

Description of Additional Supplementary Files:

Supplementary Data 1: Characteristics of the study participants. This table provides data on key demographic variables for all included participants/samples. For longitudinal studies in ADNI and ROS/MAP, participant numbers are provided for all included follow-up time points (coded numerically in years, i.e. 0 = baseline, 1 = 1 year follow-up and so on). * Numbers after filtering out rare genotype combinations. ** Numbers for the last visit prior to death.

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; Mayo LOAD = Mayo Clinic Study of Late-Onset Alzheimer's Disease; ROS/MAP = Religious Order Study/Ruch Memory and Aging Project; KORA = Kooperative Gesundheitsforschung in der Region Augsburg study; AGES-RS = Age, Gene/Environment Susceptibility – Reykjavik Study; AGES-RS II = AGES-RS follow-up visit after 5 years; CN = cognitively normal; EMCI = early mild cognitive impairment (MCI); LMCI = late MCI; MCI+ = MCI plus other pathology; AD = clinical Alzheimer's disease (unless otherwise specified for Mayo LOAD participants); AD+ = AD plus other pathology; NP diagnosis = diagnosis based on AD neuropathology; ADAS-Cog. 13 = 13-item AD assessment scale-cognitive subscale; CSF = cerebrospinal fluid; FDG-PET = [18F]fluorodeoxyglucose-positron emission tomography; CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

Supplementary Data 2: List of acylcarnitine species included in the study and assessed quality metrics. Key quality control statistics, including the intraclass correlation coefficient (ICC), the coefficient of variation (CV) in repeated measurements, and the total percentage of missing measurements (imputed using kNN imputation) across study samples are provided.

Supplementary Data 3: Association results of cluster pairs with clinical and demographic variables. Cluster pairs, defined by branching points identified in columns B and C, along with their respective sample sizes are displayed. Associations with an adjusted P-value ≤ 0.05 were deemed significant. Total and actual sample sizes and type of statistical test are provided. All tests were two-sided and both raw and adjusted P-values are reported.

Supplementary Data 4: Targeted sensitivity analysis of significant association results presented in Supplementary Data 3. Associations were adjusted for age, sex, body mass index, copies of APOE $\epsilon 4$ and years of education. Total and actual sample sizes and type of statistical test are provided. All tests were two-sided and raw P-values are reported.

Supplementary Data 5: Previously reported acylcarnitine-associated SNPs and top-associated acylcarnitine species. This table lists SNPs reported by Shin et al. (Nature Genetics, 2014, DOI: 10.1038/ng.2982) as genome-wide significantly associated with acylcarnitines. Annotated predicted causal genes as reported in the study are provided, along with the information if the respective SNP has been included in epistatic analysis here.

Supplementary Data 6: Results of targeted genetic association analysis between acylcarnitines and previously reported SNPs in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Sex- and age-adjusted additive genetic association results are provided for all 32 variants (cf. Supplementary Data 5) and all 23 acylcarnitines included in the subgroup identification analysis. All tests were two-sided and both raw and FDR-adjusted P-values are reported.

Supplementary Data 7: Association results of cluster pairs with the 32 acylcarnitine-associated SNPs. This table presents branching points defining cluster pairs, sample sizes, and associations with the 32 single SNPs (additive tests). Associations with an adjusted P-value ≤ 0.05 in logistic regression analysis were considered significant. All tests were two-sided and both raw and FDR-adjusted P-values are reported.

Supplementary Data 8: Estimates of variance explained by single SNPs significantly associated with the clustering. This table provides R^2 values at the single SNP level (additive tests) for each significant association between single SNPs and branching points.

Supplementary Data 9: Association results of cluster pairs with genetic proxies (single SNPs and epistatic models) for acylcarnitines. This table presents cluster pairs defined by branching points and associations significant at an adjusted P-value ≤ 0.05 (genotypic tests). It also includes estimates of variance explained by single SNPs/SNP combinations significantly associated with the clustering. As we used a different genetic model for association testing, R^2 values for single SNPs can slightly deviate from results in Summary Table 8.

Supplementary Data 10: Association P-values of genetic proxies for acylcarnitines with Alzheimer's disease, A-T-(N)-(C) measures, and AD neuropathologies. This table includes information on the acylcarnitine associated with included SNPs, single SNPs/epistatic models used, and raw association P-values from two-sided tests for AD and biomarkers in ADNI, ROS/MAP and the Mayo LOAD study.

Supplementary Data 11: Cross-validation results of the age predictor in the Cooperative Health Research in the Region of Augsburg (KORA) study. This table provides statistics for 10-fold cross-validation with 3 repeats, with root mean square error (RMSE), explained variance (R^2) and mean absolute error (MAE) values.

Supplementary Data 12: Pearson correlation between predicted bioenergetic age and chronological age in KORA (training set), ADNI, and AGES-RS. Correlations are also provided separately for different diagnostic groups in ADNI and AGES-RS. Correlation tests were two-sided and raw P-values are provided.

Supplementary Data 13: Association results of trait-associated cluster pairs with chronological age, predicted bioenergetic age, and their delta. This table includes the association data underlying Figure 3, emphasizing the differences in predicted bioenergetic ages for all relevant groups. Results from two-sided t-tests with equal variance are reported, including sample sizes per group and raw P-values.

Supplementary Data 14: Association results of predicted bioenergetic age in ADNI with A-T-(N)-(C) measures. Results are provided for all ADNI participants and separately for the diagnostic groups and participants in the resilience cluster 7. Statistics were obtained using two-sided association tests using covariate-adjusted linear regression and raw P-values are reported.

Supplementary Data 15: Association results of predicted bioenergetic age in AGES-RS with AD and biomarkers. Results are provided for cognitive scores, grey matter volume, and diagnosis at baseline, as well as diagnosis after 5 years follow up (AGES-RS II). All tests were two-sided (covariate-adjusted linear regression), raw P-values are reported, and sample sizes for group comparisons are included.

Supplementary Data 16: Associations of longitudinal cognitive trajectories with baseline predicted bioenergetic age and the genetic interaction. This table includes results for baseline predicted bioenergetic age, the binary allelic grouping of the two-SNP interaction model (c.f. Supplementary Data 17), the threefold interaction in ADNI for the contrast of bioenergetic age percentiles within the protective genotype grouping, and the replication of the SNP interaction in ROS/MAP. Results from two-sided association tests using linear mixed models for repeated measurements with raw P-values and available degrees of freedom are reported. * Results are provided for the contrast of high vs. low bioenergetic age within the generally protective genotype grouping.

Supplementary Data 17: Associations of allelic groupings of ADNI participants for all common allele combinations of SNPs rs17806888 and rs924135 across three cognitive scores. Results are from two-sided association tests using linear mixed models for repeated measurements with raw P-values for memory, executive function (Exec. function), and the 13-item AD Assessment Scale - Cognitive Subscale (ADAS-Cog. 13). Results are ranked by the meta-analysis P-value obtained using Fisher's sum of logs method.

Supplementary Data 18: Characteristics of ADNI participants selected for the simulated clinical trial at baseline. * P-values were obtained using the Wilcoxon Rank Sum Test for continuous variables and using the Fisher Exact Test for categorical variables. All tests were two-sided and raw P-values are reported. † Global Clinical Dementia Rating (CDR) scores range from 0 to 3, with higher scores indicating greater impairment. a Scores on the CDR-Sum of Boxes (CDR-SB) range from 0 to 18, with higher scores indicating greater impairment. b Scores on the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog. 13)

range from 0 to 85, with higher scores indicating greater impairment. c Scores on the Mini-Mental State Examination (MMSE) range from 0 to 30, with lower scores indicating greater impairment. d Scores on the Functional Activities Questionnaire (FAQ) range from 0 to 30, with higher scores indicating greater impairment.

Supplementary Data 19: Coefficients of the prediction model for bioenergetic age. These coefficients are to be used with metabolite concentrations scaled to zero mean and unit variance in the reference set.