**Supplementary Table e-1**: cardiometabolic condition frequencies.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | ***APOE* e4 absent** | ***APOE* e4 present** |
| Diabetes | Yes | 11,081 (5%) | 3,756 (4%) |
|  | No | 220,729 (95%) | 81,962 (96%) |
|  | Missing | 491 | 168 |
| Hypertension | Yes | 61,426 (26%) | 22,814 (27%) |
|  | No | 170,529 (74%) | 62,939 (73%) |
|  | Missing | 346 | 133 |
| Coronary heart disease | Yes | 9,492 (4%) | 4,001 (5%) |
|  | No | 81,752 (96%) | 81,752 (95%) |
|  | Missing | 346 | 133 |

**Supplementary Table e-2**: individual two-way interactions between *APOE* e4 genotype and variables, on cognitive phenotypes.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Partially adjusted | | | | Fully adjusted | | | |
|  | Standardised b | lower | upper | p | Standardised b | lower | upper | p |
| Log reaction time |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex | 0.02 | <0.01 | 0.03 | 0.043 | 0.02 | <0.01 | 0.03 | 0.045 |
| *APOE* e4\*smoking | <0.01 | -0.03 | 0.02 | 0.717 | <0.01 | -0.03 | 0.02 | 0.832 |
| *APOE* e4\*alcohol | 0.01 | -0.01 | 0.03 | 0.415 | 0.01 | -0.01 | 0.03 | 0.522 |
| *APOE* e4\*obesity | -0.04 | -0.09 | 0.01 | 0.140 | -0.03 | -0.09 | 0.02 | 0.204 |
| *APOE* e4\*physical activity | <0.01 | -0.03 | 0.03 | 0.911 | <0.01 | -0.03 | 0.03 | 0.943 |
| Fluid reasoning scores |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex | 0.02 | <0.01 | 0.05 | 0.082 | 0.03 | <0.01 | 0.05 | 0.034 |
| *APOE* e4\*smoking | -0.03 | -0.08 | 0.02 | 0.255 | -0.03 | -0.08 | 0.02 | 0.187 |
| *APOE* e4\*alcohol | 0.02 | -0.02 | 0.06 | 0.224 | 0.03 | -0.01 | 0.06 | 0.162 |
| *APOE* e4\*obesity | 0.04 | -0.06 | 0.13 | 0.459 | 0.04 | -0.05 | 0.13 | 0.437 |
| *APOE* e4\*physical activity | 0.04 | -0.01 | 0.09 | 0.148 | 0.02 | -0.03 | 0.07 | 0.425 |
| Log TMT-A times |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex | <0.01 | -0.03 | 0.03 | 0.985 | <0.01 | -0.03 | 0.03 | 0.977 |
| *APOE* e4\*smoking | -0.01 | -0.07 | 0.06 | 0.877 | <0.01 | -0.06 | 0.07 | 0.989 |
| *APOE* e4\*alcohol | -0.03 | -0.08 | 0.01 | 0.166 | -0.03 | -0.08 | 0.01 | 0.151 |
| *APOE* e4\*obesity | <0.01 | -0.13 | 0.12 | 0.945 | <0.01 | -0.13 | 0.13 | 0.952 |
| *APOE* e4\*physical activity | 0.03 | -0.03 | 0.08 | 0.312 | 0.02 | -0.03 | 0.08 | 0.368 |
| Log TMT-B times |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex | 0.01 | -0.02 | 0.04 | 0.581 | 0.01 | -0.02 | 0.04 | 0.540 |
| *APOE* e4\*smoking | -0.01 | -0.08 | 0.05 | 0.701 | <0.01 | -0.06 | 0.06 | 0.998 |
| *APOE* e4\*alcohol | -0.04 | -0.08 | 0.01 | 0.109 | -0.04 | -0.09 | 0.00 | 0.075 |
| *APOE* e4\*obesity | -0.01 | -0.14 | 0.11 | 0.829 | -0.01 | -0.14 | 0.11 | 0.860 |
| *APOE* e4\*physical activity | 0.03 | -0.03 | 0.08 | 0.343 | 0.02 | -0.03 | 0.07 | 0.452 |
| Digit symbol scores |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex | -0.01 | -0.04 | 0.02 | 0.556 | -0.01 | -0.04 | 0.02 | 0.544 |
| *APOE* e4\*smoking | 0.05 | -0.01 | 0.11 | 0.076 | 0.04 | -0.01 | 0.10 | 0.135 |
| *APOE* e4\*alcohol | -0.02 | -0.06 | 0.02 | 0.324 | -0.02 | -0.06 | 0.02 | 0.370 |
| *APOE* e4\*obesity | 0.23 | 0.11 | 0.35 | <0.001 | 0.22 | 0.11 | 0.34 | <0.001 |
| *APOE* e4\*physical activity | 0.02 | -0.03 | 0.06 | 0.505 | 0.02 | -0.03 | 0.07 | 0.390 |

Partially adjusted: age, sex, assessment centre, genotypic array. Fully adjusted: (also) Townsend deprivation scores, degree yes vs. no, self-report diabetes, hypertension and CHD. Each dependent variable (cognitive score) is underlined in the left-hand column.

**Supplementary Table e-3**: individual three-way interactions between *APOE* e4 genotype, sex, and lifestyle variables, on cognitive phenotypes.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Partially adjusted | | | | Fully adjusted | | | |
|  | Standardised b | lower | upper | p | Standardised b | lower | upper | p |
| Log reaction time |  |  |  |  |  |  |  |  |
| APOE *e4\**sex*\**smoking | -0.02 | -0.06 | 0.03 | 0.495 | -0.02 | -0.06 | 0.03 | 0.489 |
| *APOE* e4\*sex\*alcohol | 0.03 | <0.01 | 0.07 | 0.039 | 0.03 | <0.01 | 0.07 | 0.043 |
| *APOE* e4\*sex\*obesity | -0.01 | -0.12 | 0.10 | 0.845 | -0.02 | -0.13 | 0.09 | 0.726 |
| *APOE* e4\*sex\*physical activity | <0.01 | -0.02 | 0.03 | 0.715 | <0.01 | -0.02 | 0.03 | 0.810 |
| Fluid reasoning scores |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex\*smoking | 0.04 | -0.05 | 0.13 | 0.430 | 0.04 | -0.04 | 0.13 | 0.342 |
| *APOE* e4\*sex\*alcohol | 0.06 | <0.01 | 0.12 | 0.035 | 0.07 | 0.01 | 0.12 | 0.017 |
| *APOE* e4\*sex\*obesity | 0.06 | -0.13 | 0.26 | 0.521 | 0.08 | -0.11 | 0.27 | 0.407 |
| *APOE* e4\*sex\*physical activity | <0.01 | -0.05 | 0.04 | 0.861 | 0.01 | -0.04 | 0.05 | 0.799 |
| Log TMT-A times |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex\*smoking | 0.01 | -0.12 | 0.13 | 0.931 | 0.01 | -0.12 | 0.13 | 0.923 |
| *APOE* e4\*sex\*alcohol | 0.01 | -0.05 | 0.08 | 0.650 | 0.02 | -0.05 | 0.08 | 0.591 |
| *APOE* e4\*sex\*obesity | -0.04 | -0.31 | 0.24 | 0.790 | -0.04 | -0.31 | 0.23 | 0.761 |
| *APOE* e4\*sex\*physical activity | 0.02 | -0.03 | 0.07 | 0.425 | 0.02 | -0.03 | 0.06 | 0.459 |
| Log TMT-B times |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex\*smoking | 0.09 | -0.03 | 0.21 | 0.152 | 0.08 | -0.03 | 0.20 | 0.164 |
| *APOE* e4\*sex\*alcohol | -0.01 | -0.07 | 0.06 | 0.842 | -0.01 | -0.07 | 0.06 | 0.870 |
| *APOE* e4\*sex\*obesity | -0.02 | -0.29 | 0.25 | 0.871 | -0.01 | -0.27 | 0.26 | 0.960 |
| *APOE* e4\*sex\*physical activity | 0.03 | -0.02 | 0.07 | 0.231 | 0.02 | -0.02 | 0.07 | 0.295 |
| Digit symbol scores |  |  |  |  |  |  |  |  |
| *APOE* e4\*sex\*smoking | -0.01 | -0.12 | 0.10 | 0.815 | -0.03 | -0.13 | 0.08 | 0.652 |
| *APOE* e4\*sex\*alcohol | 0.02 | -0.04 | 0.07 | 0.597 | 0.01 | -0.04 | 0.07 | 0.608 |
| *APOE* e4\*sex\*obesity | -0.09 | -0.34 | 0.15 | 0.462 | -0.11 | -0.36 | 0.13 | 0.366 |
| *APOE* e4\*sex\*physical activity | <0.01 | -0.04 | 0.05 | 0.860 | <0.01 | -0.04 | 0.05 | 0.860 |

Partially adjusted: age, sex, assessment centre, genotypic array. Fully adjusted: (also) Townsend deprivation scores, degree yes vs. no, self-report diabetes, hypertension and CHD. Each three-way interaction includes the two-way interactions plus main effects in the model(s). Each dependent variable (cognitive score) is underlined in the left-hand column.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Odds ratio (CI’s) | Smoking | Alcohol | Obesity | Physical activity | Degree | *APOE* e4 |
| Smoking status (never/previous vs. never) | - |  |  |  |  |  |
| Alcohol (heavy vs. not) | 1.88 (1.81-1.94) \*\* | - |  |  |  |  |
| Obesity (obese vs. not) | 1.00 (0.92-1.09) | 0.22 (0.21-0.25) \*\* | - |  |  |  |
| Physical activity quintile (1-5; ordinal). | 0.96 (0.88-1.06) | 0.97 (0.89-1.05) | 1.09 (0.09-1.33) | - |  |  |
| Degree (college and above vs. not) | 0.51 (0.49-0.52) \*\* | 2.19 (2.14-2.24) \*\* | 0.58 (0.55-0.62) \*\* | 0.89 (0.84=0.93) \*\* | - |  |
| *APOE* e4 allele presence (vs. absence) | 0.95 (0.93 to 0.98) \*\* | 1.01 (0.98-1.03) | 0.98 (0.93-1.04) | 0.98 (0.93-1.04) | 1.02 (1.00-1.03)\* | - |

**Supplementary Table e-4** – lifestyle and *APOE* e4 intercorrelations.

Odds ratios reflect logistic regressions of a 1-unit change in the independent variable (y-axis) vs. dependent variable (x-axis). \*P<0.05; \*\*P<0.001.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ***APOE* e4 absent** | | ***APOE* e4 present** | |
|  | **Light drinker** | **Heavy drinker** | **Light drinker** | **Heavy drinker** |
| Reasoning scores (mean; SD) | 5.89 (2.07) | 6.54 (2.09) | 5.85 (2.07) | 6.56 (2.08) |
| N | 18,773 | 16,708 | 6,608 | 6,145 |
|  |  |  |  |  |
| Reaction time (msecs; median and interquartile range) | 543 (485-617) | 531 (470-601) | 543 (484-614) | 531 (477-598) |
| N | 56,389 | 50,038 | 20,652 | 18,424 |
|  |  |  |  |  |
| Trail making test A (secs; median and interquartile range) | 35.88 (29.20 – 45.18) | 35.41 (29.33-43.97) | 36.28 (29.54-46.18) | 35.26 (29.31-43.54) |
| N | 10,656 | 12,483 | 3,859 | 4,465 |
|  |  |  |  |  |
| Trail making test B (secs median and interquartile range) | 61.11 (49.40 – 76.80) | 61.05 (49.78-76.03) | 62.00 (50.06 – 78.88) | 60.96 (49.77 – 75.11) |
| N | 10,659 | 12,504 | 3,859 | 4,469 |
|  |  |  |  |  |
| Digit symbol substitution score (mean; SD) | 19.62 (5.26) | 19.66 (4.96) | 19.50 (5.39) | 19.51 (5.12) |
| N | 12,434 | 14,297 | 4,476 | 5,152 |

**Supplementary Table e-5** – alcohol intake by *APOE* e4 status.

SD = standard deviation. Scores are medians for reaction time and trail making test scores because they were not normally distributed. Reasoning and Digit symbol scores are means.

**Supplementary Figure e-1**: three-way *APOE* e4, alcohol intake and sex plot for reasoning scores (estimated marginal means based on fully-adjusted model; see ‘analysis’).

