



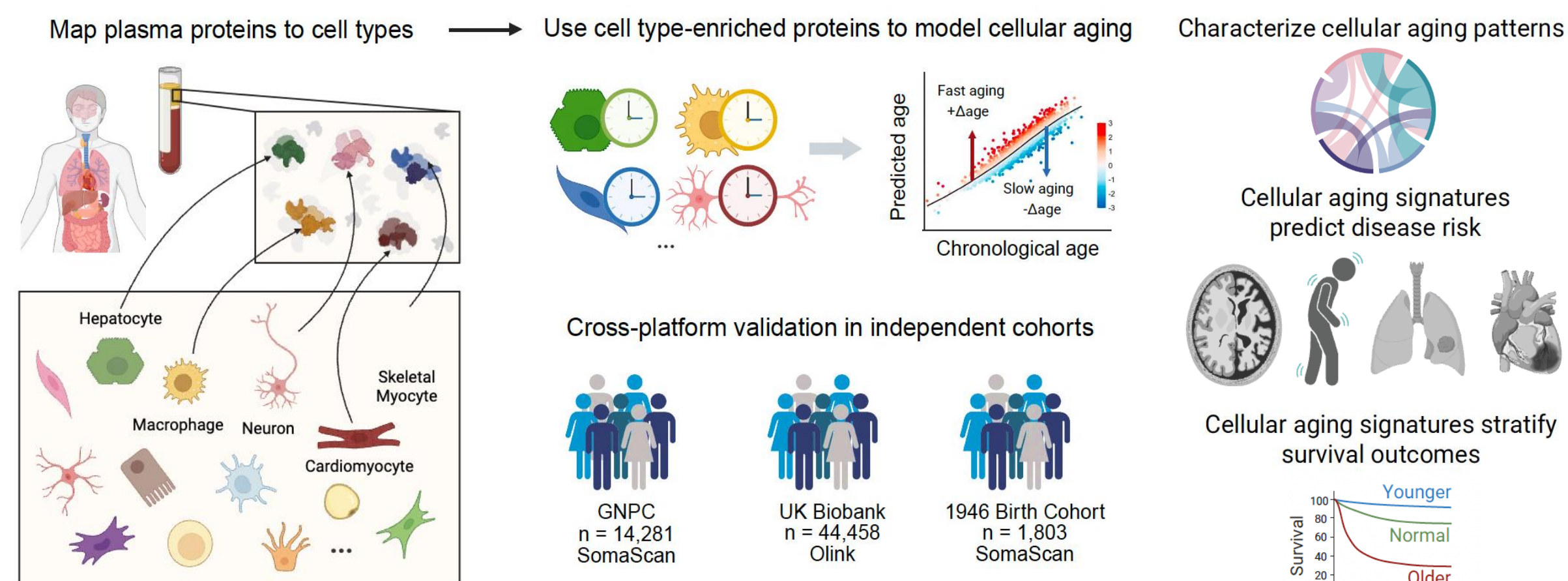
Plasma proteomic signatures of cellular aging predict human disease

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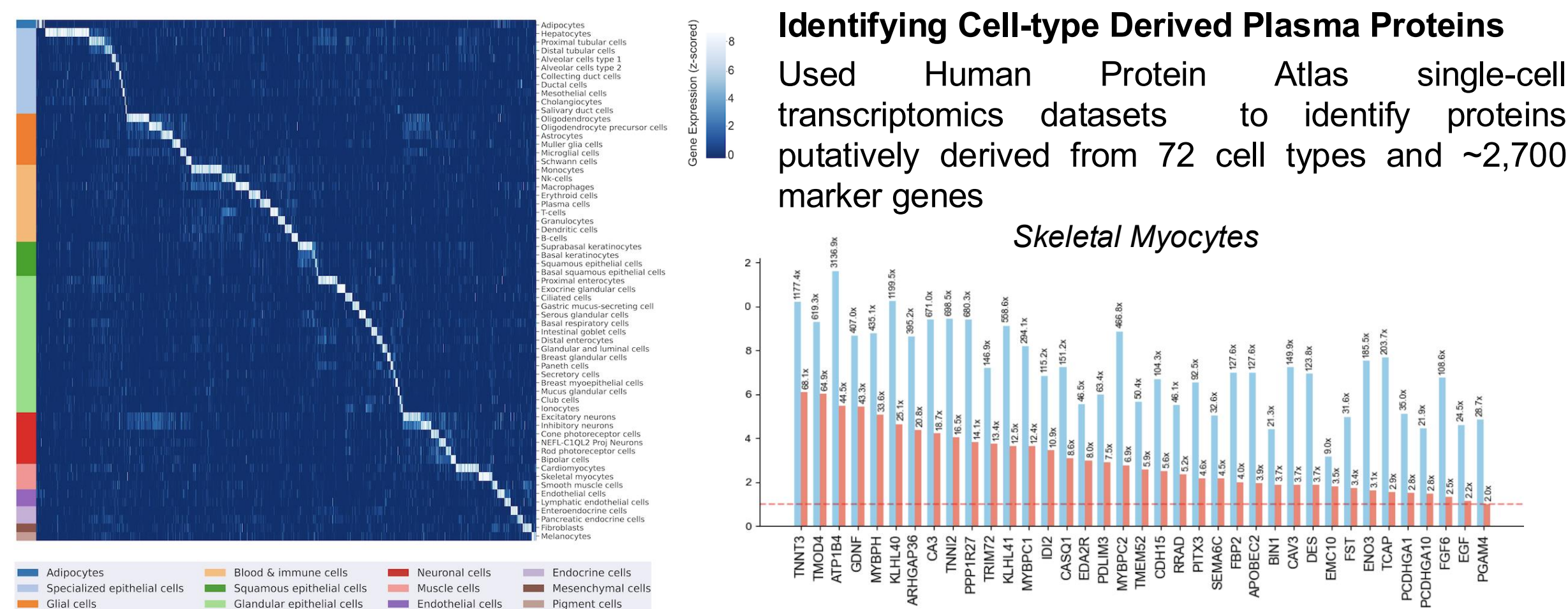
Introduction

Aging is a complex process that affects individuals from the scale of the whole body to the cell.¹ In this work, we examine the aging trajectories of over 40 cell types using 7,000 proteins measured in the blood of 60,542 people with machine learning models.



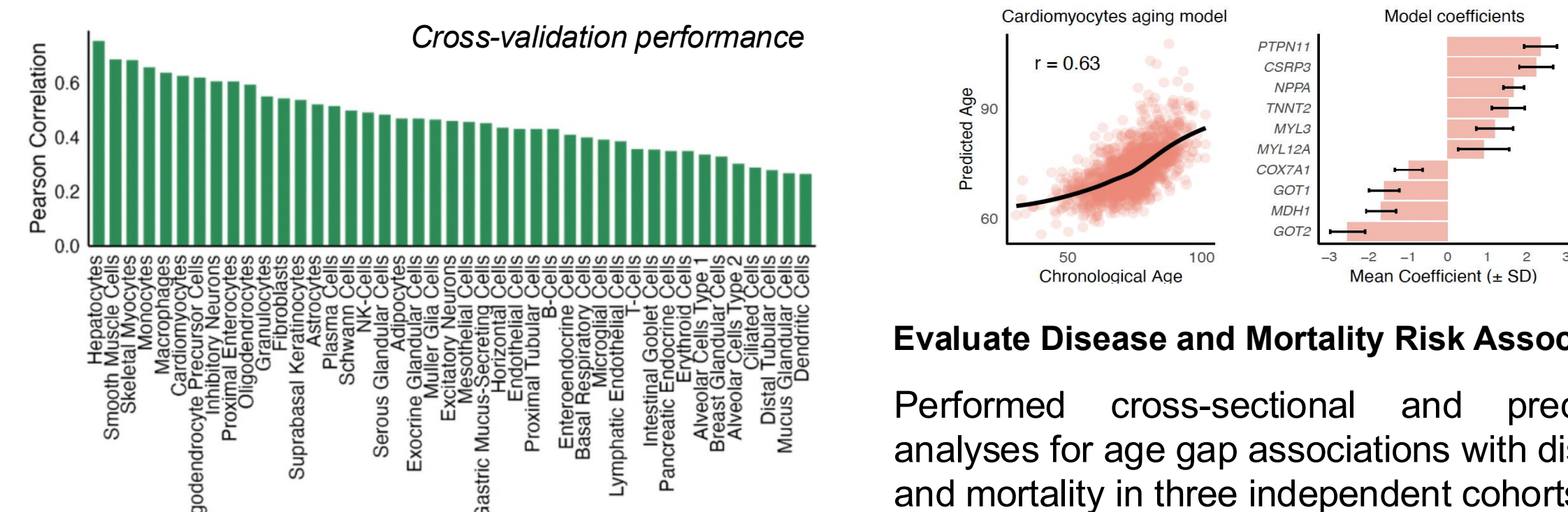
Our results suggest cellular aging is heterogenous between people and individual cell-types. Aging maps to disease risk in a cell-type specific manner. The accumulation of aged cell types is linked to increased mortality risk. Circulating cellular aging signatures emerge as robust disease predictors, comparable to known risk factors.

Methods



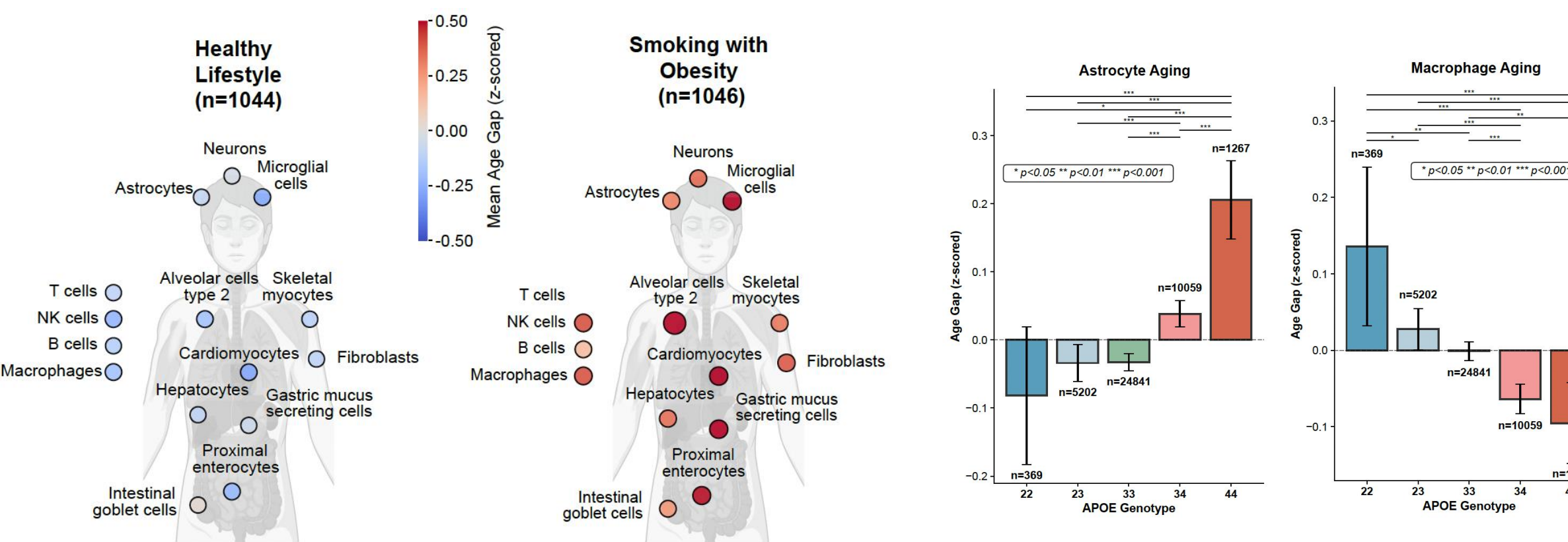
Machine Learning Models to Estimate Cellular Aging

Trained elastic net machine learning models using mapped signatures from both Olink (2,923 proteins measured) and Somalogic (7,289 proteins measured) to generate age gaps. Imputation for missing values was performed using KNN in UK Biobank. Training was performed in GNPC and UK Biobank.



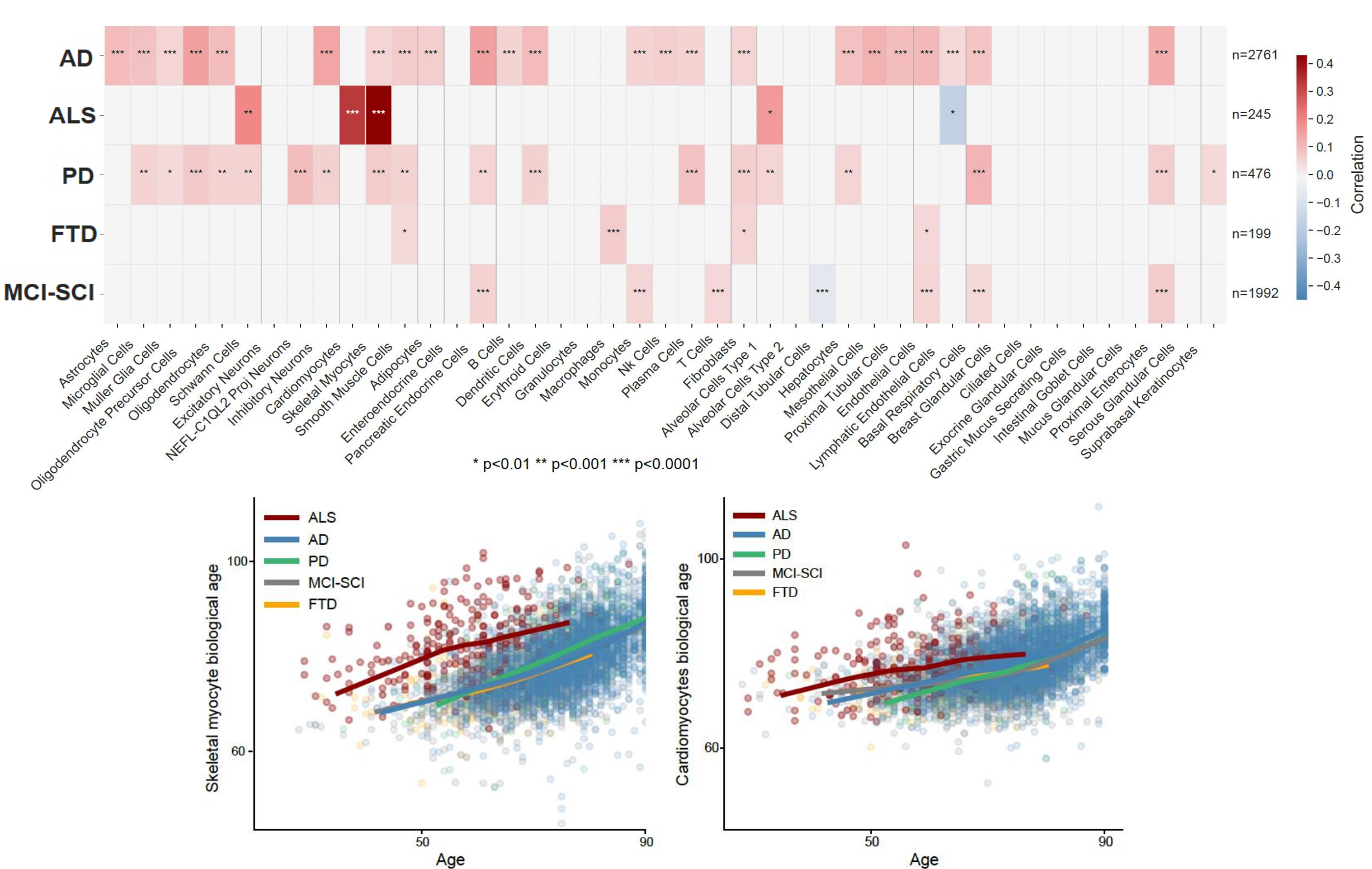
Experimental

Heterogenous Cellular Aging Patterns by Lifestyle and APOE Genotype



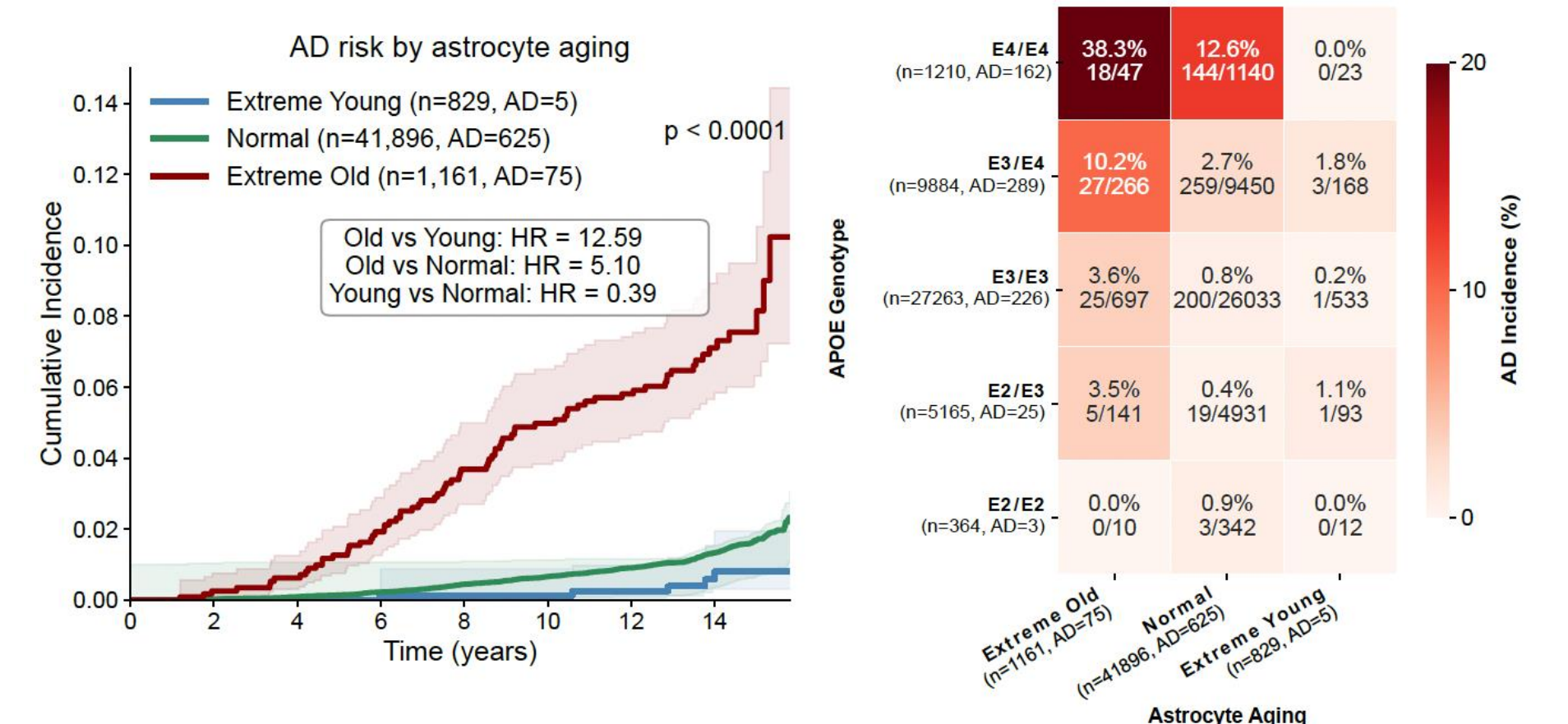
Accelerated cell-type aging is linked to detrimental lifestyle habits (left); astrocytes and macrophages display contrasting aging patterns by APOE genotype (right).

ALS Maps to Accelerated Skeletal and Cardiomyocyte Aging



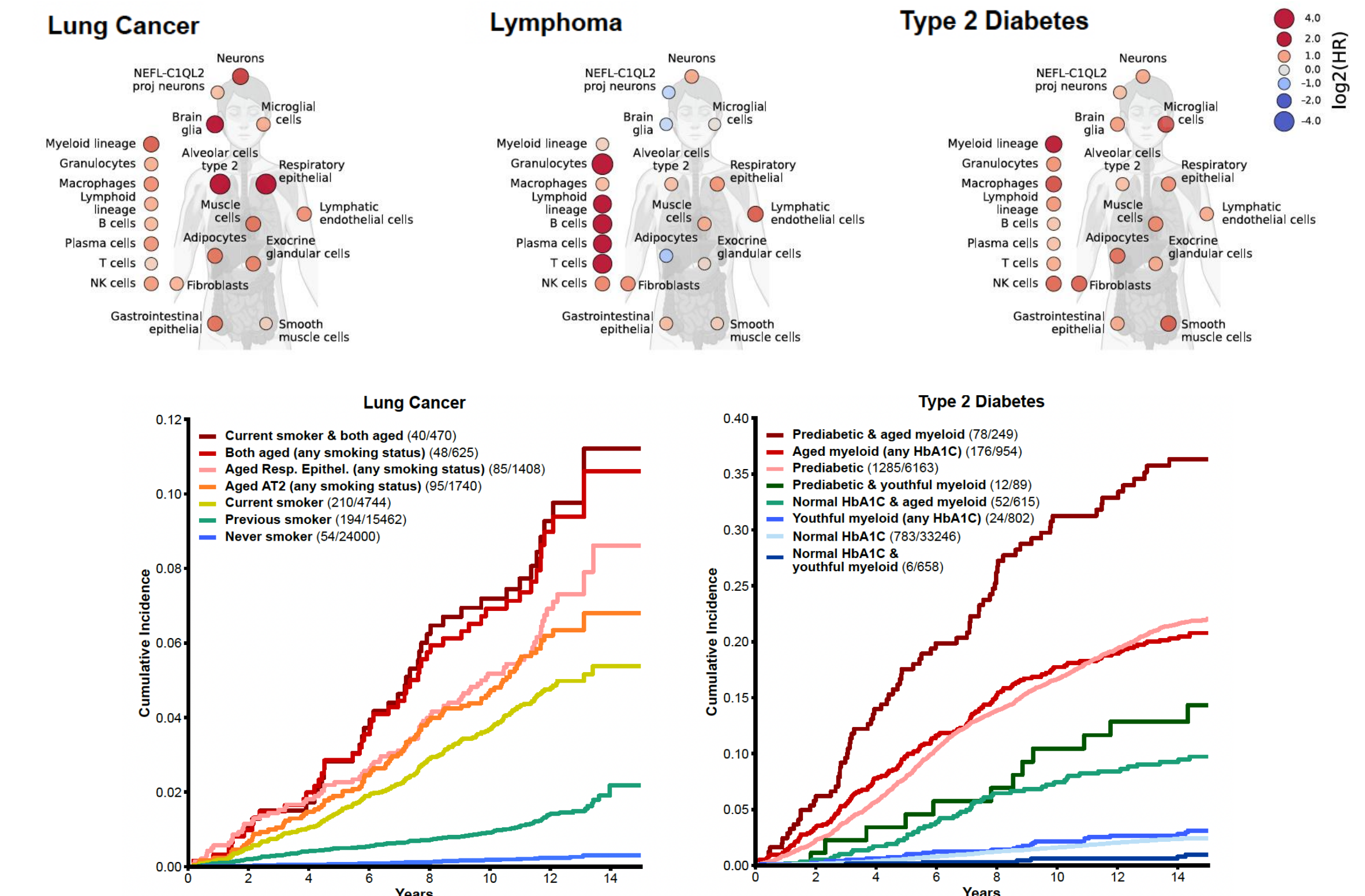
Point biserial correlation analysis of neurodegenerative disease diagnosis and cell-type age gaps in GNPC (top); skeletal and cardiomyocyte biological age is elevated in individuals with amyotrophic lateral sclerosis (ALS) (bottom).

Youthful Astrocyte Aging is Linked to Reduced AD Incidence in APOE4 Carriers



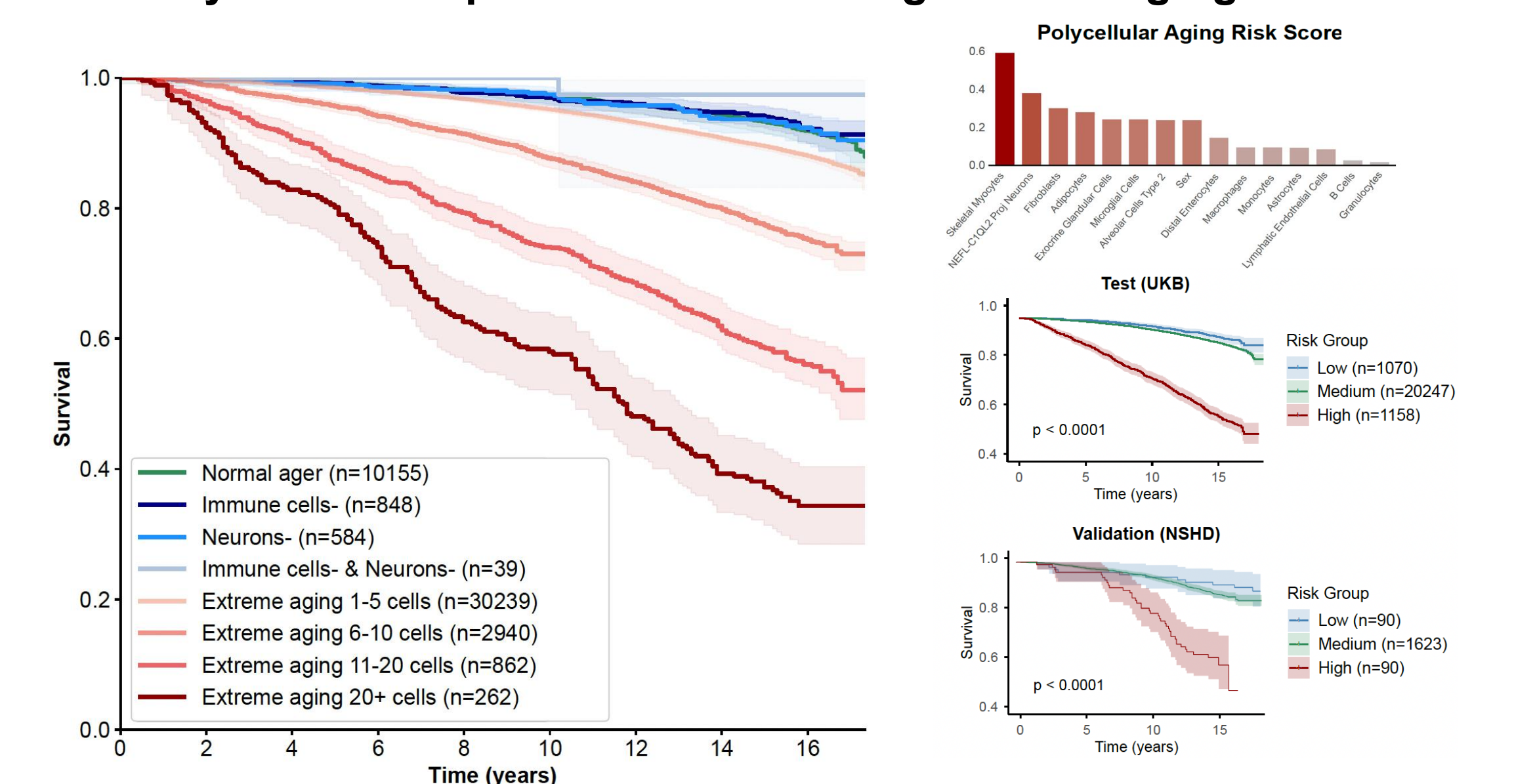
Astrocyte aging identifies a resilient population of APOE4 homozygotes in the UKB.

Blood Plasma Encodes Cellular Aging States that Predict Disease



Plasma proteins forecast chronic disease in a cell-type specific manner over 15-years of follow-up in the UK Biobank (top). Cell-type aging identifies smokers at a 58% higher lung cancer risk and distinguishes normoglycemic individuals with elevated risk of developing type 2 diabetes (bottom).

Mortality Risk is Amplified with Increasing Cellular Aging Burden



Accumulation of accelerated aged cell types amplifies mortality risk, whereas youthful neuronal and immune cells promote longevity. A polycellular risk score representing a composite of cell types stratifies well- and poorly surviving populations across independent cohorts and proteomics platforms.

In the future, we wish to refine our strategy for mapping plasma proteins to individual cell types using experimentally-derived evidence and/or deconvolution approaches. With particular interest in ALS and AD, we wish to stress-test astrocyte, skeletal- and cardiomyocyte models and measure their utility alongside known risk factors. We are curious to explore whether these models can be mapped to pathological mechanisms of disease.

[1] Oh, H., Rutledge, J., et al. (2023). Organ aging signatures in the plasma proteome track health and disease. *Nature*, 624, 164-172.