

## Description of Additional Supplementary Files

**File name:** Supplementary Data 1

**Description:** Gene-Tissue Expression (GTEX) transcripts per million (TPM) values for apolipoprotein B (APOB) for tissues displayed in Fig. 2.

**File name:** Supplementary Data 2

**Description:** Meta-analytic Mendelian randomization (MR) results for 103 nuclear magnetic resonance (NMR)-measured circulating metabolites on healthspan.

**File name:** Supplementary Data 3

**Description:** Mendelian randomization (MR) single-nucleotide polymorphism (SNP) data (for calculating the Wald ratios that were meta-analyzed in Supplementary Data 2) for 103 nuclear magnetic resonance (NMR)-measured circulating metabolites on healthspan.

**File name:** Supplementary Data 4

**Description:** Detailed meta-analytic Mendelian randomization (MR) results (bottom; below the green bar at line 16; columns W-A0) for Kettunen apolipoprotein B (APOB) (outliers removed) on healthspan.

**File name:** Supplementary Data 5

**Description:** Genetic correlations between healthspan, lifespan, low-density lipoprotein cholesterol (LDL), and apolipoprotein (APOB).

**File name:** Supplementary Data 6

**Description:** Meta-analytic Mendelian randomization (MR) results and instrument selection (bottom; below the green bar at line 96; columns V-AT) and SNP data (including Wald ratios; above green line) for UK Biobank-measured (circulating, non-fasted) APOB on healthspan.

**File name:** Supplementary Data 7

**Description:** Meta-analytic Mendelian randomization (MR) results and instrument selection (bottom; below the green bar at line 95; columns V-AT) and SNP data (including Wald ratios; above green line) for UK Biobank-measured (circulating, non-fasted) LDL on healthspan.

**File name:** Supplementary Data 8

**Description:** Multivariable MR results for APOB and LDL on healthspan.

**File name:** Supplementary Data 9

**Description:** Meta-analytic Mendelian randomization (MR) results and instrument selection (bottom; below the green bar at line 137) and SNP data (including Wald ratios; above green line) for UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on Alzheimer's disease.

**File name:** Supplementary Data 10

**Description:** Partial replication with meta-analytic Mendelian randomization (MR) results and instrument selection (bottom; below the green bar at line 138) and SNP data (including Wald ratios; above green line) for UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on Jansen et al. (2019) Alzheimer's disease.

**File name:** Supplementary Data 11

**Description:** Meta-analytic Mendelian randomization (MR) results and instrument selection (bottom; below the green bar at line 128) and SNP data (including Wald ratios; above green line) for UK Biobank-measured (circulating, non-fasted) low-density lipoprotein cholesterol (LDL) on Alzheimer's disease.

**File name:** Supplementary Data 12

**Description:** Exploration of linkage disequilibrium ( $r^2$ ) between apolipoprotein E (APOE) SNPs also associated with apolipoprotein B (APOB) and the APOB instruments on chromosome 19 used as a genetic instrument for the Mendelian randomization (MR) test of APOB on Alzheimer's disease.

**File name:** Supplementary Data 13

**Description:** All summary-data based Mendelian randomization (SMR) results in blood for circulating apolipoprotein B (APOB) levels.

**File name:** Supplementary Data 14

**Description:** Bonferroni significant summary-data based Mendelian randomization (SMR) results in blood for circulating apolipoprotein B (APOB) levels.

**File name:** Supplementary Data 15

**Description:** Bayesian colocalization (coloc) findings for the top 10-most (genome-wide) significant summary-based Mendelian randomization (SMR) of apolipoprotein B (APOB) results (columns Z-AC).

**File name:** Supplementary Data 16

**Description:** Instrument sensitivity analysis removing instruments with outcome p-values  $<0.05$  (outliers detected and removed with RadialMR prior) for the meta-analytic Mendelian randomization (MR) of UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on healthspan.

**File name:** Supplementary Data 17

**Description:** Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on healthspan (outliers removed with RadialMR first).

**File name:** Supplementary Data 18

**Description:** Instrument sensitivity analysis removing instruments with outcome p-values  $<0.05$  (outliers detected and removed with RadialMR prior) for the meta-analytic Mendelian randomization (MR) of UK Biobank-measured (circulating, non-fasted) low-density lipoprotein cholesterol (LDL) on healthspan.

**File name:** Supplementary Data 19

**Description:** Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) low-density lipoprotein cholesterol (LDL) on healthspan (outliers removed with RadialMR first).

**File name:** Supplementary Data 20

**Description:** Instrument sensitivity analysis removing instruments with outcome p-values  $<0.05$  (outliers detected and removed with RadialMR prior) for the meta-analytic Mendelian randomization (MR) of UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on Alzheimer's disease.

**File name:** Supplementary Data 21

**Description:** Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on Alzheimer's disease (no outliers removed with RadialMR).

**File name:** Supplementary Data 22

**Description:** Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on Alzheimer's disease (outliers removed with RadialMR first).

**File name:** Supplementary Data 23

**Description:** Instrument sensitivity analysis removing instruments with outcome p-values  $<0.05$  (outliers detected and removed with RadialMR prior) for the meta-analytic Mendelian randomization (MR) of UK Biobank-measured (circulating, non-fasted) low-density lipoprotein cholesterol (LDL) on Alzheimer's disease.

**File name:** Supplementary Data 24

**Description:** Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) low-density lipoprotein cholesterol (LDL) on Alzheimer's disease (outliers removed with RadialMR first).

**File name:** Supplementary Data 25

**Description:** MR-PRESSO sensitivity analysis of the meta-analytic MR of UK Biobank-measured (circulating, non-fasted) APOB on Jansen Alzheimer's disease (outliers removed with RadialMR first).

**File name:** Supplementary Data 26

**Description:** MRlap sensitivity analysis of the UK Biobank-measured (circulating, non-fasted) apolipoprotein B (APOB) on healthspan.

**File name:** Supplementary Data 27

**Description:** Genetic covariance intercept sensitivity analysis of the summary statistics for Jansen et al. (2019) Alzheimer's disease (AD) with Kunkle et al. (2019) AD, UK Biobank (UKBB) apolipoprotein B (APOB), parental lifespan, healthspan, and UKBB low-density lipoprotein cholesterol (LDL).