

Description of additional supplementary files

File name: Supplementary Data S1

Description: The source data behind the frailty index panel in Figure 1B. (A) Frailty index scores. (B) Body temperature measurements.

File name: Supplementary Data S2

Description: Plasma lipidomics differential abundance and enrichment analyses. (A) Limma significantly regulated lipids between control *APOE3* and control *APOE4* plasma by lipidomics (FDR <5%). (B) Limma significantly regulated lipids between control *APOE3* and 17 alpha-estradiol treated *APOE4* plasma by lipidomics (FDR <5%). (C) LION functional enrichment analysis for differential lipids between control *APOE3* and *APOE4* plasma higher in *APOE3*. (D) LION functional enrichment analysis for differential lipids between control *APOE3* and *APOE4* plasma higher in *APOE4*.

File name: Supplementary Data S3

Description: Microglia bulk RNA-seq differential expression and enrichment analyses. (A) DESeq2 significantly regulated genes between control *APOE3* and control *APOE4* microglia by RNA-seq (FDR <5%). (B) DESeq2 significantly regulated genes between control *APOE3* and 17 alpha-estradiol treated *APOE4* microglia by RNA-seq (FDR <5%). (C) DESeq2 significantly regulated genes between control *APOE3* and 17 alpha-estradiol treated *APOE3* microglia by RNA-seq (FDR <5%). (D) DESeq2 significantly regulated genes between control *APOE4* and 17 alpha-estradiol treated microglia by RNA-seq (FDR <5%). (E) GSEA Gene Ontology (FDR <5%) for differential regulation between control *APOE3* and control *APOE4* microglia by RNA-seq. (F) GSEA Gene Ontology (FDR <5%) for differential regulation between control *APOE3* and 17 alpha-estradiol treated *APOE4* microglia by RNA-seq. (G) GSEA Gene Ontology (FDR <5%) for differential regulation between control *APOE3* and 17 alpha-estradiol treated *APOE3* microglia by RNA-seq. (H) GSEA Gene Ontology (FDR <5%) for differential regulation between control *APOE4* and 17 alpha-estradiol treated *APOE3* microglia by RNA-seq

File name: Supplementary Data S4

Description: The source data behind Figures 1, 2, 3 and 6, and Supplementary Figures 1, 2 and 4. (A) Source data to Figure 1. (B) Source data to Figure 2. (C) Source data to Figure 3. (D) Source data to Figure 6. (E) Source data to Supplementary Figure 1. (F) Source data to Supplementary Figure 2. (G) Source data to Supplementary Figure 4.

File name: Supplementary Data S5

Description: Statistics of all comparisons. All data were checked for normal distribution using the Shapiro-Wilk test. If a dataset was found not normally distributed, Mann-Whitney tests were used.