**Supplementary Material 1.** Details on the Alzheimer's disease GWAS that was used to generate the polygenic scores in Generation Scotland

#### Material and methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry [1]. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

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1. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet., 2013;45(12):1452-58.

Supplementary Table 1. Comparison of cognitive outcomes by genetic risk for AD and *APOE* status in an unrelated Generation Scotland sub-group of 2,677 adults aged between 60 and 70 years. All models adjust for age, sex, and pedigree-based relatedness.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Effect per SD of PGRS** | | |
| **Variable** | **beta** | **SE** | **P** |
| Digit Symbol Test | -0.27 | 0.27 | 0.31 |
| Logical Memory | -0.37 | 0.15 | 0.015 |
|  |  |  |  |
|  | **Top vs Bottom 5% of PGRS** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -2.57 | 1.76 | 0.14 |
| Logical Memory | -1.86 | 0.95 | 0.052 |
|  |  |  |  |
|  | ***APOE* e4e4 vs e3e3** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -3.68 | 0.96 | 1.3x10-4 |
| Logical Memory | -3.76 | 1.71 | 0.028 |

Supplementary Table 2. Comparison of cognitive outcomes by genetic risk for AD and *APOE* status in a Generation Scotland sub-group of 3,353 adults aged between 60 and 70 years with at least 5 years of full time education. All models adjust for age, sex, and pedigree-based relatedness.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Effect per SD of PGRS** | | |
| **Variable** | **beta** | **SE** | **P** |
| Digit Symbol Test | -0.36 | 0.25 | 0.14 |
| Logical Memory | -0.36 | 0.14 | 0.008 |
|  |  |  |  |
|  | **Top vs Bottom 5% of PGRS** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -2.27 | 1.55 | 0.14 |
| Logical Memory | -2.01 | 0.84 | 0.017 |
|  |  |  |  |
|  | ***APOE* e4e4 vs e3e3** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -2.94 | 1.56 | 0.060 |
| Logical Memory | -2.71 | 0.88 | 0.002 |

Supplementary Table 3. Comparison of cognitive outcomes by genetic risk for AD and *APOE* status in a Generation Scotland sub-group of 6,853 middle-aged (45-60 years) adults. All models adjust for age, sex, and pedigree-based relatedness.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Effect per SD of PGRS** | | |
| **Variable** | **beta** | **SE** | **P** |
| Digit Symbol Test | -0.27 | 0.18 | 0.13 |
| Logical Memory | -0.15 | 0.09 | 0.10 |
|  |  |  |  |
|  | **Top v. Bottom 5% of PGRS** | | |
| **Variable** | **beta** | **SE** | **P** |
| Digit Symbol Test | -1.80 | 1.12 | 0.11 |
| Logical Memory | -1.05 | 0.58 | 0.07 |
|  |  |  |  |
|  | ***APOE* e4e4 vs e3e3** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -0.45 | 1.07 | 0.67 |
| Logical Memory | -0.87 | 0.57 | 0.13 |

Supplementary Table 4. Comparison of cognitive outcomes by genetic risk for AD and *APOE* status in a Generation Scotland sub-group of 820 older (>70 years) adults. All models adjust for age, sex, and pedigree-based relatedness.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Effect per SD of PGRS** | | |
| **Variable** | **beta** | **SE** | **P** |
| Digit Symbol Test | -0.15 | 0.47 | 0.74 |
| Logical Memory | -0.45 | 0.30 | 0.13 |
|  |  |  |  |
|  | **Top vs Bottom 5% of PGRS** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | 1.47 | 3.08 | 0.63 |
| Logical Memory | -4.10 | 1.84 | 0.026 |
|  |  |  |  |
|  | ***APOE* e4e4 vs e3e3** | | |
| **Variable** | **Beta** | **SE** | **P** |
| Digit Symbol Test | -5.38 | 4.06 | 0.19 |
| Logical Memory | -0.19 | 2.58 | 0.94 |