**Figure 1. CVM Co-occurrence and SPARE-CVM dimensions** **Center:** Venn diagram of CVM co-occurrence in the training dataset indicates a highly heterogeneous training dataset. **Sub-figures 1 A-D** show 3 dimensional projections of the SPARE-CVMs to illustrate the influence of single- vs multi-morbidity in the corresponding SPARE scores. Each ellipsoid represents the SPARE-CVM scores which were closest to the mean for the corresponding combination of CVM statuses. In each plot, participants who were CVM- for all 3 CVMs (All-) had the lowest SPARE-CVMs while those with CVM+ status for the 3 CVMs (All+) had the highest SPARE-CVMs. Participants with CVM+ in only one of the 3 CVMs had higher scores in the corresponding SPARE-CVM dimension. For co-occurring sets of CVMs, please refer to Figure S2.

A computer screen shot of a diagram

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**Figure 2:** **SPARE-CVM spatial sMRI patterns.** Volumes of gray matter (GM), white matter (WM), and white matter hyperintensities (WMH) significantly associated (p<0.001, Bonferroni corrected for multiple comparisons) with SPARE-CVMs. Regression coefficients from the multiple regression analyses are displayed on 3D surface maps for regional GM volumes, and glass brain plots for lobar volumes of WM and WMH. Hot colors (red) indicate a positive association, i.e., higher volumes associated with higher SPARE-CVMs, and cold colors (blue) indicate a negative association, i.e., lower volumes associated with higher SPARE-CVMs.

A diagram of the brain

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**Figure 3: Individualized SPARE-CVMs. Illustration of individualized SPARE-HTN, SPARE-OB and SPARE-T2D scores as** 3 dimensional projections for participants with single- vs multi-morbidity of the underlying CVMs. Each circle (1-8) represents the SPARE-CVM scores of an individual with the lines starting at origin - 0,0,0. Participants who were CVM- for all 3 CVMs (1,2 All-) had the lowest SPARE-CVMS while those with CVM+ status for the 3 CVMs (All+ 6, 7, and 8) had the highest SPARE-CVMs. Participants with CVM+ in only one of the 3 CVMs had higher scores in the corresponding SPARE-CVM dimension.

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**Figure 4:** SPARE-CVM measures show better sensitivity to CVM-related changes than traditionally employed volumetric measures and machine-learning based imaging markers for Alzheimer’s disease and brain age. A) Heat-map showing the Cohen’s d effect sizes of imaging markers (columns) for differentiating CVM+ from CVM- participants for each CVM (rows). Highlighted in blue are the effect sizes for the one-to-one correspondence between SPARE model and target CVM. B) Distribution of imaging markers and SPARE-CVM indices across clinical stages. Sub-clinical (undiagnosed) stages defined by continuous clinical measures were not part of the training dataset (see Methods section). Abbreviations: SPARE-: Spatial Patterns of Abnormality Related to-, AD: Alzheimer’s Diseases, BA-Gap: Brain Age gap, CVM: Cardiovascular and Metabolic risk factors, GM: Gray Matter, WMH: White Matter Hyperintensities, L-Ventricles: Lateral Ventricles.

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| A) Effect sizes for imaging measures from the nested cross-validated training sample  A screenshot of a computer  Description automatically generated |
| B) Plots showing the distributions of imaging markers across clinical stages  A screenshot of a chart  Description automatically generated |

**Figure 5:** Separability of SPARE-CVMs across mid-older ages

Plot showing the effect sizes of SPARE-CVMs across different mid-older age windows.

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**Figure 6:** **Association between cognitive performance and SPARE-CVMs or CVM status.**

The results of the multivariate regression models predicting cognitive performance in UKBiobank using SPARE-CVMs or CVM status, while adjusting for the confounding covariates of study, age, sex, and number of years of education, are shown below. The scatter points (circles) in the figure represent the regression coefficients for each model. The lines show the limits of the 95% confidence interval for each coefficient. SPARE-CVMs were corrected for confounding covariates age, sex and DLICV. Abbreviations- DSST: Digit symbol substitution test, TMT-A/B: Trail making test -A/B; P-Mem: Prospective memory. False discovery rate corrected p-values are indicated by: \* p< 0.05, \*\* p < 0.01, ꝉ p< 0.001, and ꝉ ꝉ p<<0.001. For similar analyses on other cohorts in iSTAGING, please refer to Figure S-10.

A diagram of different colors

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