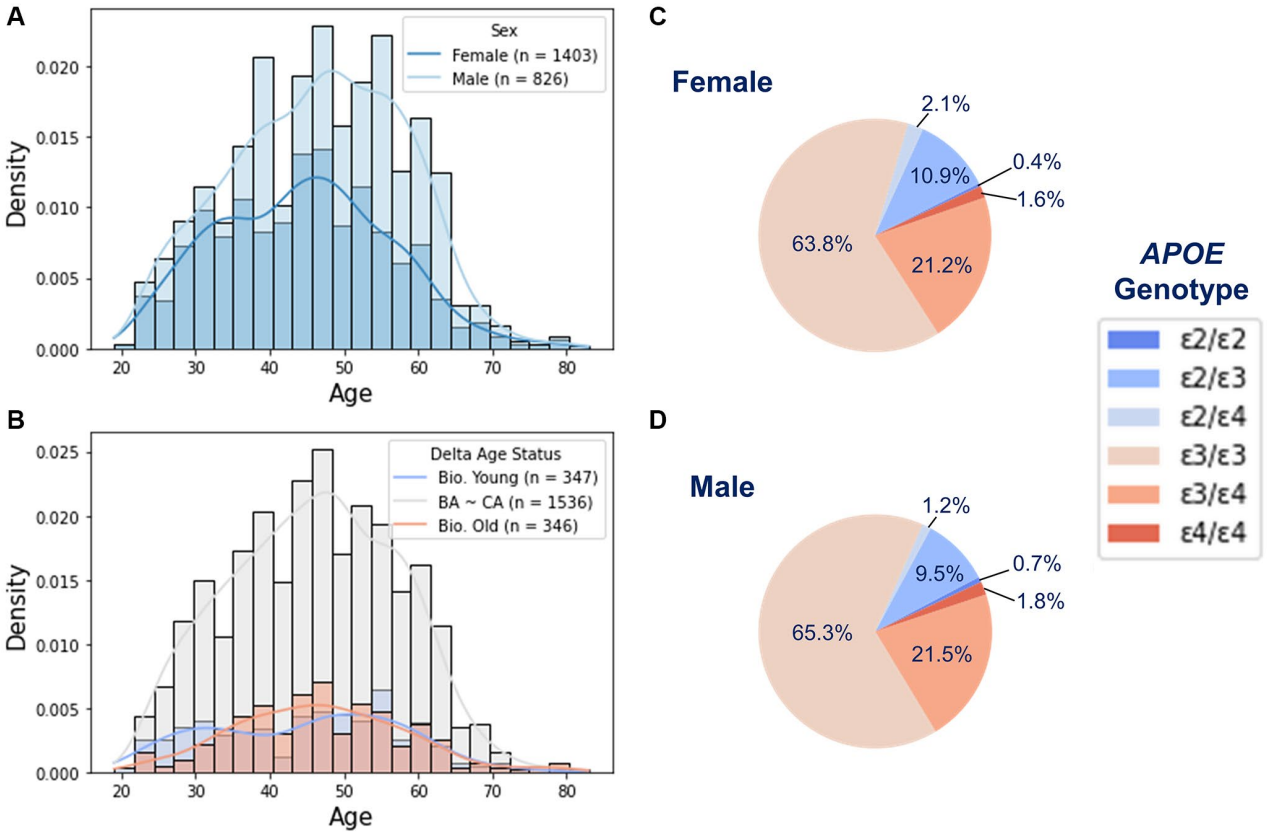
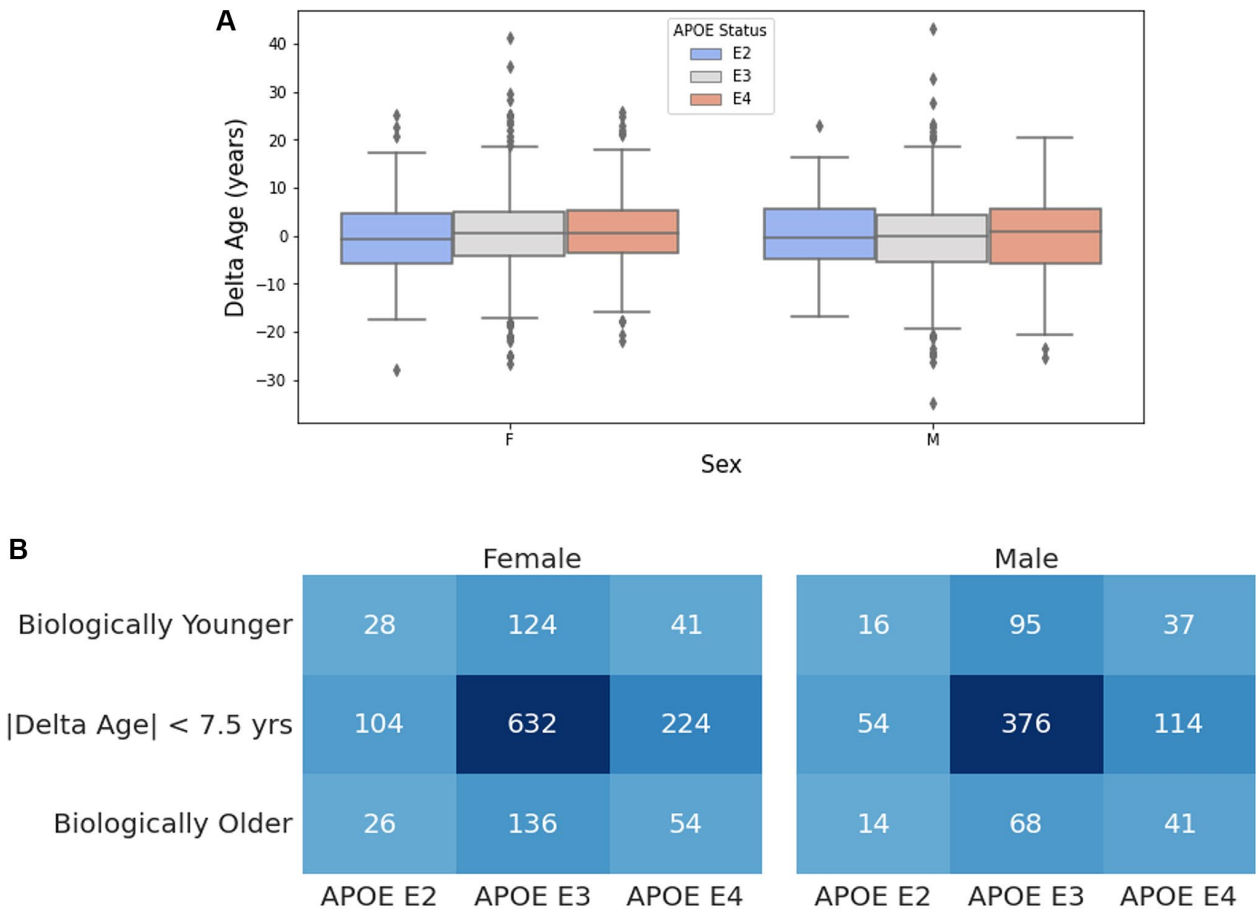
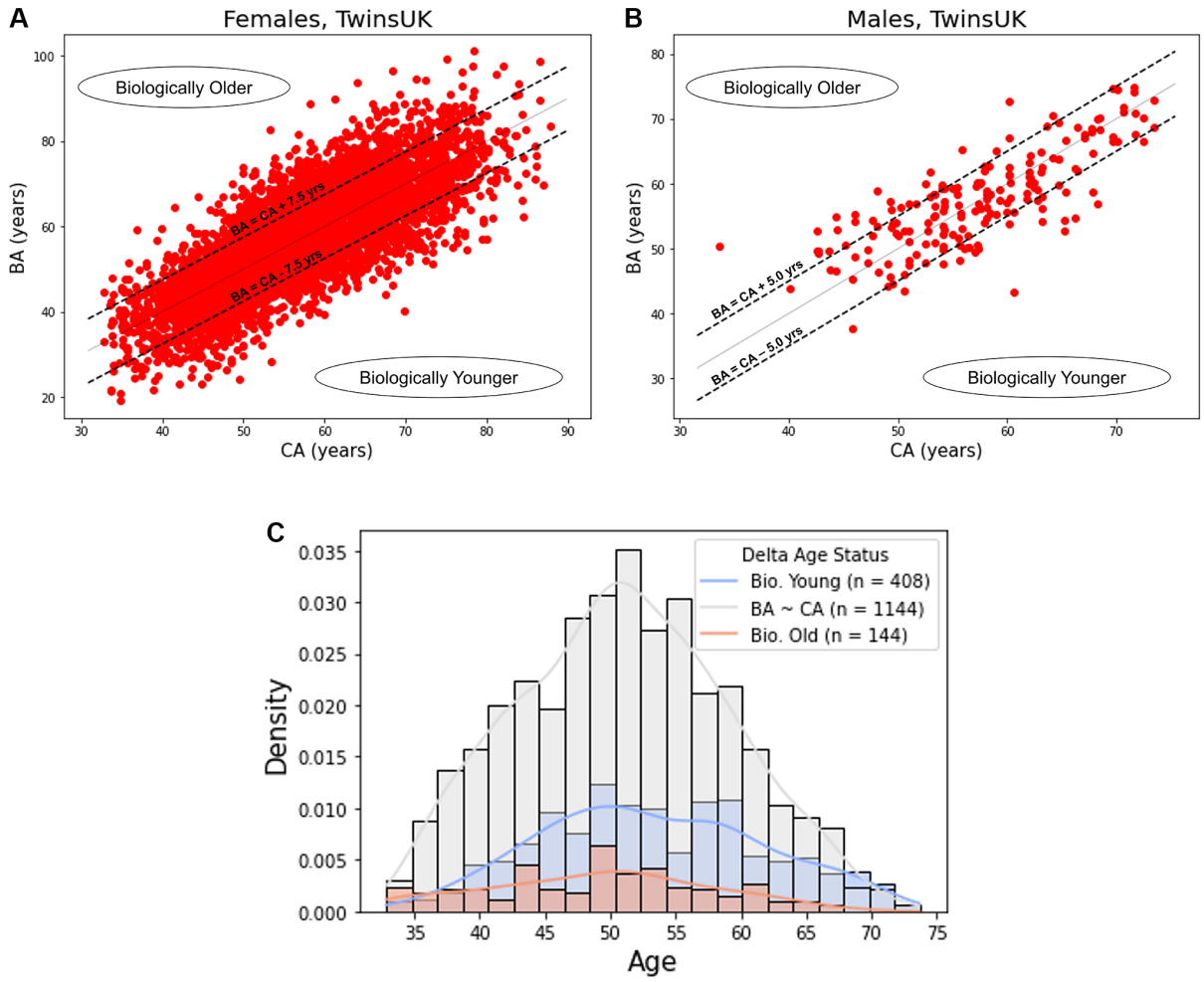
SUPPLEMENTARY FIGURES



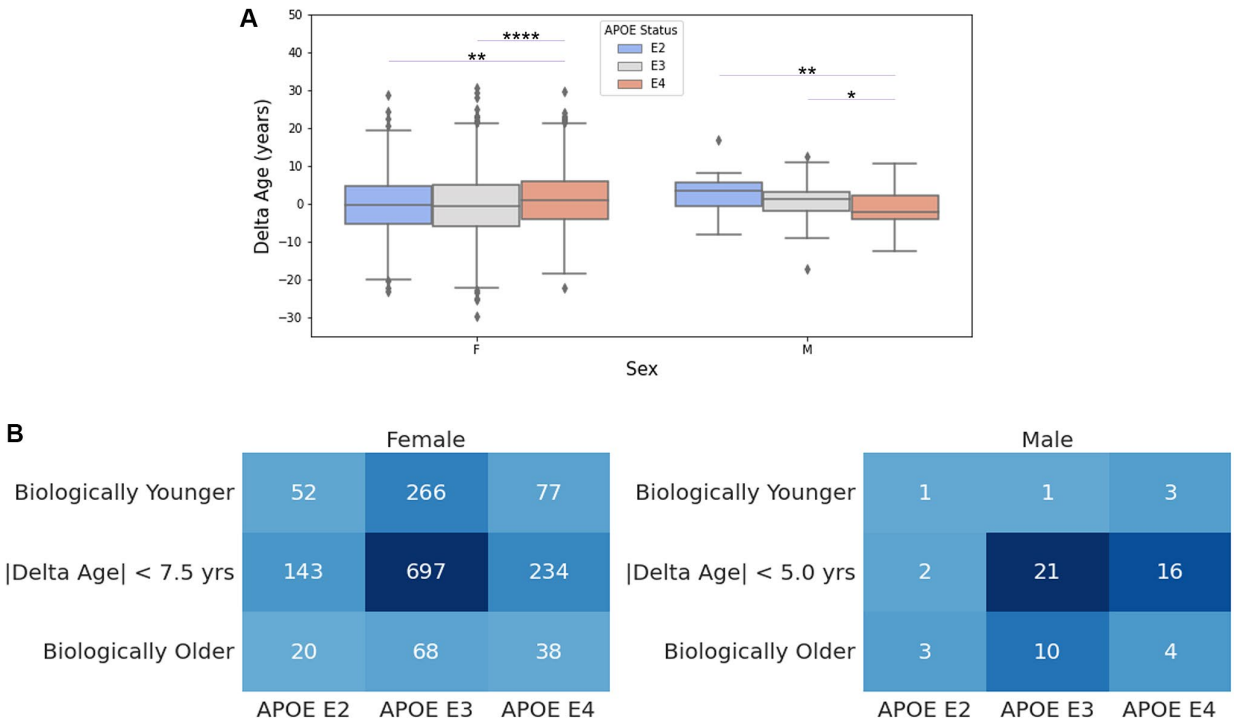
Supplementary Figure 1. The Arivale cohort contains a range of community dwelling individuals spread across ages, delta age statuses, and *APOE* genotypes. (**A**, **B**) Density histograms of baseline chronological ages in the Arivale cohort stratified by sex (**A**) and delta age status, with biologically young and old defined as having a biological age 7.5 years younger or older than chronological age, respectively (**B**). The lines indicate the kernel density estimates. (**C**, **D**) Pie charts displaying *APOE* genotype frequencies in the female (**C**) and male (**D**) Arivale participants. Presented is the baseline data used in interaction analyses.



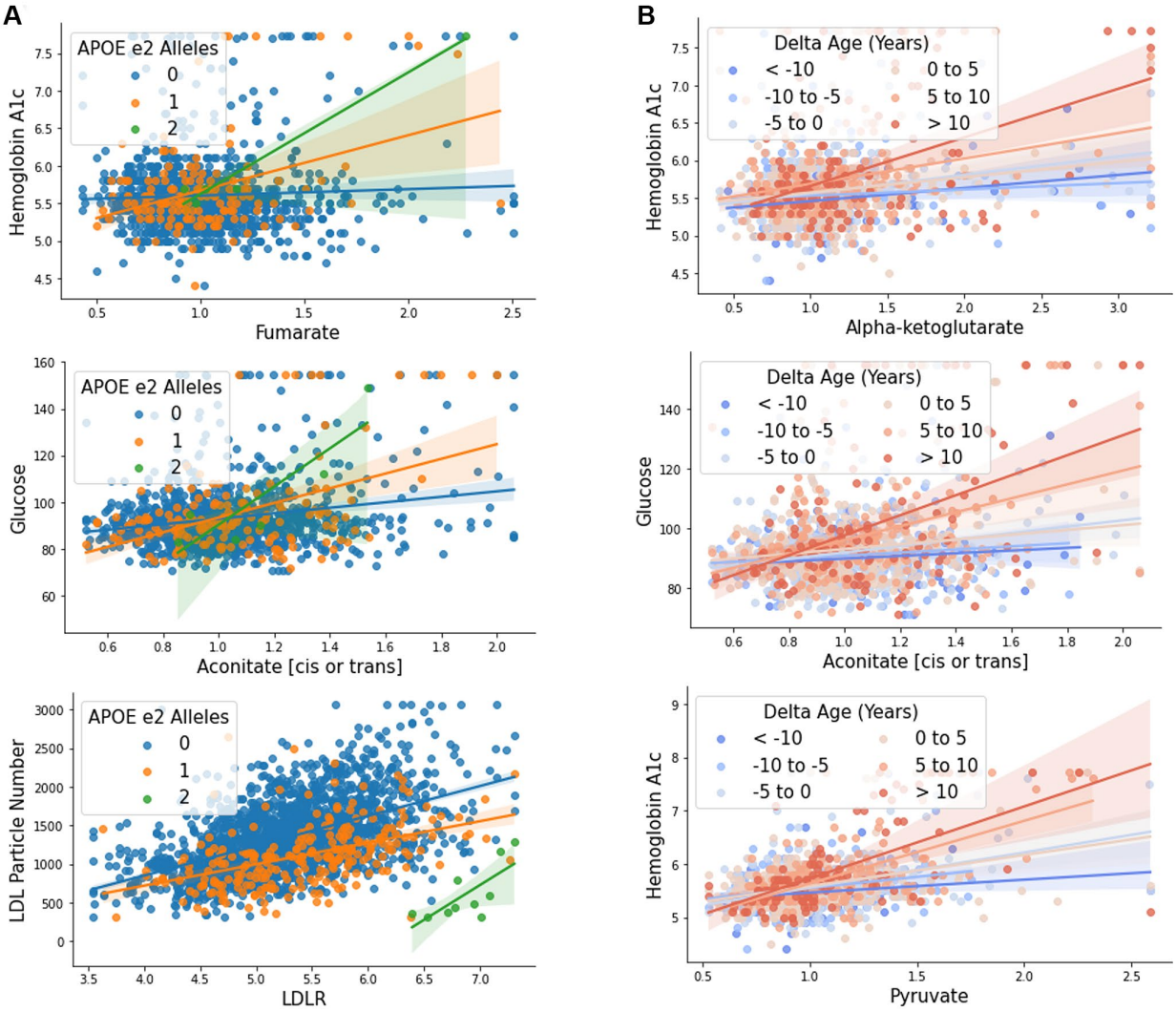
Supplementary Figure 2. Delta age and delta age-based stratifications are not significantly different across APOE statuses for either males or females in Arivale. (**A**) Box plot of delta age across APOE statuses. Pairwise Mann–Whitney *U*-tests between APOE statuses within male and female showed non-significant *p*-values (smallest *p*-value = 0.062 between female E2 and E4). *n* = 158 (Female E2), *n* = 892 (Female E3), *n* = 319 (Female E4), *n* = 84 (Male E2), *n* = 539 (Male E3), *n* = 192 (Male E4). (**B**) Counts of individuals in APOE and delta age categories, stratified by sex. The chi-squared tests yielded *p* = 0.59 for females and *p* = 0.041 for males.



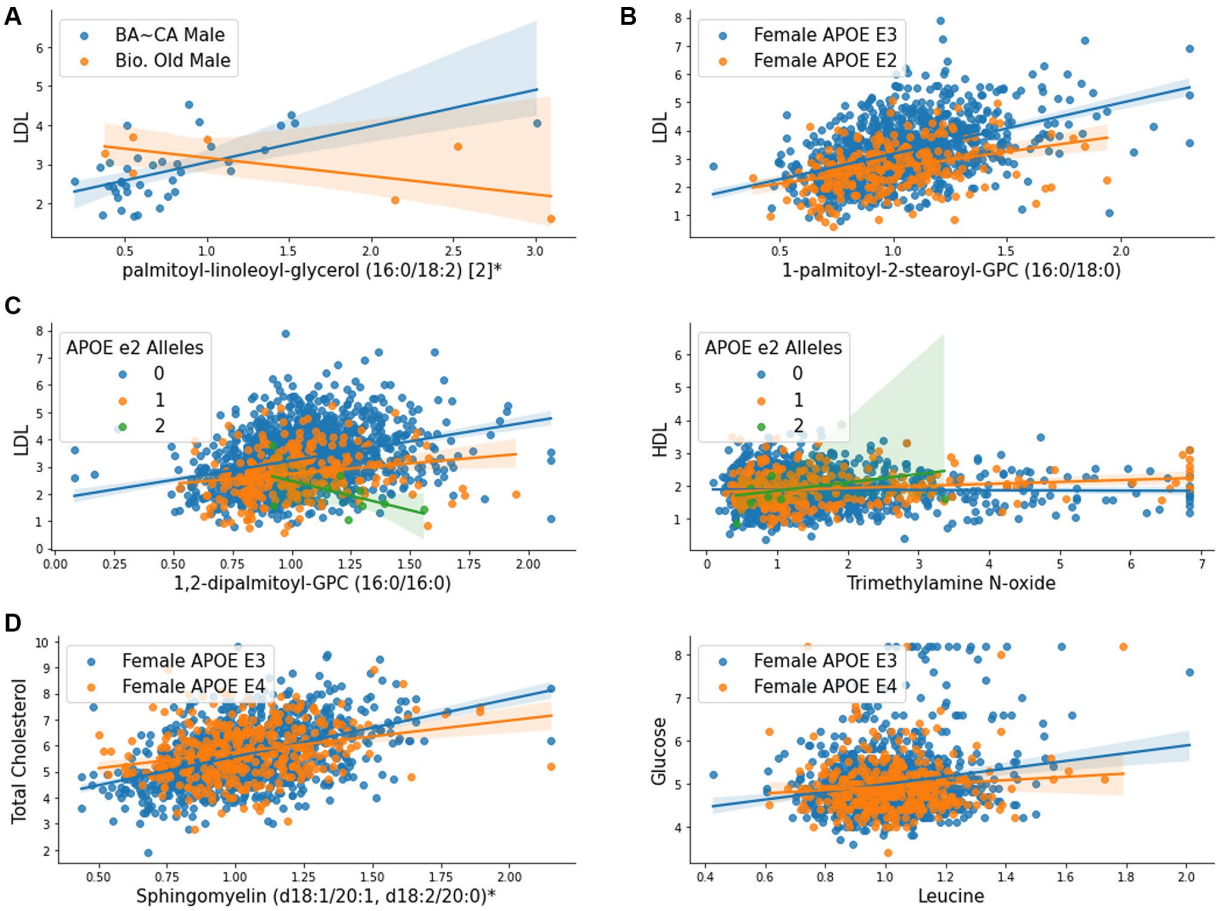
Supplementary Figure 3. Metabolomic BA was predicted by fitting a model to TwinsUK data. (**A**, **B**) The scatterplot of BA and CA for female (*n* = 1,635 individuals, Pearson's r = 0.778) (A) and male (*n* = 61, r = 0.776) (**B**) TwinsUK participants. The solid line indicates BA = CA, and the dotted lines indicate cutoffs for defining the Biologically Younger and Older groups. See Methods for model details. (**C**) A density histogram of baseline chronological ages in the TwinsUK cohort stratified by delta age status. The lines indicate the kernel density estimates.



Supplementary Figure 4. Delta age is significantly different across APOE statuses in the TwinsUK cohort. (**A**) Box plot of delta age across APOE statuses for all TwinsUK participants, including longitudinal. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.00001$ based on pairwise Mann-Whitney *U*-tests. $n = 641$ (Female E2), $n = 3050$ (Female E3), $n = 1043$ (Female E4), $n = 18$ (Male E2), $n = 95$ (Male E3), $n = 69$ (Male E4). (**B**) Counts of individuals in APOE and delta age categories at baseline visit, stratified by sex. The chi-squared tests yielded $p = 0.26$ for females and $p = 0.08$ for males.



Supplementary Figure 5. Inter-omic associations are modified by ε2 allele dosage and continuous delta age. Scatter plots of inter-omic analyte pairs with associations significantly modified by *APOE* ε2 allele dosage (**A**) and by delta age (**B**). Line indicates simple linear regression, with shading indicating the 95% confidence interval.



Supplementary Figure 6. Inter-omic associations involving lipids are modified by APOE and delta age statuses in the TwinsUK validation cohort. Scatter plots of inter-omic analyte pairs with associations significantly modified by biological oldness in males (**A**), APOE E2 in females (**B**), the APOE ε2 allele (**C**), APOE E4 in females (**D**) in the TwinsUK cohort. Line indicates simple linear regression, with shading indicating the 95% confidence interval.