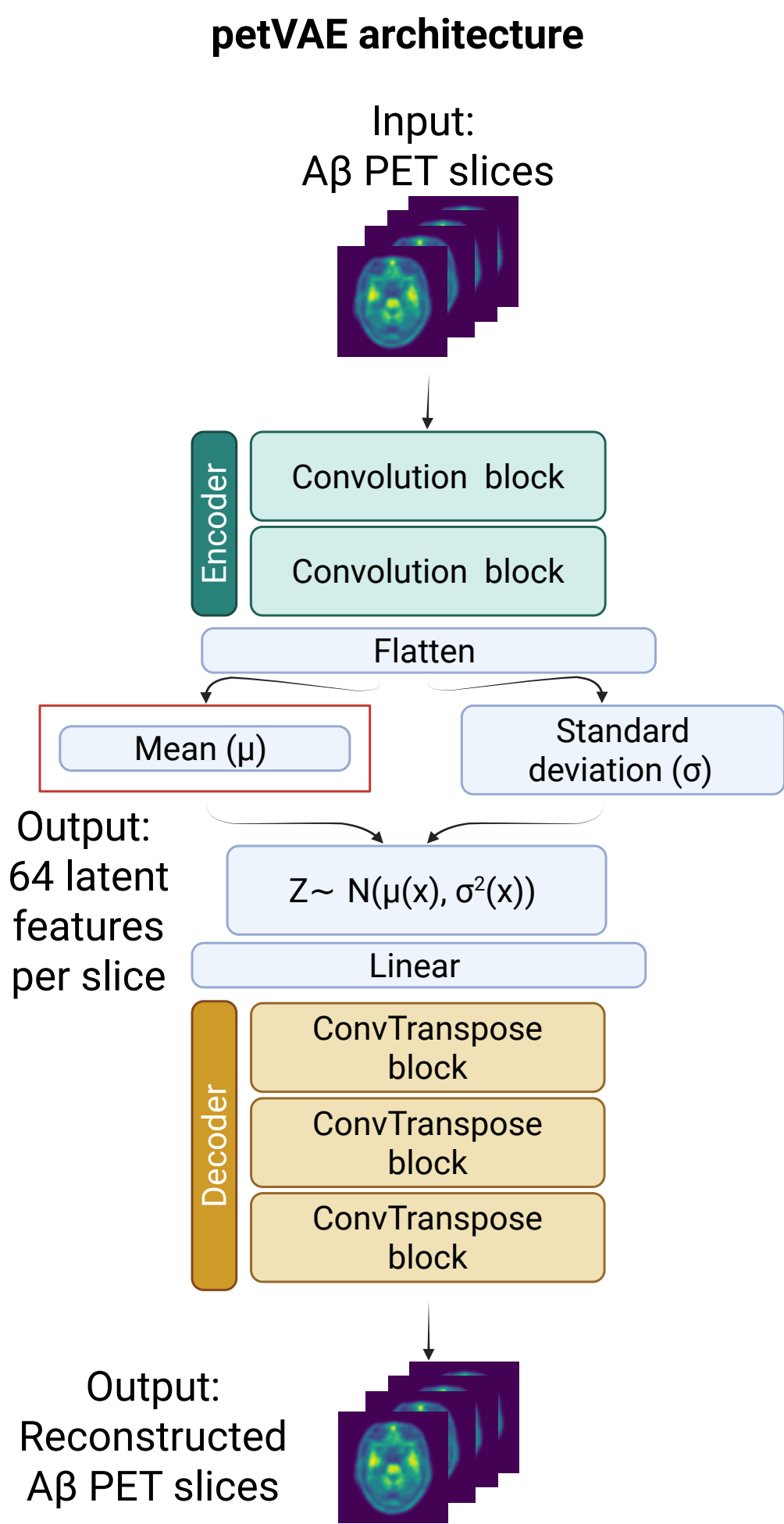


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Background & Aim

Amyloid-β (Aβ), a core biomarker of Alzheimer's disease (AD) [1], is commonly quantified using standardized uptake value ratio (SUVR) or Centiloid (CL) approaches, which rely on predefined thresholds for determining amyloid positivity [2,3]. These cut-off values are study-specific and may vary depending on several factors, including the image processing pipeline, reference region selection, and cohort characteristics [2,4]. In this study, we aimed to develop a data-driven deep learning model capable of learning an Alzheimer's disease Aβ continuum directly from Aβ PET scans, enabling threshold-free and biologically meaningful clustering of individuals.

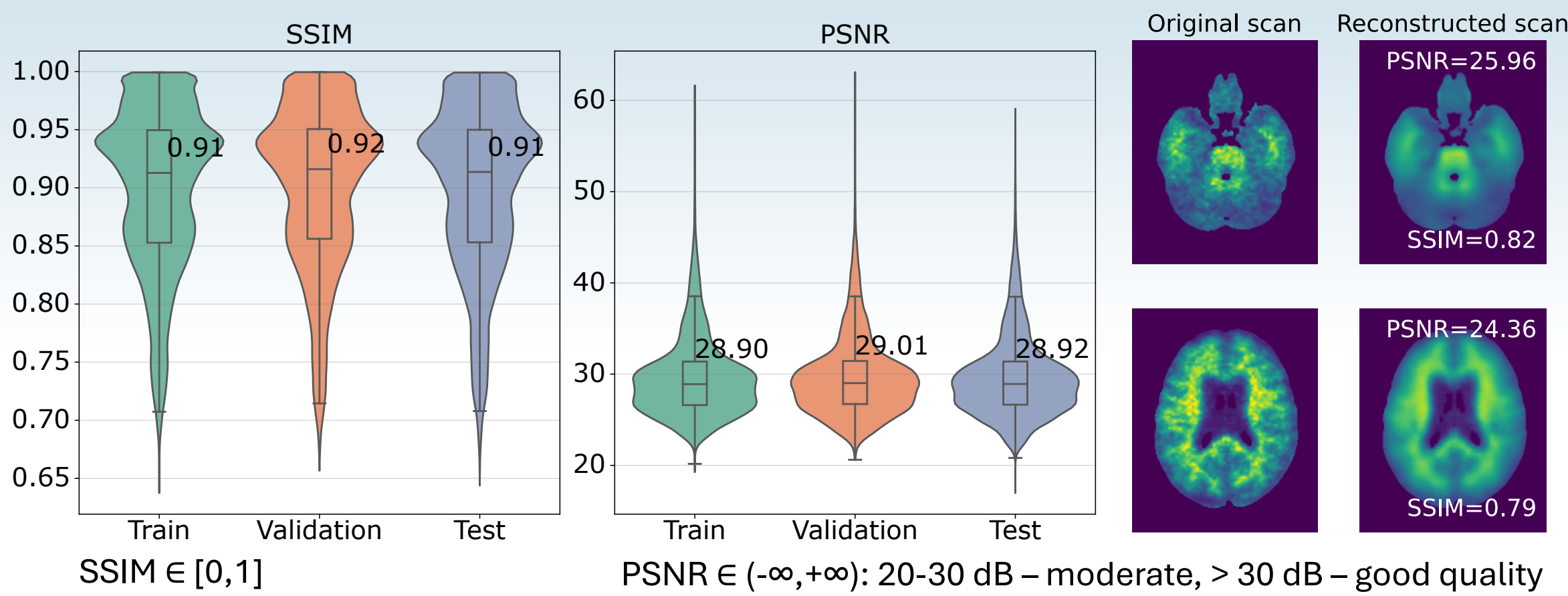
Methods



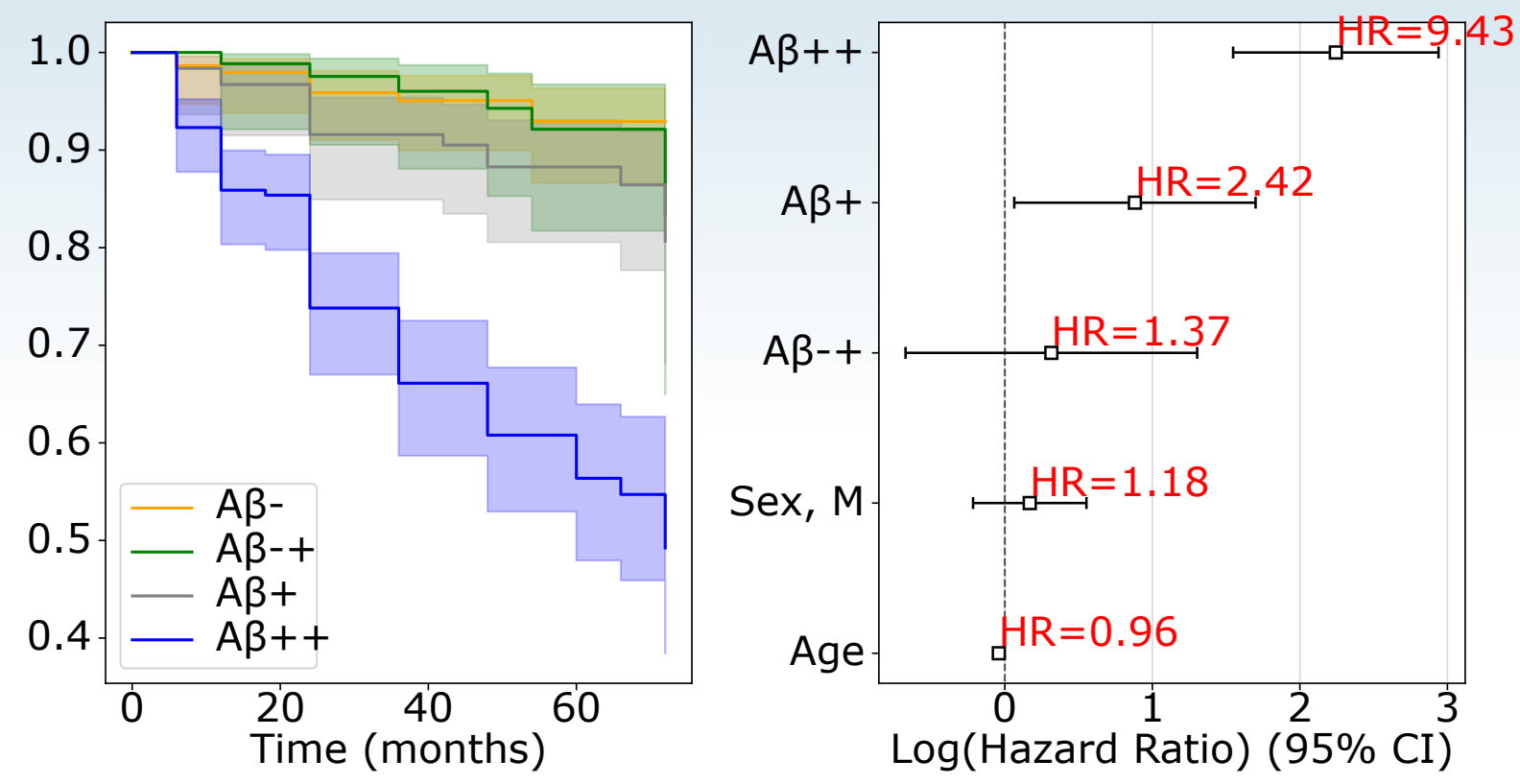
- Trained an unsupervised variational autoencoder (**petVAE**) on ~360,000 Aβ PET slices from 1,991 ADNI and A4 PET scans.
- Model performance** was assessed using validation loss (MSE + KLD), structural similarity index (SSIM), and peak signal-to-noise ratio (PSNR).
- petVAE learned **latent representations** of amyloid burden directly from PET images.
- Ranked latent features using Random Forest and constructed an **Aβ continuum**.
- Identified **four subgroups** along the Aβ continuum by hierarchical clustering.
- Evaluated subgroup associations with PET, Aβ /tau/ptau CSF, APOE ε4, and cognitive measures.
- Compared subgrouping with **Centiloid-based classification**.
- Assessed AD progression using **Cox proportional hazards survival analysis** (n = 574).

Results

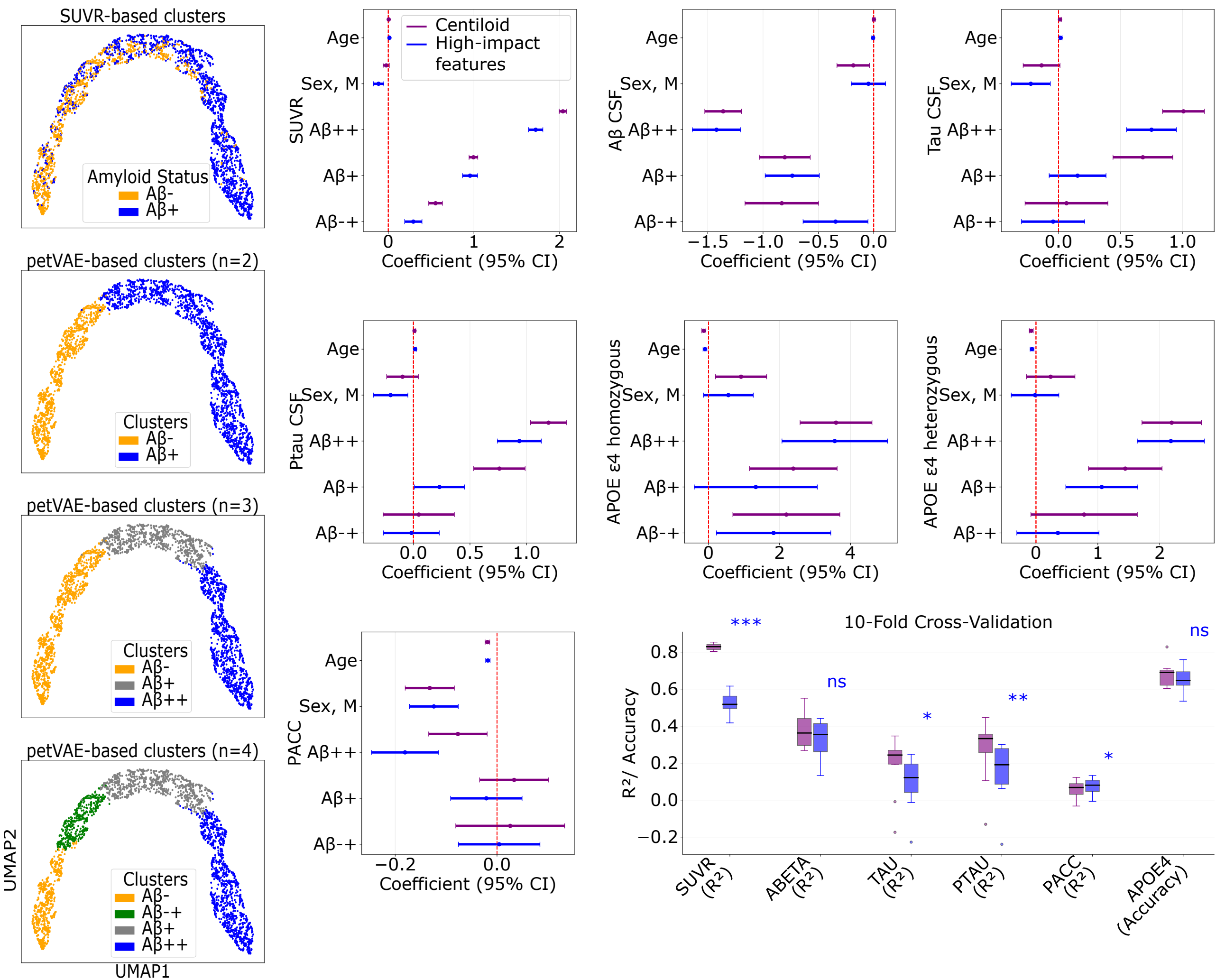
1. petVAE reconstructed Aβ PET slices with high accuracy



3. Clusters Aβ+ and Aβ++ are associated with elevated risk of progression to AD



2. Four subgroups along the Aβ continuum show distinct AD biomarker profiles



PetVAE accurately reconstructed Aβ PET slices (PSNR = 28.92 dB, SSIM = 0.91), and the derived continuum resolved four biologically distinct clusters following the AD biomarker cascade, differing in amyloid burden, tau, APOE ε4, and cognition, with markedly different AD progression risks (Aβ+++ : HR = 9.43; Aβ+ : HR = 2.42 vs. Aβ-). Centiloid- and petVAE-based clustering provided complementary information, with Centiloid clusters better aligned with amyloid and tau measures, and petVAE clusters showing additional sensitivity to cognitive markers.

Acknowledgments:
The study is funded by the University of Helsinki Doctoral Programme in Population Health and supported by the Finnish Brain Foundation, Yrjö Jahnsson Foundation, Research Council of Finland, and Sigrid Jusélius Foundation. Data were obtained from ADNI and the A4/LEARN study.

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