Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1: Association between AD-GRS and Alzheimer’s Disease diagnosis in UK Biobank

We conducted a multivariate logistic regression to assess the association between AD-GRS and a diagnosis of Alzheimer’s disease in UK Biobank.

The ICD codes used to define dementia diagnosis variable were as follows: ICD 10 codes – F00 Dementia in Alzheimer’s disease; F00.0 Dementia in Alzheimer’s disease with early onset; F00.1 Dementia in Alzheimer’s disease with late onset; F00.2 Dementia in Alzheimer’s disease, atypical or mixed type; F00.9 Dementia in Alzheimer’s disease, unspecified; G30 Alzheimer’s disease; G30.0 Alzheimer’s disease with early onset; G30.1 Alzheimer’s disease with late onset; G30.8 Other Alzheimer’s disease; G30.9 Alzheimer’s disease unspecified. ICD9 code – 331.0 Alzheimer’s disease.

We regressed AD diagnosis variable on z-scored AD-GRS, adjusted for a linear combination of age at cognitive assessment, self-reported sex, genotyping assay (a binary indicator for whether the UK BiLEVE or UK Biobank Axiom array was used), assessment center, and 10 genetic ancestry principal components (PCs) provided by the UK Biobank to account for population stratification in the sample.

The data included 408,833 participants, 632 of whom had a diagnosis of AD. The z-scored AD-GRS showed a highly statistically significant association with the AD-GRS that included APOE (b=0.848, p < 0.001, eTable 11). The association between the AD-GRS was also statistically significant, but the strength of its relationship with dementia was attenuated (b=0.250, p=0.065, eTable 8).
eAppendix 2: Variable descriptions

Codes for other variables
UK Biobank variables (variable code) included: sex (31), genotype measurement batch (22000), assessment center (54), and 10 genetic ancestry PCs (22009_0_1 to 22009_0_10); age at test was derived from: age at baseline (21022), month of birth (52), year of birth (34), date attending assessment center (53), age when attended assessment center (21003), when pairs test completed (20134), when fluid intelligence test completed (20135), when trail making test completed (20136), when symbol digit substitution test completed (20137), when numeric memory test completed (20138).
eAppendix 3: Cognitive tests description
In-person trail making and symbol digit substitution were not conducted until 2016, at the time neuroimaging was added to the study. For all other variables, we used baseline data from the initial assessment visit (2006-2010). Many tests were also administered in an online format. For the online variables where the test was administered in multiple study waves, we used the first available assessment. More information on the tests as fielded by UK Biobank is available the UK Biobank Data Showcase.¹²

**Fluid intelligence**
This logic/reasoning test gave participants two minutes to answer as many questions as possible across 14 (online) or 13 (in person) questions. For comparability, we used the sum of correct answers across the 13 common questions as the phenotype variable. Participants were scored zero for all unattempted questions.

**Numeric memory**
In this test of short-term memory capacity and attention, the participant was first shown a 2-digit number. After a brief pause, they were asked to recall the digits in the correct order. Each time the participant correctly remembers a sequence, they are shown a new sequence that is one-digit-longer number, until they make an error or 12 digits are reached. The online version had only 1 round, whereas the in-person test repeated this sequence 3 times. For comparability, we used the maximum number of digits remembered correctly in the first round as the phenotype variable.

**Pairs matching**
Pairs matching is a visual short-term memory and attention task in which participants are shown an arrangement of cards for 5 seconds and are asked to memorize their position. They must then match them from memory. The online version asks participants to match 3, 6, and 8 cards in three separate rounds. The 8 pair round was only presented if they had 0-1 errors in the 6 card round. The in-person version only tested participants on 3 and 6 pairs. Thus we look only at the 3 and 6 pair tests (separately). Participants were allowed to abandon the task. Outcomes for each round were the time to complete the round (there was no time limit), number of correct matches by the end of the round and number of incorrect attempts made in the round.

**Symbol digit substitution**
This processing speed task presents participants with a key that matches 8 symbols to the numbers 1-8. They are then shown an array of numbers and are asked to draw (“substitute”) the correct symbols for each item in the array by referring to the key. Participants were instructed to perform as many substitutions as they could within a time limit of one minute, working as quickly and accurately as they could. Outcomes are coded as the number of symbol digit matches made correctly, and the time to complete the first 10 substitutions (participants completed different numbers of substitutions, but 77% of participants who attempted the test completed the first 10).

**Trail making test, parts A (numeric) and B (alphanumeric)**
In part A, participants are asked to draw connections between the numbers 1-25 as quickly as possible. In part B, they are asked to alternate between connecting numbers and letters, i.e. connecting the sequence 1,A,2,B etc. Numeric sequencing is primarily a measure of processing speed, whereas the alphanumeric sequencing requires set-shifting, a subdomain of executive functioning. For each condition, we analyzed the time to complete and the number of errors.

**Reaction time**
This reaction time task presented participants with two cards at a time. They were asked to respond as quickly as possible if the cards matched. The outcome was mean reaction time to identify matches, excluding training rounds 1-4, in milliseconds.

**Prospective memory**
For this prospective memory task, participants were asked to perform an action at a future time, “At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead.” If participants correctly recalled this instruction and chose the orange circle, they were scored as correct. Any other answer was scored as incorrect.
Appendix 4: Functional form and cross-validation details

Functional Form

The functional form of the regressions is:

\[ Y \sim \text{link}(t^2 + t + ADGRS_z \times I(t > t_{\text{threshold}}) \times (t - t_{\text{threshold}})^3 + \sum W_i) \]

Where:

- \( t \) is the difference between age at assessment and the reference age (40 years).
- \( W_i \) are covariates: age at cognitive assessment, self-reported sex, genotyping assay (a binary indicator for whether a UK BiLEVE or UK Biobank Axiom array was used), assessment center (for assessment-center based measures only), practice effect (for online measures only) and 10 genetic ancestry PCs.
- “link” is the identity transform for continuous variables, and the logit transform for binary variables
- \( ADGRS_z \) is the “z-scored” or “standardized” value of each participants genetic risk score obtained from:

\[
ADGRS_z = \frac{ADGRS - \text{mean}(ADGRS)}{\text{sd}(ADGRS)}
\]

Where mean(AD-GRS) and sd(AD-GRS) are the mean and standard deviation AD-GRS scores in the full sample.

Using this functional form, we assume that the mean level of the cognitive measure changes quadratically with age below the threshold, and diverges smoothly (in terms of first derivatives) from this curve as \( t \) increases above the threshold.

Cross-validation

For each phenotype we conducted 10-fold cross-validation in which \( t_{\text{threshold}} \) was varied in 1-year increments over the range of values supported by the age range in the sample for the phenotype in order to choose the value of \( t_{\text{threshold}} \), the time (relative to the centered reference age) at which the predicted value for individuals with the same covariates, but different AD-GRS, would begin to diverge. The data set was divided randomly into 10 subsets called “folds”. For each possible value of \( t_{\text{threshold}} \), one cross-validation was conducted using each fold as the test set, and the rest of the sample as the training set, and we measured the mean-squared prediction error (MSPE) for the fold as the mean squared difference in predicted and observed phenotype values. The total error for the model with \( t_{\text{threshold}} \) was then the sum of these 10 fold-specific MSPEs. We chose \( t_{\text{threshold}} \) for each phenotype based on which model had the lowest total error, which indicated the best out-of-sample prediction accuracy. For comparability, the same 10 folds were used for each value of \( t_{\text{threshold}} \).

Additionally, to check the performance of the cross-validation, we visually examined the total error as a function of \( t_{\text{threshold}} \). We expected smooth U-shaped curves with a single global minimum and no local minima, or monotonic curves indicating that the true minimum lies outside the support of the data. See eFigure 1 for an example.
eAppendix 5: Sensitivity analysis ADGRS with alternative functional forms for age

Using a more flexible functional form (eEquation 4) for the relationship between age and ADGRS led to the same or earlier estimated ages of divergence for all measures (eTable 14) compared to the quadratic functional form (eTable 6) except the indicator of first or second attempt correct for the in-person version of the prospective memory test (see eTable 15). The more rigid functional form (eEquation 3, eTable 13) did not fit the data as well as the quadratic models (eTable 6), and estimated a mix of earlier and later ages of divergence across measures (eTable 15).

eEquation 3: Linear age term with quadratic divergence term

\[ Y \sim \text{link}(b_0 + (b_1 t) + b_2 \ ADGRS_z \times I(t > t_{\text{threshold}}) \times (t - t_{\text{threshold}})^2 + \sum_i b_i W_i) \] (eEquation 3)

eEquation 4: Cubic age term with 4th-order divergence term

\[ Y \sim \text{link}(b_0 + (b_1 t + b_2 t^2 + b_3 t^3) + b_4 \ ADGRS_z \times I(t > t_{\text{threshold}}) \times (t - t_{\text{threshold}})^4 + \sum_i b_i W_i) \] (eEquation 4)

eAppendix 6: Sensitivity analysis using count of APOE ε4 alleles

In sensitivity analyses using the count of APOE ε4 alleles instead of the AD-GRS, there was evidence that the count of APOE ε4 alleles modified the association of age with 11 measures derived from the pairs matching, symbol digit substitution, numeric memory and trail-making tests (eTable 7), with west-fitting models indicated divergence by age 60 for these measures (eTable 8).

For sensitivity analyses presented in eTables 9 and 10 we used the following functional form:

\[ Y \sim \text{link}(b_0 + b_1 \text{age} + b_2 \text{APOE} + b_3 \text{APOE} \times \text{age} + \sum_i b_i W_i) \] (eEquation 1)
Where cognitive score (Y) is a function of age, count of APOE ε4 alleles (APOE), their interaction, and covariates Wi.

**eAppendix 7: Sensitivity analysis using count of APOE ε4-alleles and an AD-GRS that excludes APOE**

In sensitivity analyses using both the count of APOE ε4 alleles and the AD-GRS omitting SNPs in the APOE region, there was evidence that the count of APOE ε4 alleles modified the association of age with 2 measures derived from the pairs matching, symbol digit substitution, numeric memory and trail-making tests (eTable 9), but no interactions between age and the AD-GRS were significant. Best-fitting models indicated higher ages of divergence, with 9 measures suggesting divergence by age 63, while 3 measures suggested no divergence at the highest observed age (eTable 10).

For sensitivity analyses presented in eTables 9 and 10 we used the following functional form:

$$ Y \sim \text{link} \left( b_0 + b_1 \text{age} + b_2 \text{ADGRS}_z + b_3 \text{ADGRS}_z \times \text{age} + b_3 \text{APOE} + b_4 \text{APOE} \times \text{age} + \sum_i b_i W_i \right) $$  (eEquation 2)

Where cognitive score (Y) is a function of age, z-scored AD-GRS (ADGRS$_z$), count of APOE ε4 alleles (APOE), the interaction of age with AD-GRS, the interaction of age with count of APOE ε4 alleles, and covariates Wi.

Using a more flexible functional form for the relationship between age and AD-GRS led to the same or earlier estimated ages of divergence for all measures except the indicator of first or second attempt correct for the in-person version of the prospective memory test. The more rigid functional form did not fit the data as well as the main divergence models, and estimated a mix of earlier and later ages of divergence across measures (eTables 6, 13, 14 and 15).

**eAppendix 8 Sensitivity analysis excluding APOE from the AD-GRS**

In sensitivity analyses using an AD-GRS that excluded alleles from the APOE region, the AD-GRS did not significantly modify the association of age with any cognitive measures at the Bonferroni threshold, but the interaction was significant at $p<0.05$ for 3 cognitive measures (eTable 11). Best-fitting models indicated earliest age of divergence before 50 years for 4 cognitive assessments (eTable 12).
eTable 1: Logistic regression of AD diagnosis on z-scored AD-GRS including APOE

| Term                                      | Coefficient Estimate (b) | SE  | p-value |
|-------------------------------------------|--------------------------|-----|---------|
| (Intercept)                               | -17.807                  | 177.387 | 0.920 |
| ADGRS_z                                   | 0.848                    | 0.032 | 0.000* |
| pc1                                       | 0.002                    | 0.027 | 0.927  |
| pc2                                       | 0.003                    | 0.027 | 0.905  |
| pc3                                       | 0.039                    | 0.026 | 0.143  |
| pc4                                       | 0.010                    | 0.020 | 0.606  |
| pc5                                       | -0.008                   | 0.009 | 0.402  |
| pc6                                       | 0.019                    | 0.025 | 0.459  |
| pc7                                       | 0.021                    | 0.023 | 0.367  |
| pc8                                       | 0.037                    | 0.023 | 0.104  |
| pc9                                       | -0.006                   | 0.010 | 0.565  |
| pc10                                      | -0.054                   | 0.020 | 0.008* |
| base_age_c60                              | 0.228                    | 0.010 | 0.000* |
| sex                                       | -0.073                   | 0.081 | 0.369  |
| genoChip_0_0                              | 0.105                    | 0.136 | 0.440  |
| as.factor(assessment_center)_11001        | 9.203                    | 177.387 | 0.959 |
| as.factor(assessment_center)_11002        | 7.494                    | 177.389 | 0.966 |
| as.factor(assessment_center)_11003        | 11.581                   | 177.387 | 0.948 |
| as.factor(assessment_center)_11004        | 11.522                   | 177.387 | 0.948 |
| as.factor(assessment_center)_11005        | 11.322                   | 177.387 | 0.949 |
| as.factor(assessment_center)_11006        | 10.182                   | 177.387 | 0.954 |
| as.factor(assessment_center)_11007        | 8.577                    | 177.387 | 0.961 |
| as.factor(assessment_center)_11008        | 10.727                   | 177.387 | 0.952 |
| as.factor(assessment_center)_11009        | 9.672                    | 177.387 | 0.957 |
| as.factor(assessment_center)_11010        | 11.033                   | 177.387 | 0.950 |
| as.factor(assessment_center)11011 | 8.811 | 177.387 | 0.960 |
|---------------------------------|-------|---------|-------|
| as.factor(assessment_center)11012 | 8.978 | 177.388 | 0.960 |
| as.factor(assessment_center)11013 | 11.028 | 177.387 | 0.950 |
| as.factor(assessment_center)11014 | 10.729 | 177.387 | 0.952 |
| as.factor(assessment_center)11016 | 8.050 | 177.387 | 0.964 |
| as.factor(assessment_center)11017 | 10.905 | 177.387 | 0.951 |
| as.factor(assessment_center)11018 | 10.218 | 177.387 | 0.954 |
| as.factor(assessment_center)11020 | 7.067 | 177.389 | 0.968 |
| as.factor(assessment_center)11021 | 9.820 | 177.387 | 0.956 |
| as.factor(assessment_center)11022 | 9.341 | 177.390 | 0.958 |
| as.factor(assessment_center)11023 | 10.867 | 177.390 | 0.951 |

* statistically significant at significance level 0.05; ADGRS_z: z-scored Alzheimer’s disease genetic risk score; pc1-pc10: genetic ancestry principal components; base_age_c60: age at recruitment, centered at 60; sex: female (0) or male (1); genochip_0_0: indicator for UK BiLEVE array (0) or UK Biobank Axiom array (1); assessment_center: UK Biobank assessment center ID.
eTable 2: Logistic regression of AD diagnosis on z-scored AD-GRS, adjusted for covariates

| Term                        | Coefficient Estimate (b) | SE      | p-value |
|-----------------------------|--------------------------|---------|---------|
| (Intercept)                 | -17.569                  | 185.858 | 0.925   |
| ADGRS_z                     | 0.250                    | 0.042   | 0.000*  |
| pc1                         | -0.002                   | 0.026   | 0.939   |
| pc2                         | -0.001                   | 0.027   | 0.963   |
| pc3                         | 0.039                    | 0.026   | 0.137   |
| pc4                         | 0.013                    | 0.020   | 0.502   |
| pc5                         | -0.010                   | 0.009   | 0.292   |
| pc6                         | 0.022                    | 0.025   | 0.381   |
| pc7                         | 0.021                    | 0.023   | 0.361   |
| pc8                         | 0.035                    | 0.023   | 0.124   |
| pc9                         | -0.003                   | 0.010   | 0.777   |
| pc10                        | -0.053                   | 0.020   | 0.008*  |
| base_age_c60               | 0.223                    | 0.010   | 0.000*  |
| sex                         | -0.039                   | 0.080   | 0.629   |
| genoChip_0_0               | 0.150                    | 0.135   | 0.269   |
| as.factor(assessment_center)11001 | 9.323                  | 185.859 | 0.960   |
| as.factor(assessment_center)11002 | 7.632                  | 185.861 | 0.967   |
| as.factor(assessment_center)11003 | 11.647                  | 185.858 | 0.950   |
| as.factor(assessment_center)11004 | 11.617                  | 185.858 | 0.950   |
| as.factor(assessment_center)11005 | 11.425                  | 185.858 | 0.951   |
| as.factor(assessment_center)11006 | 10.287                  | 185.858 | 0.956   |
| as.factor(assessment_center)11007 | 8.688                   | 185.858 | 0.963   |
| as.factor(assessment_center)11008 | 10.823                  | 185.858 | 0.954   |
| as.factor(assessment_center)11009 | 9.789                   | 185.858 | 0.958   |
| as.factor(assessment_center)11010 | 11.124 | 185.858 | 0.952 |
|---------------------------------|--------|---------|-------|
| as.factor(assessment_center)11011 | 8.913  | 185.858 | 0.962 |
| as.factor(assessment_center)11012 | 9.057  | 185.859 | 0.961 |
| as.factor(assessment_center)11013 | 11.114 | 185.858 | 0.952 |
| as.factor(assessment_center)11014 | 10.825 | 185.858 | 0.954 |
| as.factor(assessment_center)11016 | 8.167  | 185.859 | 0.965 |
| as.factor(assessment_center)11017 | 11.032 | 185.858 | 0.953 |
| as.factor(assessment_center)11018 | 10.297 | 185.858 | 0.956 |
| as.factor(assessment_center)11020 | 7.158  | 185.861 | 0.969 |
| as.factor(assessment_center)11021 | 9.902  | 185.858 | 0.958 |
| as.factor(assessment_center)11022 | 9.404  | 185.861 | 0.960 |
| as.factor(assessment_center)11023 | 10.795 | 185.861 | 0.954 |

*statistically significant (p<0.05)*; ADGRS_z: z-scored Alzheimer's disease genetic risk score; pc1-pc10: genetic ancestry principal components; base_age_c60: age at recruitment, centered at 60; sex: female (0) or male (1); genochip_0_0: indicator for UK BiLEVE array (0) or UK Biobank Axiom array (1); assessment_center: UK Biobank assessment center ID.
| Marker Name  | Chromosome | Closest gene | Effect Allele | Effect Estimate |
|--------------|------------|--------------|---------------|-----------------|
| rs6656401    | 1          | CR1          | A             | 0.1567          |
| rs35349669   | 2          | INPP5D       | T             | 0.0663          |
| rs6733839    | 2          | BIN1         | T             | 0.188           |
| rs190982     | 5          | MEF2C        | G             | -0.0799         |
| rs10948363   | 6          | CD2AP        | G             | 0.0978          |
| rs11771145   | 7          | EPHA1        | A             | -0.1024         |
| rs1476679    | 7          | ZCWPW1       | C             | -0.0783         |
| rs2718058    | 7          | NME8         | G             | -0.0697         |
| rs28834970   | 8          | PTK2B        | C             | 0.0959          |
| rs9331896    | 8          | CLU          | C             | -0.1457         |
| rs10792832   | 11         | PICALM       | A             | -0.1297         |
| rs10838725   | 11         | CELF1        | C             | 0.0753          |
| rs11128343   | 11         | SORL1        | C             | -0.2697         |
| rs670139     | 11         | MS4A4E       | T             | 0.0803          |
| rs983392     | 11         | MS4A6A       | G             | -0.1084         |
| rs10498633   | 14         | SLC24A4-RIN3 | T             | -0.1044         |
| rs17125944   | 14         | FERMT2       | C             | 0.1223          |
| rs8093731    | 18         | DSG2         | T             | -0.6136         |
| rs3865444    | 19         | CD33         | A             | -0.0954         |
| rs4147929    | 19         | ABCA7        | A             | 0.1348          |
| rs429358a    | 19         | APOE         | C             | 1.3503          |
| rs7412a      | 19         | APOE         | T             | -0.3871         |
| rs7274581    | 20         | CASS4        | C             | -0.1390         |

*a Excluded in AD-GRS without APOE
| Cognitive test       | Analysis variable                                      | UK Biobank variables (field ID) used to create analysis variable |
|---------------------|--------------------------------------------------------|------------------------------------------------------------------|
| Fluid intelligence  | Number of correctly answered items out of F1-F13      | In-person: 20016<br>Online: 20191                                 |
|                     | Number of attempted items out of F1-F13               | In person: 20128<br>Online: 20192 (Not available at this time)   |
| Numeric memory      | Maximum digits remembered correctly                    | In person: 4282<br>Online: 20240                                 |
| Pairs matching      | Number incorrect matches (by round, for rounds 1 and 2)| In person: 399<br>Online: 20132                                 |
|                     | Number correct matches (by round, for round 1)        | In person: 398<br>Online: 20131                                 |
|                     | Time to complete round (by round, for rounds 1 and 2) | In person: 400<br>Online: 20133                                 |
| Symbol digit substitution | Number of symbol digit matches made correctly | In person: 23324<br>Online: 20159                               |
|                     | Number of symbol digit matches attempted               | In person: 23323<br>Online: 20195                               |
|                     | Time to complete the first 10 (among those who got the first 10 correct) | In person: N/A – Time not recorded. Online: 20230 (duration to entering value), 20200 (values wanted), 20229 (values entered) |
| Trail making        | Duration to complete numeric path (trail #1)          | In person: 6348<br>Online: 20156                               |
|                     | Duration to complete alphanumeric path (trail #2)     | In person: 6350<br>Online: 20157                               |
|                          | In person | Online |
|--------------------------|-----------|--------|
| Total errors traversing numeric path (trail #1) | 6349      | 20247  |
| Total errors traversing alphanumeric path (trail #2) | 3951      | 20248  |
| **Reaction time**        |           |        |
| Mean time to correctly identify matches | 20023  | N/A    |
| **Prospective memory**   |           |        |
| Correct on first attempt | 20018  | N/A    |
| Correct on first or second attempt | 20018  | N/A    |

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**eTable 5: Association with AD-GRS and effect modification of age-slope by AD-GRS for each cognitive assessment (z-scored)**

| Test                  | Variable                          | Location       | Domain                                | Age slope per decade for person with mean GRS [95% CI] p-value \(^a\) | Difference in age slope for person with 1SD higher GRS [95% CI] p-value \(^b\) | Percent Difference in mean cognition per decade increase in age for 1 SD higher AD GRS \(^c\) |
|-----------------------|-----------------------------------|----------------|---------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| 26) Trail-making      | Number Of Errors In Numeric Trail | In Person      | processing speed                      | -0.122 [-0.145,-0.099] p<2e-16                                          | -0.02 [-0.043,0.003] p=9.0e-02                                                                              | 16.3                                                                                                         |
| 12) Pairs Matching    | Number Correct (Round 1)          | Online         | short-term memory/attention           | -0.124 [-0.132,-0.115] p<2e-16                                          | -0.014 [-0.023,-0.006] p<2e-16                                                                               | 11.5                                                                                                         |
| 28) Trail-making      | Number Of Errors In Alphanumeric Trail | In Person | processing speed/executive functioning | -0.213 [-0.236,-0.191] p<2e-16                                          | -0.024 [-0.047,-0.001] p=4.0e-02                                                                         | 11.4                                                                                                         |
| 7) Pairs Matching     | Number Correct (Round 2)          | In Person      | short-term memory/attention           | -0.093 [-0.097,-0.089] p<2e-16                                          | -0.009 [-0.013,-0.005] p<2e-16                                                                               | 9.4                                                                                                          |
| 5) Numeric Memory     | Number Correct                    | Online         | short-term memory/capacity/attention  | -0.18 [-0.189,-0.172] p<2e-16                                            | -0.016 [-0.025,-0.007] p<2e-16                                                                               | 8.8                                                                                                          |
| 1) Fluid Intelligence | Number Correct                    | In Person      | logic/reasoning                       | -0.119 [-0.126,-0.112] p<2e-16                                            | -0.01 [-0.017,-0.003] p=1.0e-02                                                                               | 8.4                                                                                                          |
| 4) Numeric Memory     | Number Correct                    | In Person      | short-term memory/capacity/attention  | -0.159 [-0.171,-0.147] p<2e-16                                            | -0.013 [-0.025,-0.001] p=4.0e-02                                                                               | 8.2                                                                                                          |
| 6) Pairs Matching     | Number Correct (Round 1)          | In Person      | short-term memory/attention           | -0.091 [-0.095,-0.087] p<2e-16                                            | -0.007 [-0.011,-0.003] p<2e-16                                                                               | 7.9                                                                                                          |
| Test Description | Measure | Task Setting | Primary Function | Effect Size (95% CI) | p-Value (Significance) |
|------------------|---------|--------------|------------------|----------------------|-----------------------|
| 27) Trail-making | Time to Complete Alphanumeric Trail | In Person | processing speed/executive functioning | -0.473 [-0.495, -0.452] | p < 2e-16 |
|                  |         |              |                  | -0.034 [-0.056, -0.012] | p < 2e-16 |
|                  |         |              |                  | 7.2                  |           |
| 32) Trail-making | Number Of Errors In Alphanumeric Trail | Online | processing speed/executive functioning | -0.128 [-0.142, -0.114] | p < 2e-16 |
|                  |         |              |                  | -0.008 [-0.022, 0.006] | p = 2.9e-01 |
|                  |         |              |                  | 6                    |           |
| 21) Symbol Digit Substitution | Number Correct | In Person | processing speed | -0.599 [-0.62, -0.579] | p < 2e-16 |
|                  |         |              |                  | -0.035 [-0.056, -0.014] | p < 2e-16 |
|                  |         |              |                  | 5.8                  |           |
| 20) Symbol Digit Substitution | Number Attempted | In Person | processing speed | -0.621 [-0.642, -0.601] | p < 2e-16 |
|                  |         |              |                  | -0.036 [-0.056, -0.015] | p < 2e-16 |
|                  |         |              |                  | 5.7                  |           |
| 25) Trail-making | Time to Complete Numeric Trail | In Person | processing speed | -0.416 [-0.438, -0.394] | p < 2e-16 |
|                  |         |              |                  | -0.022 [-0.044, 0] | p = 5.0e-02 |
|                  |         |              |                  | 5.4                  |           |
| 10) Pairs Matching | Time To Complete (Round 1) | In Person | short-term memory/attention | -0.207 [-0.211, -0.203] | p < 2e-16 |
|                  |         |              |                  | -0.011 [-0.015, -0.007] | p < 2e-16 |
|                  |         |              |                  | 5.3                  |           |
| 3) Fluid Intelligence | Number Correct | Online | logic/reasoning | -0.188 [-0.196, -0.179] | p < 2e-16 |
|                  |         |              |                  | -0.01 [-0.018, -0.002] | p = 2.0e-02 |
|                  |         |              |                  | 5.2                  |           |
| 14) Pairs Matching | Number Incorrect (Round 2) | Online | short-term memory/attention | -0.217 [-0.24, -0.195] | p < 2e-16 |
|                  |         |              |                  | -0.011 [-0.034, 0.012] | p = 3.4e-01 |
|                  |         |              |                  | 5.2                  |           |
| 13) Pairs Matching | Number Incorrect (Round 1) | Online | short-term memory/attention | -0.188 [-0.197, -0.18] | p < 2e-16 |
|                  |         |              |                  | -0.01 [-0.018, -0.001] | p = 3.0e-02 |
|                  |         |              |                  | 5.1                  |           |
| 18) Prospective Memory | 1st Or 2nd Attempt Correct | In Person | prospective memory | -2.975 [-3.185, -2.765] | p < 2e-16 |
|                  |         |              |                  | -0.141 [-0.349, 0.066] | p = 1.8e-01 |
|                  |         |              |                  | 4.8                  |           |
| Test Code | Test Name | Round | Time to Complete | Environment | PROCESSING SPEED | p-Value | Estimated Effect Size |
|-----------|-----------|-------|------------------|-------------|------------------|---------|----------------------|
| 24)       | Symbol Digit Substitution | Time To Complete 10 Substitutions | Online | processing speed | -0.521 [-0.53, -0.512] | p<2e-16 | -0.0024 [-0.033, -0.015] | 4.5 |
| 8)        | Pairs Matching | Number Incorrect (Round 1) | In Person | short-term memory/attention | -0.144 [-0.148, -0.14] | p<2e-16 | -0.006 [-0.01, -0.002] | 4.4 |
| 17)       | Prospective Memory | 1st Attempt Correct | In Person | prospective memory | -1.182 [-1.229, -1.135] | p<2e-16 | -0.043 [-0.09, 0.004] | 3.6 |
| 15)       | Pairs Matching | Time To Complete (Round 1) | Online | short-term memory/attention | -0.44 [-0.448, -0.432] | p<2e-16 | -0.015 [-0.023, -0.007] | 3.5 |
| 16)       | Pairs Matching | Time To Complete (Round 2) | Online | short-term memory/attention | -0.438 [-0.459, -0.416] | p<2e-16 | -0.014 [-0.036, 0.008] | 3.3 |
| 30)       | Trail-making | Time to Complete Alphanumeric Trail | Online | processing speed/executive functioning | -0.474 [-0.483, -0.466] | p<2e-16 | -0.013 [-0.022, -0.005] | 2.8 |
| 11)       | Pairs Matching | Time To Complete (Round 2) | In Person | short-term memory/attention | -0.312 [-0.315, -0.308] | p<2e-16 | -0.008 [-0.012, -0.004] | 2.5 |
| 22)       | Symbol Digit Substitution | Number Correct | Online | processing speed | -0.587 [-0.594, -0.579] | p<2e-16 | -0.014 [-0.022, -0.007] | 2.4 |
| 23)       | Symbol Digit Substitution | Number Attempted | Online | processing speed | -0.617 [-0.624, -0.61] | p<2e-16 | -0.012 [-0.02, -0.005] | 2 |
| 2)        | Fluid Intelligence | Number Attempted | In Person | logic/reasoning | -0.175 [-0.182, -0.168] | p<2e-16 | -0.003 [-0.01, 0.004] | 1.7 |
| 9)        | Pairs Matching | Number Incorrect (Round 2) | In Person | short-term memory/attention | -0.185 [-0.189, -0.181] | p<2e-16 | -0.002 [-0.006, 0.002] | 1.2 |
| 29) Trail-making | Time to Complete Numeric Trail | Online | processing speed | -0.371 [-0.38,- 0.363] p<2e-16 | -0.004 [- 0.012,0.005] p=4.2e-01 | 1 |
|------------------|--------------------------------|--------|-------------------|---------------------------------|---------------------------------|----|
| 19) Reaction Time | Mean Time                      | In Person | reaction time     | -0.373 [-0.377,- 0.369] p<2e-16 | 0.001 [- 0.003,0.004] p=7.5e-01 | -0.2 |
| 31) Trail-making | Number Of Errors In Numeric Trail | Online | processing speed  | -0.089 [-0.107,- 0.072] p<2e-16 | 0.002 [- 0.015,0.02] p=8.1e-01 | -2.4 |

*a Coefficient on age term (b_2) in equation 1  
*b Coefficient on ADGRS×age term (b_3) in equation 1  
*c (100*b_3/b_2) using the coefficients from equation 1
# eTable 6: Age of divergence in main analysis

| Test                  | Variable                                      | Location      | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|-----------------------|-----------------------------------------------|---------------|--------------------|--------------------|-------------------|---------------------------------|
| 6) Pairs Matching a   | Number Correct (Round 1)                      | In Person     | 41                 | 70                 | <=41              | 55                              |
| 9) Pairs Matching     | Number Incorrect (Round 2)                    | In Person     | 41                 | 70                 | <=41              | 70+                             |
| 11) Pairs Matching a  | Time To Complete (Round 2)                    | In Person     | 41                 | 70                 | <=41              | 70+                             |
| 2) Fluid Intelligence | Number Attempted                              | In Person     | 41                 | 70                 | 42                | 70+                             |
| 4) Numeric Memory     | Number Correct                                | In Person     | 41                 | 70                 | 42                | 70+                             |
| 8) Pairs Matching a   | Number Incorrect (Round 1)                    | In Person     | 41                 | 70                 | 45                | 70+                             |
| 3) Fluid Intelligence | Number Correct                                | Online        | 45.4               | 69.4               | <=45.4            | 59                              |
| 5) Numeric Memory a   | Number Correct                                | Online        | 45.4               | 69.4               | <=45.4            | 60                              |
| 23) Symbol Digit Substitution a | Number Attempted                      | Online        | 45.4               | 69.4               | <=45.4            | 56                              |
| 22) Symbol Digit Substitution a | Number Correct                        | Online        | 45.4               | 69.4               | <=45.4            | 56                              |
| 30) Trail-making      | Time to Complete Alphanumeric Trail           | Online        | 45.4               | 69.4               | <=45.4            | 56                              |
| 29) Trail-making      | Time to Complete Numeric Trail                | Online        | 45.4               | 69.4               | <=45.4            | 61                              |
| 16) Pairs Matching    | Time To Complete (Round 2)                    | Online        | 45.5               | 69.5               | <=45.5            | 62                              |
| 32) Trail-making      | Number Of Errors In Alphanumeric Trail        | Online        | 45.5               | 69.5               | <=45.5            | 62                              |
| 13) Pairs Matching    | Number Incorrect (Round 1)                    | Online        | 45.4               | 69.4               | 46.4              | 59                              |
| 15) Pairs Matching a  | Time To Complete (Round 1)                    | Online        | 45.4               | 69.4               | 46.4              | 56                              |
| 20) Symbol Digit Substitution a | Number Attempted                      | In Person     | 47                 | 70                 | <=47              | 60                              |
| 21) Symbol Digit Substitution a | Number Correct                        | In Person     | 47                 | 70                 | <=47              | 62                              |
| Test Description                                      | Condition   | Time to Complete | Correct Number | Errors |
|-------------------------------------------------------|-------------|------------------|----------------|--------|
| 27) Trail-making Time to Complete Alphanumeric Trail  | In Person   | 47               | 70             | <=47   |
| 25) Trail-making Time to Complete Numeric Trail       | In Person   | 47               | 70             | <=47   |
| 12) Pairs Matching a Number Correct (Round 1)         | Online      | 45.4             | 69.4           | 47.4   |
| 1) Fluid Intelligence Number Correct                  | In Person   | 41               | 70             | 49     |
| 24) Symbol Digit Substitution Time To Complete 10 Substitutions | Online | 45.4 | 69.4 | 49.4 |
| 7) Pairs Matching a Number Correct (Round 2)          | In Person   | 41               | 70             | 50     |
| 10) Pairs Matching a Time To Complete (Round 1)       | In Person   | 41               | 70             | 56     |
| 26) Trail-making Number Of Errors In Numeric Trail   | In Person   | 47               | 70             | 59     |
| 28) Trail-making Number Of Errors In Alphanumeric Trail | In Person | 47           | 70             | 61     |
| 14) Pairs Matching Number Incorrect (Round 2)         | Online      | 45.5             | 69.5           | 64.5   |
| 18) Prospective Memory 1st Or 2nd Attempt Correct    | In Person   | 41               | 70             | 66     |
| 19) Reaction Time Mean Time                           | In Person   | 41               | 70             | 68     |
| 31) Trail-making Number Of Errors In Numeric Trail   | Online      | 45.4             | 69.4           | 69.4   |
| 17) Prospective Memory 1st Attempt Correct            | In Person   | 41               | 70             | 70     |

a Significant modification of the effect of age by AD-GRS in linear model.
### eTable 7: Association of APOE count at age 40 and effect modification of age-slope by count of APOE ε4 alleles for each cognitive assessment (z-scored)

| Test                          | Variable                          | Location    | Domain                               | Age slope per decade for person with mean GRS [95% CI] \(^a\) | Difference in age slope for person with an additional copy of APOE ε4 (95% CI) \(^b\) | Percent Difference in mean cognition per decade increase in age per additional copy of APOE ε4 \(^c\) |
|-------------------------------|-----------------------------------|-------------|--------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 12) Pairs Matching (Round 1)  | Number Correct                    | Online      | short-term memory/attention          | -0.115 [-0.125, -0.106] p<2e-16                                | -0.028 [-0.044, -0.011] p<2e-16                                                 | 23.8                                                                             |
| 28) Trail-making              | Number Of Errors                  | In Person   | processing speed/executive functioning | -0.2 [-0.226, -0.174] p<2e-16                                 | -0.046 [-0.091, -0.001] p=4.0e-02                                               | 23                                                                               |
| 4) Numeric Memory             | Number Correct                    | In Person   | short-term memory capacity/attention | -0.151 [-0.165, -0.137] p<2e-16                                | -0.026 [-0.05, -0.003] p=3.0e-02                                                | 17.3                                                                             |
| 5) Numeric Memory             | Number Correct                    | Online      | short-term memory capacity/attention | -0.171 [-0.181, -0.161] p<2e-16                                | -0.03 [-0.047, -0.013] p=2e-16                                                  | 17.3                                                                             |
| 7) Pairs Matching (Round 2)   | Number Correct                    | In Person   | short-term memory/attention          | -0.088 [-0.093, -0.083] p<2e-16                                | -0.015 [-0.023, -0.008] p<2e-16                                                 | 17.3                                                                             |
| 1) Fluid Intelligence         | Number Correct                    | In Person   | logic/reasoning                      | -0.113 [-0.121, -0.105] p<2e-16                                | -0.019 [-0.033, -0.006] p=1.0e-02                                                | 17.1                                                                             |
| 26) Trail-making              | Number Of Errors                  | In Person   | processing speed                     | -0.116 [-0.143, -0.09] p<2e-16                                 | -0.019 [-0.064, 0.026] p=4.0e-01                                               | 16.6                                                                             |
| Test                          | Condition              | Measure                                      | Domain                      | Effect Size | 95% CI               | p-Value    | Effect Size (95% CI) | p-Value    |
|-------------------------------|------------------------|----------------------------------------------|-----------------------------|-------------|----------------------|------------|----------------------|------------|
| 14) Pairs Matching            | Number Incorrect       | Online                                       | short-term memory/attention | -0.208      | [-0.235,-0.182]     | p<2e-16    | -0.03 [-0.075,0.016] | p=2.0e-01 |
|                               | (Round 2)              |                                              |                             |             |                      |            |                      |            |
| 6) Pairs Matching             | Number Correct         | In Person                                    | short-term memory/attention | -0.087      | [-0.092,-0.082]     | p<2e-16    | -0.012 [-0.02,-0.005] | p<2e-16    |
|                               | (Round 1)              |                                              |                             |             |                      |            |                      |            |
| 3) Fluid Intelligence        | Number Correct         | Online                                       | logic/reasoning             | -0.181      | [-0.19,-0.171]      | p<2e-16    | -0.023 [-0.039,-0.007] | p<2e-16    |
| 16) Pairs Matching            | Time To Complete       | Online                                       | short-term memory/attention | -0.422      | [-0.447,-0.397]     | p<2e-16    | -0.055 [-0.098,-0.011] | p=1.0e-02 |
|                               | (Round 2)              |                                              |                             |             |                      |            |                      |            |
| 27) Trail-making              | Time to Complete       | In Person                                    | processing speed/executive | -0.458      | [-0.483,-0.433]     | p<2e-16    | -0.052 [-0.095,-0.009] | p=2.0e-02 |
|                               | Alphanumeric Trail     |                                              | functioning                 |             |                      |            |                      |            |
| 10) Pairs Matching            | Time To Complete       | In Person                                    | short-term memory/attention | -0.2       | [-0.205,-0.196]     | p<2e-16    | -0.022 [-0.029,-0.014] | p<2e-16    |
|                               | (Round 1)              |                                              |                             |             |                      |            |                      |            |
| 13) Pairs Matching            | Number Incorrect       | Online                                       | short-term memory/attention | -0.183      | [-0.192,-0.173]     | p<2e-16    | -0.018 [-0.034,-0.002] | p=3.0e-02 |
|                               | (Round 1)              |                                              |                             |             |                      |            |                      |            |
| 8) Pairs Matching             | Number Incorrect       | In Person                                    | short-term memory/attention | -0.14       | [-0.145,-0.136]     | p<2e-16    | -0.013 [-0.021,-0.006] | p<2e-16    |
|                               | (Round 1)              |                                              |                             |             |                      |            |                      |            |
| 24) Symbol Digit Substitution | Time To Complete       | Online                                       | processing speed            | -0.507      | [-0.517,-0.496]     | p<2e-16    | -0.048 [-0.065,-0.03] | p<2e-16    |
|                               | 10 Substitutions       |                                              |                             |             |                      |            |                      |            |
| 18) Prospective Memory        | 1st Or 2nd Attempt     | In Person                                    | prospective memory          | -2.898      | [-3.144,-2.651]     | p<2e-16    | -0.257 [-0.66,0.146]  | p=2.1e-01 |
|                               | Correct                |                                              |                             |             |                      |            |                      |            |
| 20) Symbol Digit Substitution | Number Attempted       | In Person                                    | processing speed            | -0.606      | [-0.63,-0.583]      | p<2e-16    | -0.051 [-0.091,-0.01] | p=1.0e-02 |
|                               |                       |                                              |                             |             |                      |            |                      |            |
| Test                                                                 | Subtest                                      | Method          | Outcome Measure                          | Effect Size (95% CI) | p-Value (95% CI) |
|----------------------------------------------------------------------|----------------------------------------------|-----------------|------------------------------------------|-----------------------|-----------------|
| 32) Trail-making                                                    | Number Of Errors In Alphanumeric Trail      | Online          | processing speed/executive functioning  | -0.125 [-0.141, -0.108] | p<2e-16         |
| 25) Trail-making                                                    | Time to Complete Numeric Trail              | In Person       | processing speed                         | -0.407 [-0.432, -0.381] | p=4.8e-01       |
| 21) Symbol Digit Substitution                                        | Number Correct                              | In Person       | processing speed                         | -0.587 [-0.611, -0.563] | p=4.0e-02       |
| 30) Trail-making                                                    | Time to Complete Alphanumeric Trail         | Online          | processing speed/executive functioning   | -0.465 [-0.474, -0.455] | p<2e-16         |
| 15) Pairs Matching                                                  | Time To Complete (Round 1)                  | Online          | short-term memory/attention              | -0.431 [-0.441, -0.422] | p=1.3e-01       |
| 2) Fluid Intelligence                                               | Number Attempted                            | In Person       | logic/reasoning                          | -0.171 [-0.18, -0.163]  | p=2.1e-01       |
| 22) Symbol Digit Substitution                                        | Number Correct                              | Online          | processing speed                         | -0.577 [-0.586, -0.568]  | p<2e-16         |
| 11) Pairs Matching                                                  | Time To Complete (Round 2)                  | In Person       | short-term memory/attention              | -0.307 [-0.311, -0.302]  | p<2e-16         |
| 17) Prospective Memory                                              | 1st Attempt Correct                         | In Person       | prospective memory                       | -1.164 [-1.219, -1.11]   | p=2.1e-01       |
| 23) Symbol Digit Substitution                                        | Number Attempted                            | Online          | processing speed                         | -0.608 [-0.617, -0.6]    | p<2e-16         |

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| 9) Pairs Matching | Number Incorrect (Round 2) | In Person | short-term memory/attention | -0.183 [-0.188, -0.179] | p<2e-16 | -0.006 [-0.013, 0.002] | p=1.4e-01 | 3.1 |
| 29) Trail-making | Time to Complete Numeric Trail | Online | processing speed | -0.368 [-0.378, -0.358] | p<2e-16 | -0.01 [-0.027, 0.007] | p=2.7e-01 | 2.6 |
| 19) Reaction Time | Mean Time | In Person | reaction time | -0.374 [-0.378, -0.37] | p<2e-16 | 0.003 [-0.004, 0.01] | p=4.0e-01 | -0.8 |
| 31) Trail-making | Number Of Errors In Numeric Trail | Online | processing speed | -0.093 [-0.114, -0.073] | p<2e-16 | 0.012 [-0.022, 0.046] | p=5.0e-01 | -12.9 |

*a Coefficient on age term (b2) in eEquation 1
b Coefficient on APOE×age term (b3) in eEquation 1
c (100*b3/b2) using the coefficients from eEquation 1
d Cognitive measure with significant interaction effect (b3)
### eTable 8: Age of divergence in sensitivity analysis excluding APOE from the AD-GRS

| Test | Variable                                      | Location     | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|------|-----------------------------------------------|--------------|--------------------|--------------------|-------------------|-------------------------------|
| 6) Pairs Matching | Number Correct (Round 1) | In Person    | 41                 | 70                 | <=41              | 70+                           |
| 3) Fluid Intelligence | Number Correct | Online       | 45.4               | 69.4               | <=45.4            | 70+                           |
| 5) Numeric Memory a | Number Correct | Online       | 45.4               | 69.4               | <=45.4            | 70+                           |
| 23) Symbol Digit Substitution a | Number Attempted | Online       | 45.4               | 69.4               | <=45.4            | 70+                           |
| 22) Symbol Digit Substitution a | Number Correct | Online       | 45.4               | 69.4               | <=45.4            | 70+                           |
| 30) Trail-making a | Time to Complete Alphanumeric Trail | Online       | 45.4               | 69.4               | <=45.4            | 70+                           |
| 16) Pairs Matching | Time To Complete (Round 2) | Online       | 45.5               | 69.5               | <=45.5            | 70+                           |
| 20) Symbol Digit Substitution | Number Attempted | In Person    | 47                 | 70                 | <=47              | 70+                           |
| 21) Symbol Digit Substitution | Number Correct | In Person    | 47                 | 70                 | <=47              | 70+                           |
| 27) Trail-making | Time to Complete Alphanumeric Trail | In Person    | 47                 | 70                 | <=47              | 70+                           |
| 25) Trail-making | Time to Complete Numeric Trail | In Person    | 47                 | 70                 | <=47              | 70+                           |
| 12) Pairs Matching a | Number Correct (Round 1) | Online       | 45.4               | 69.4               | 49.4              | 70+                           |
| 2) Fluid Intelligence | Number Attempted | In Person    | 41                 | 70                 | 51                | 70+                           |
| 28) Trail-making | Number Of Errors In Alphanumeric Trail | In Person    | 47                 | 70                 | 53                | 70+                           |
| 9) Pairs Matching | Number Incorrect (Round 2) | In Person    | 41                 | 70                 | 54                | 70+                           |
| 11) Pairs Matching a | Time To Complete (Round 2) | In Person    | 41                 | 70                 | 54                | 70+                           |
| Test Description                  | Measurement                          | In Person | Online  | Online  | Online  | Online  |
|----------------------------------|--------------------------------------|-----------|---------|---------|---------|---------|
| 1) Fluid Intelligence            | Number Correct                       |           | 41      | 70      | 55      | 70+     |
| 7) Pairs Matching                | Number Correct (Round 2)             |           | 41      | 70      | 56      | 70+     |
| 24) Symbol Digit Substitution    | Time To Complete 10 Substitutions     | Online    | 45.4    | 69.4    | 56.4    | 70+     |
| 15) Pairs Matching               | Time To Complete (Round 1)           | Online    | 45.4    | 69.4    | 57.4    | 70+     |
| 8) Pairs Matching                | Number Incorrect (Round 1)           | In Person | 41      | 70      | 58      | 70+     |
| 13) Pairs Matching               | Number Incorrect (Round 1)           | Online    | 45.4    | 69.4    | 58.4    | 70+     |
| 14) Pairs Matching               | Number Incorrect (Round 2)           | Online    | 45.5    | 69.5    | 58.5    | 70+     |
| 10) Pairs Matching               | Time To Complete (Round 1)           | In Person | 41      | 70      | 60      | 70+     |
| 18) Prospective Memory           | 1st Or 2nd Attempt Correct           | In Person | 41      | 70      | 61      | 70+     |
| 17) Prospective Memory           | 1st Attempt Correct                  | In Person | 41      | 70      | 62      | 70+     |
| 29) Trail-making                 | Time to Complete Numeric Trail       | Online    | 45.4    | 69.4    | 63.4    | 70+     |
| 19) Reaction Time                | Mean Time                            | In Person | 41      | 70      | 64      | 70+     |
| 26) Trail-making                 | Number Of Errors In Numeric Trail    | In Person | 47      | 70      | 67      | 70+     |
| 4) Numeric Memory                | Number Correct                       | In Person | 41      | 70      | 68      | 70+     |
| 31) Trail-making                 | Number Of Errors In Numeric Trail    | Online    | 45.4    | 69.4    | 69.4    | 70+     |
| 32) Trail-making                 | Number Of Errors In Alphanumeric Trail | Online  | 45.5    | 69.5    | 69.5    | 70+     |

*a Significant modification of the effect of age by AD-GRS in interaction models*
**eTable 9: Association of AD-GRS (excluding APOE) at age 40 and effect modification of age-slope by AD-GRS for each cognitive assessment (z-scored)**

| Test                  | Variable                          | Location   | Domain                        | Age slope per decade for person with mean GRS [95% CI] \(^a\) | Difference in age slope for person with 1SD higher GRS [95% CI] \(^b\) | Difference in mean cognition per decade increase in age for 1 SD higher AD GRS \(^c\) | Difference in age slope for person with an additional copy of APOE ε4 (95% CI) \(^d\) | Percent Difference in mean cognition per decade increase in age per additional copy of APOE ε4 \(^e\) |
|-----------------------|-----------------------------------|------------|-------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 26) Trail-making      | Number Of Errors In Numeric Trail | In Person  | processing speed               | -0.116 [-0.142, -0.089] p<2e-16                                 | -0.021 [-0.044, 0.002] p=7.0e-02                                        | 18.1                                                                                                                              | -0.02 [-0.065, 0.025] p=3.9e-01                                                                  | 17.1                                                                                           |
| 32) Trail-making      | Number Of Errors In Alphanumeric Trail | Online   | processing speed/executive functioning | -0.125 [-0.141, -0.108] p<2e-16                                 | -0.007 [-0.021, 0.008] p=3.5e-01                                        | 5.4                                                                                                                              | -0.01 [-0.038, 0.018] p=4.8e-01                                                                  | 8                                                                                               |
| 21) Symbol Digit Substitution | Number Correct                      | In Person  | processing speed               | -0.586 [-0.61, -0.562] p<2e-16                                  | -0.03 [-0.051, -0.009] p<2e-16                                          | 5.1                                                                                                                              | -0.043 [-0.084, -0.003] p=4.0e-01                                                                  | 7.4                                                                                           |
| 17) Prospective Memory | 1st Attempt Correct                | In Person  | prospective memory             | -1.163 [-1.218, -1.109] p<2e-16                                  | -0.055 [-0.103, -0.007] p=3.0e-02                                       | 4.7                                                                                                                              | -0.058 [-0.15, 0.033] p=2.1e-01                                                                  | 5                                                                                               |
| 20) Symbol Digit Substitution | Number Attempted                     | In Person  | processing speed               | -0.606 [-0.629, -0.582] p<2e-16                                  | -0.027 [-0.048, -0.007] p=4.5                                            | 4.5                                                                                                                              | -0.051 [-0.091, -0.013] p=4.0e-01                                                                  | 8.4                                                                                           |
| Task                        | Corrected Data | Statistic | p-Value | Statistic | p-Value | Statistic | p-Value |
|-----------------------------|----------------|-----------|---------|-----------|---------|-----------|---------|
| **12) Pairs Matching**     | Number Correct (Round 1) | Online | short-term memory/attention | -0.115 [-0.125,-0.106] | p<2e-16 | -0.005 [-0.013,0.004] | p=2.8e-01 |
|                            |                |          |         | 4.1       | p<2e-16 | 4.1       | p<2e-16 |
| **7) Pairs Matching**      | Number Correct (Round 2) | In Person | short-term memory/attention | -0.088 [-0.093,-0.083] | p<2e-16 | -0.004 [-0.008,0.001] | p=9.0e-02 |
|                            |                |          |         | 4         | p<2e-16 | 4         | p<2e-16 |
| **27) Trail-making**       | Time to Complete Alphanumeric Trail | In Person | processing speed/executive functioning | -0.458 [-0.483,-0.432] | p<2e-16 | -0.018 [-0.04,0.004] | p=1.2e-01 |
|                            |                |          |         | 3.9       | p<2e-16 | 3.9       | p<2e-16 |
| **6) Pairs Matching**      | Number Correct (Round 1) | In Person | short-term memory/attention | -0.087 [-0.092,-0.082] | p<2e-16 | -0.003 [-0.007,0.001] | p=1.4e-01 |
|                            |                |          |         | 3.5       | p<2e-16 | 3.5       | p<2e-16 |
| **1) Fluid Intelligence**  | Number Correct | In Person | logic/reasoning | -0.113 [-0.121,-0.105] | p<2e-16 | -0.003 [-0.011,0.004] | p=3.4e-01 |
|                            |                |          |         | 3.1       | p<2e-16 | 3.1       | p=1.0e-02 |
| **25) Trail-making**       | Time to Complete Numeric Trail | In Person | processing speed | -0.406 [-0.432,-0.381] | p<2e-16 | -0.012 [-0.035,0.01] | p=2.7e-01 |
|                            |                |          |         | 3.1       | p<2e-16 | 3.1       | p=1.4e-01 |
| **5) Numeric Memory**      | Number Correct | Online | short-term memory capacity/attention | -0.171 [-0.181,-0.161] | p<2e-16 | -0.004 [-0.013,0.004] | p=3.3e-01 |
|                            |                |          |         | 2.5       | p<2e-16 | 2.5       | p<2e-16 |
| Test Type                           | Condition                          | Correct/Incorrect | In Person/Online | Short-term Memory Capacity/Attention | Prospective Memory | Reaction Time | Symbol Digit Substitution | Trail-Making | Pairs Matching Round 1 | Pairs Matching Round 2 | Online Short-term Memory Capacity/Attention |
|------------------------------------|------------------------------------|-------------------|-----------------|-------------------------------------|-------------------|---------------|---------------------------|--------------|------------------------|------------------------|-----------------------------------------------|
| 4) Numeric Memory                  | Number Correct                     | In Person         | short-term memory capacity/attention | -0.151 [-0.165,-0.137] p=2e-16 | -0.003 [-0.016,0.009] p=5.8e-01 | 2.3           | -0.026 [-0.05,-0.003] p=3.0e-02 | 17.4         |
| 14) Pairs Matching                 | Number Incorrect (Round 2)          | Online            | short-term memory/attention          | -0.208 [-0.235,-0.182] p=2e-16 | -0.004 [-0.027,0.019] p=7.2e-01 | 2             | -0.03 [-0.075,0.016] p=2.0e-01 | 14.3         |
| 18) Prospective Memory             | 1st Or 2nd Attempt Correct          | In Person         | prospective memory                  | -2.896 [-3.143,-2.649] p=2e-16 | -0.053 [-0.268,0.162] p=6.3e-01 | 1.8           | -0.256 [-0.659,0.147] p=2.1e-01 | 8.8          |
| 28) Trail-making                   | Number Of Errors In Alphanumeric Trail | In Person   | processing speed/executive functioning | -0.2 [-0.226,-0.174] p=2e-16 | -0.003 [-0.026,0.02] p=8.0e-01 | 1.4           | -0.046 [-0.091,-0.001] p=4.0e-02 | 22.9         |
| 10) Pairs Matching                 | Time To Complete (Round 1)          | In Person         | short-term memory/attention          | -0.2 [-0.205,-0.195] p=2e-16 | -0.002 [-0.006,0.002] p=2.9e-01 | 1.1           | -0.022 [-0.029,-0.014] p<2e-16 | 10.8         |
| 24) Symbol Digit Substitution      | Time To Complete 10 Substitutions    | Online            | processing speed                     | -0.507 [-0.517,-0.496] p=2e-16 | -0.004 [-0.013,0.005] p=3.5e-01 | 0.9           | -0.048 [-0.065,-0.03] p<2e-16 | 9.4          |
| 19) Reaction Time                  | Mean Time                           | In Person         | reaction time                        | -0.374 [-0.378,-0.37] p=2e-16 | -0.003 [-0.006,0.001] p=2.0e-01 | 0.7           | 0.003 [-0.004,0.01] p=4.0e-01 | -0.8         |
| 15) Pairs Matching                 | Time To Complete (Round 1)          | Online            | short-term memory/attention          | -0.431 [-0.441,-0.44] p=5.3e-01 | -0.003 [-0.011,0.006] p=5.3e-01 | 0.6           | -0.028 [-0.044,-] p=4.0e-01 | 6.5          |
| Task                          | Condition         | Variable                          | In Person | Online | p-value Online | p-value In Person | Estimate | 95% CI      | Estimate | 95% CI      |
|-------------------------------|-------------------|-----------------------------------|-----------|--------|----------------|-------------------|----------|-------------|----------|-------------|
| 8) Pairs Matching             | Number Incorrect  | short-term memory/attention       | -0.14     | -0.145 | p<2e-16        | p<2e-16           | -0.001   | [-0.005,0.003] | 0.5      | [-7.4e-01,0.001] |
| Round 1                       | In Person         |                                   |           |        |                |                   |          |             | 0.012    | [-0.021,-0.006] |
| 11) Pairs Matching            | Time To Complete  | short-term memory/attention       | -0.307    | -0.311 | p<2e-16        | p<2e-16           | -0.001   | [-0.005,0.003] | 0.4      | [-0.024,-0.009] |
| Round 2                       | In Person         |                                   |           |        |                |                   |          |             | -0.183   | [-0.013,0.002] |
| 9) Pairs Matching             | Number Incorrect  | short-term memory/attention       | -0.183    | -0.188 | p<2e-16        | p<2e-16           | 0       | [0.004,0.004] | 0        | [1.4e-01,1] |
| Round 2                       | In Person         |                                   |           |        |                |                   |          |             | -0.577   | [-0.048,-0.018] |
| 22) Symbol Digit Substitution | Number Correct    | processing speed                  | -0.577    | -0.586 | p<2e-16        | p<2e-16           | 0.001    | [0.007,0.009] | -0.2     | [2e-16,5.7] |
| 23) Symbol Digit Substitution | Number Attempted  | processing speed                  | -0.608    | -0.617 | p<2e-16        | p<2e-16           | 0.001    | [0.007,0.009] | -0.2     | [2e-16,4.8] |
| Time to Complete              | Online            |                                   |           |        |                |                   |          |             | -0.029   | [-0.044,-0.014] |
| Numeric Trail                 | Online            |                                   |           |        |                |                   |          |             | -0.368   | [-0.038,-0.058] |
| 29) Trail-making              | Time to Complete  | processing speed                  | -0.368    | -0.378 | p<2e-16        | p<2e-16           | 0.003    | [0.006,0.011] | -0.7     | [2.7e-01,2.6] |
| Numeric Trail                 | Online            |                                   |           |        |                |                   |          |             | -0.181   | [-0.039,-0.007] |
| 3) Fluid Intelligence         | Number Correct    | logic/reasoning                   | -0.181    | -0.19   | p<2e-16        | p<2e-16           | 0.002    | [0.007,0.01]  | -1       | [2e-16,12.8] |

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| 30) Trail-making | Time to Complete Alphanumeric Trail | Online | processing speed/executive functioning | -0.465 [-0.474,-0.455] p<2e-16 | 0.005 [-0.003,0.014] p=2.3e-01 | -0.032 [-0.049,-0.015] p<2e-16 | 6.9 |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 13) Pairs Matching | Number Incorrect (Round 1) | Online | short-term memory/attention | -0.183 [-0.192,-0.173] p<2e-16 | 0.002 [-0.006,0.011] p=6.0e-01 | -0.018 [-0.034,-0.002] p=3.0e-02 | 9.9 |
| 31) Trail-making | Number Of Errors In Numeric Trail | Online | processing speed | -0.093 [-0.114,-0.073] p<2e-16 | 0.001 [-0.017,0.019] p=8.9e-01 | 0.012 [-0.022,0.046] p=5.0e-01 | -12.9 |
| 2) Fluid Intelligence | Number Attempted | In Person | logic/reasoning | -0.172 [-0.18,-0.163] p<2e-16 | 0.005 [-0.002,0.012] p=1.7e-01 | -0.01 [-0.024,0.003] p=1.4e-01 | 6 |
| 16) Pairs Matching | Time To Complete (Round 2) | Online | short-term memory/attention | -0.422 [-0.447,-0.397] p<2e-16 | 0.012 [-0.01,0.034] p=2.7e-01 | -0.055 [-0.098,-0.011] p=1.0e-02 | 13 |

*a Coefficient on age term ($b_2$) in eEquation 2
*b Coefficient on ADGRS$z$×age term ($b_3$) in eEquation 2
*c $(100*b_3/b_6)$ using the coefficients from eEquation 2
*d Coefficient on APOE×age term ($b_3$) in eEquation 2
*e $(100*b_3/b_4)$ using the coefficients from eEquation 2
### eTable 10: Age of divergence in sensitivity analysis using count of APOE ε4-alleles and an AD-GRS that excludes APOE

| Test                          | Variable                                      | Location | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|-------------------------------|-----------------------------------------------|----------|--------------------|--------------------|-------------------|---------------------------------|
| 3) Fluid Intelligence         | Number Correct                                | Online   | 45.4               | 69.4               | <=45.4            | 63                              |
| 13) Pairs Matching            | Number Incorrect (Round 1)                    | Online   | 45.4               | 69.4               | <=45.4            | 70+                             |
| 25) Trail-making              | Time to Complete Numeric Trail                | In Person| 47                 | 70                 | <=47              | 70+                             |
| 26) Trail-making              | Number Of Errors In Numeric Trail             | In Person| 47                 | 70                 | 48                | 65                              |
| 23) Symbol Digit Substitution | Number Attempted                              | Online   | 45.4               | 69.4               | 50.4              | 67                              |
| 12) Pairs Matching            | Number Correct (Round 1)                      | Online   | 45.4               | 69.4               | 52.4              | 65                              |
| 22) Symbol Digit Substitution | Number Correct                                | Online   | 45.4               | 69.4               | 53.4              | 66                              |
| 15) Pairs Matching            | Time To Complete (Round 1)                    | Online   | 45.4               | 69.4               | 54.4              | 64                              |
| 32) Trail-making              | Number Of Errors In Alphanumeric Trail        | Online   | 45.5               | 69.5               | 55.5              | 67                              |
| 10) Pairs Matching            | Time To Complete (Round 1)                    | In Person| 41                 | 70                 | 57                | 70+                             |
| 11) Pairs Matching            | Time To Complete (Round 2)                    | In Person| 41                 | 70                 | 57                | 70+                             |
| 6) Pairs Matching             | Number Correct (Round 1)                      | In Person| 41                 | 70                 | 61                | 70+                             |
| 7) Pairs Matching             | Number Correct (Round 2)                      | In Person| 41                 | 70                 | 61                | 70+                             |
| 24) Symbol Digit Substitution | Time To Complete 10 Substitutions             | Online   | 45.4               | 69.4               | 62.4              | 68                              |
| 9) Pairs Matching             | Number Incorrect (Round 2)                    | In Person| 41                 | 70                 | 64                | 70+                             |
| 31) Trail-making              | Number Of Errors In Numeric Trail             | Online   | 45.4               | 69.4               | 64.4              | 70+                             |
| Test Type | Description                                                                 | Group   | 45.5 | 69.5 | 64.5 | 70+  |
|-----------|-------------------------------------------------------------------------------|---------|------|------|------|------|
| 14) Pairs Matching | Number Incorrect (Round 2) | Online  | 45.5 | 69.5 | 64.5 | 70+  |
| 16) Pairs Matching | Time To Complete (Round 2) | Online  | 45.5 | 69.5 | 64.5 | 70+  |
| 27) Trail-making | Time to Complete Alphanumeric Trail | In Person | 47   | 70   | 66   | 70+  |
| 28) Trail-making | Number Of Errors In Alphanumeric Trail | In Person | 47   | 70   | 67   | 70+  |
| 2) Fluid Intelligence | Number Attempted | In Person | 41   | 70   | 68   | 70+  |
| 4) Numeric Memory | Number Correct | In Person | 41   | 70   | 68   | 70+  |
| 19) Reaction Time | Mean Time | In Person | 41   | 70   | 69   | 70+  |
| 5) Numeric Memory | Number Correct | Online   | 45.4 | 69.4 | 69.4 | 70+  |
| 30) Trail-making | Time to Complete Alphanumeric Trail | Online  | 45.4 | 69.4 | 69.4 | 70+  |
| 29) Trail-making | Time to Complete Numeric Trail | Online  | 45.4 | 69.4 | 69.4 | 70+  |
| 1) Fluid Intelligence | Number Correct | In Person | 41   | 70   | 70   | 70+  |
| 8) Pairs Matching | Number Incorrect (Round 1) | In Person | 41   | 70   | 70   | 70+  |
| 17) Prospective Memory | 1st Attempt Correct | In Person | 41   | 70   | 70   | 70+  |
| 18) Prospective Memory | 1st Or 2nd Attempt Correct | In Person | 41   | 70   | 70   | 70+  |
| 20) Symbol Digit Substitution | Number Attempted | In Person | 47   | 70   | 70   | 70+  |
| 21) Symbol Digit Substitution | Number Correct | In Person | 47   | 70   | 70   | 70+  |
| Test | Variable | Location | Domain | Age slope per decade for person with mean GRS [95% CI] | Difference in age slope for person with 1SD higher GRS [95% CI] | Percent Difference in mean cognition per decade increase in age for 1 SD higher AD GRS |
|------|----------|----------|--------|---------------------------------------------------|---------------------------------------------------------------|------------------------------------------|
| 26) Trail-making | Number Of Errors In Numeric Trail | In Person | processing speed | -0.121 [-0.143, 0.098] p<2e-16 | -0.021 [-0.044, 0.002] p=8.0e-02 | 17.1 |
| 32) Trail-making | Number Of Errors In Alphanumeric Trail | Online | processing speed/executive functioning | -0.128 [-0.142, 0.114] p<2e-16 | -0.007 [-0.021, 0.008] p=3.5e-01 | 5.4 |
| 21) Symbol Digit Substitution | Number Correct | In Person | processing speed | -0.598 [-0.618, 0.577] p<2e-16 | -0.03 [-0.05, 0.009] p=1.0e-02 | 4.9 |
| 17) Prospective Memory | 1st Attempt Correct | In Person | prospective memory | -1.181 [-1.228, 1.134] p<2e-16 | -0.055 [-0.103, 0.007] p=2.0e-02 | 4.6 |
| 20) Symbol Digit Substitution | Number Attempted | In Person | processing speed | -0.62 [-0.64, 0.599] p<2e-16 | -0.027 [-0.047, 0.006] p=1.0e-02 | 4.3 |
| 7) Pairs Matching (Round 2) | Number Correct | In Person | short-term memory/attention | -0.093 [-0.097, 0.089] p<2e-16 | -0.004 [-0.008, 0] p=9.0e-02 | 3.8 |
| 12) Pairs Matching (Round 1) | Number Correct | Online | short-term memory/attention | -0.123 [-0.131, 0.115] p<2e-16 | -0.005 [-0.013, 0.004] p=2.8e-01 | 3.8 |
| Test | Task | Type | Condition | Measure | Effect Size | Confidence Interval | p value | Significant? |
|------|------|------|-----------|---------|-------------|---------------------|---------|-------------|
| 27) Trail-making | Time to Complete Alphanumeric Trail | In Person | processing speed/executive functioning | -0.472 [-0.494,-0.45] | p<2e-16 | -0.017 [-0.039,0.005] | p=1.3e-01 | 3.6 |
| 6) Pairs Matching | Number Correct (Round 1) | In Person | short-term memory/attention | -0.091 [-0.095,-0.087] | p<2e-16 | -0.003 [-0.007,0.001] | p=1.4e-01 | 3.3 |
| 1) Fluid Intelligence | Number Correct | In Person | logic/reasoning | -0.119 [-0.126,-0.112] | p<2e-16 | -0.003 [-0.011,0.004] | p=3.4e-01 | 2.9 |
| 25) Trail-making | Time to Complete Numeric Trail | In Person | processing speed | -0.415 [-0.437,-0.393] | p<2e-16 | -0.012 [-0.034,0.01] | p=2.9e-01 | 2.9 |
| 5) Numeric Memory | Number Correct | Online | short-term memory capacity/attention | -0.18 [-0.188,-0.171] | p<2e-16 | -0.004 [-0.013,0.004] | p=3.3e-01 | 2.4 |
| 4) Numeric Memory | Number Correct | In Person | short-term memory capacity/attention | -0.159 [-0.171,-0.147] | p<2e-16 | -0.003 [-0.016,0.009] | p=5.9e-01 | 2.2 |
| 14) Pairs Matching | Number Incorrect (Round 2) | Online | short-term memory/attention | -0.216 [-0.239,-0.193] | p<2e-16 | -0.004 [-0.027,0.019] | p=7.3e-01 | 1.9 |
| 18) Prospective Memory | 1st Or 2nd Attempt Correct | In Person | prospective memory | -2.978 [-3.188,-2.768] | p<2e-16 | -0.054 [-0.27,0.161] | p=6.2e-01 | 1.8 |
| 28) Trail-making | Number Of Errors In Alphanumeric Trail | In Person | processing speed/executive functioning | -0.213 [-0.236,-0.19] | p<2e-16 | -0.003 [-0.025,0.02] | p=8.2e-01 | 1.2 |
| 10) Pairs Matching | Time To Complete (Round 1) | In Person | short-term memory/attention | -0.207 [-0.211,-0.203] | p<2e-16 | -0.002 [-0.006,0.002] | p=2.9e-01 | 1.1 |
| Test Type                  | Category                          | Data Type                          | Online vs In Person | Cohen’s d (p-value)                                      |
|---------------------------|-----------------------------------|------------------------------------|---------------------|--------------------------------------------------------|
| 24) Symbol Digit Substitution | Time To Complete 10 Substitutions | processing speed                   | Online              | -0.52 [-0.529,-0.511] p<2e-16 0.004 [-0.013,0.005] p=3.6e-01 0.8 |
| 19) Reaction Time         | Mean Time                         | reaction time                      | In Person           | -0.373 [-0.377,-0.369] p<2e-16 -0.003 [-0.006,0.001] p=2.0e-01 0.7 |
| 15) Pairs Matching        | Time To Complete (Round 1)        | short-term memory/attention        | Online              | -0.439 [-0.447,-0.431] p<2e-16 -0.003 [-0.011,0.006] p=5.3e-01 0.6 |
| 8) Pairs Matching         | Number Incorrect (Round 1)        | short-term memory/attention        | In Person           | -0.144 [-0.148,-0.14] p<2e-16 -0.001 [-0.005,0.003] p=7.4e-01 0.5 |
| 11) Pairs Matching        | Time To Complete (Round 2)        | short-term memory/attention        | In Person           | -0.312 [-0.315,-0.308] p<2e-16 -0.001 [-0.005,0.003] p=5.7e-01 0.4 |
| 9) Pairs Matching         | Number Incorrect (Round 2)        | short-term memory/attention        | In Person           | -0.185 [-0.189,-0.181] p<2e-16 0 [-0.004,0.004] p=9.9e-01 0 |
| 22) Symbol Digit Substitution | Number Correct                   | processing speed                   | Online              | -0.586 [-0.593,-0.578] p<2e-16 0.001 [-0.007,0.009] p=8.0e-01 -0.2 |
| 23) Symbol Digit Substitution | Number Attempted                  | processing speed                   | Online              | -0.616 [-0.624,-0.609] p<2e-16 0.001 [-0.007,0.009] p=8.1e-01 -0.2 |
| 29) Trail-making          | Time to Complete Numeric Trail    | processing speed                   | Online              | -0.371 [-0.38,-0.362] p<2e-16 0.003 [-0.006,0.011] p=5.7e-01 -0.7 |
| 3) Fluid Intelligence     | Number Correct                   | logic/reasoning                    | Online              | -0.187 [-0.195,-0.179] p<2e-16 0.002 [-0.007,0.01] p=6.8e-01 -0.9 |
| ID  | Test Type                  | Measure                                      | Mode     | Domain                        | Effect Size | Confidence Interval             | p-value          |
|-----|----------------------------|----------------------------------------------|----------|-------------------------------|-------------|---------------------------------|-----------------|
| 30  | Trail-making               | Time to Complete Alphanumeric Trail          | Online   | processing speed/executive functioning | -0.474      | [-0.482, -0.465]               | p<2e-16         |
|     |                            |                                              |          |                               | 0.005       | [-0.003, 0.014]                | p=2.3e-01       |
| 13  | Pairs Matching             | Number Incorrect (Round 1)                   | Online   | short-term memory/attention    | -0.188      | [-0.196, -0.18]                | p<2e-16         |
|     |                            |                                              |          |                               | 0.002       | [-0.006, 0.011]                | p=6.0e-01       |
|     |                            |                                              |          |                               |             |                                 |                 |
| 31  | Trail-making               | Number Of Errors In Numeric Trail            | Online   | processing speed               | -0.09       | [-0.107, -0.072]               | p<2e-16         |
|     |                            |                                              |          |                               | 0.001       | [-0.017, 0.019]                | p=8.9e-01       |
|     |                            |                                              |          |                               |             |                                 |                 |
| 2   | Fluid Intelligence         | Number Attempted                             | In Person| logic/reasoning                | -0.175      | [-0.182, -0.168]               | p<2e-16         |
|     |                            |                                              |          |                               | 0.005       | [-0.002, 0.012]                | p=1.7e-01       |
|     |                            |                                              |          |                               |             |                                 |                 |
| 16  | Pairs Matching             | Time To Complete (Round 2)                   | Online   | short-term memory/attention    | -0.437      | [-0.458, -0.415]               | p<2e-16         |
|     |                            |                                              |          |                               | 0.013       | [-0.01, 0.035]                 | p=2.7e-01       |

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\( a \) Coefficient on age term \((b_2)\) in equation 1

\( b \) Coefficient on ADGRS × age term \((b_3)\) in equation 1

\( c \) \((100*b_2/b_3)\) using the coefficients from equation 1

eTable 12: Age of divergence in sensitivity analysis excluding APOE from the AD-GRS

| Test | Variable                        | Location         | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|------|---------------------------------|------------------|--------------------|--------------------|-------------------|-------------------------------|
| 3)   | Fluid Intelligence Number Correct | Online           | 45.4               | 69.4               | <=45.4            | 63                            |
| 13)  | Pairs Matching Number Incorrect (Round 1) | Online           | 45.4               | 69.4               | <=45.4            | 70+                           |
| 25)  | Trail-making Time to Complete Numeric Trail | In Person        | 47                 | 70                 | <=47              | 70+                           |
| 26)  | Trail-making Number Of Errors In Numeric Trail | In Person        | 47                 | 70                 | 48                | 65                            |
| 23)  | Symbol Digit Substitution Number Attempted | Online           | 45.4               | 69.4               | 50.4              | 67                            |
| 12)  | Pairs Matching Number Correct (Round 1) | Online           | 45.4               | 69.4               | 52.4              | 65                            |
| 22)  | Symbol Digit Substitution Number Correct | Online           | 45.4               | 69.4               | 53.4              | 66                            |
| 15)  | Pairs Matching Time To Complete (Round 1) | Online           | 45.4               | 69.4               | 54.4              | 64                            |
| 32)  | Trail-making Number Of Errors In Alphanumeric Trail | Online           | 45.5               | 69.5               | 55.5              | 67                            |
| 10)  | Pairs Matching Time To Complete (Round 1) | In Person        | 41                 | 70                 | 57                | 70+                           |
| 11)  | Pairs Matching Time To Complete (Round 2) | In Person        | 41                 | 70                 | 57                | 70+                           |
| 6)   | Pairs Matching Number Correct (Round 1) | In Person        | 41                 | 70                 | 61                | 70+                           |
| 7)   | Pairs Matching Number Correct (Round 2) | In Person        | 41                 | 70                 | 61                | 70+                           |
| 24)  | Symbol Digit Substitution Time To Complete 10 Substitutions | Online           | 45.4               | 69.4               | 62.4              | 68                            |
| 16)  | Pairs Matching Time To Complete (Round 2) | Online           | 45.5               | 69.5               | 63.5              | 70+                           |
| 9)   | Pairs Matching Number Incorrect (Round 2) | In Person        | 41                 | 70                 | 64                | 70+                           |
| 31)  | Trail-making Number Of Errors In Numeric Trail | Online           | 45.4               | 69.4               | 64.4              | 70+                           |
| 14)  | Pairs Matching Number Incorrect (Round 2) | Online           | 45.5               | 69.5               | 64.5              | 70+                           |
| 28)  | Trail-making Number Of Errors In Alphanumeric Trail | In Person        | 47                 | 70                 | 67                | 70+                           |
| 27)  | Trail-making Time To Complete Alphanumeric Trail | In Person        | 47                 | 70                 | 67                | 70+                           |
| Test Type                  | Measurement                  | Setting   | Value 1 | Value 2 | Value 3 | Value 4 |
|---------------------------|------------------------------|-----------|---------|---------|---------|---------|
| Fluid Intelligence        | Number Correct               | In Person | 41      | 70      | 68      | 70+     |
| Numeric Memory            | Number Correct               | In Person | 41      | 70      | 68      | 70+     |
| Reaction Time             | Mean Time                    | In Person | 41      | 70      | 68      | 70+     |
| Numeric Memory            | Number Correct               | Online    | 45.4    | 69.4    | 69.4    | 70+     |
| Trail-making              | Time to Complete Alphanumeric Trail | Online | 45.4    | 69.4    | 69.4    | 70+     |
| Trail-making              | Time to Complete Numeric Trail | Online    | 45.4    | 69.4    | 69.4    | 70+     |
| Fluid Intelligence        | Number Correct               | In Person | 41      | 70      | 70      | 70+     |
| Pairs Matching            | Number Incorrect (Round 1)   | In Person | 41      | 70      | 70      | 70+     |
| Prospective Memory        | 1st Attempt Correct          | In Person | 41      | 70      | 70      | 70+     |
| Prospective Memory        | 1st Or 2nd Attempt Correct   | In Person | 41      | 70      | 70      | 70+     |
| Symbol Digit Substitution | Number Attempted             | In Person | 47      | 70      | 70      | 70+     |
| Symbol Digit Substitution | Number Correct               | In Person | 47      | 70      | 70      | 70+     |
eTable 13: Age of divergence in sensitivity analysis with linear age term and quadratic divergence term

| Test                      | Variable                                | Location       | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|---------------------------|-----------------------------------------|----------------|--------------------|--------------------|-------------------|---------------------------------|
| 8) Pairs Matching         | Number Incorrect (Round 1)              | In Person      | 41                 | 70                 | <=41              | 70+                             |
| 9) Pairs Matching         | Number Incorrect (Round 2)              | In Person      | 41                 | 70                 | <=41              | 70+                             |
| 11) Pairs Matching        | Time To Complete (Round 2)              | In Person      | 41                 | 70                 | <=41              | 70+                             |
| 19) Reaction Time         | Mean Time                               | In Person      | 41                 | 70                 | <=41              | 70+                             |
| 10) Pairs Matching        | Time To Complete (Round 1)              | In Person      | 41                 | 70                 | 43                | 70+                             |
| 4) Numeric Memory         | Number Correct                          | In Person      | 41                 | 70                 | 45                | 70+                             |
| 13) Pairs Matching        | Number Incorrect (Round 1)              | Online         | 45.4               | 69.4               | <=45.4            | 54                              |
| 15) Pairs Matching        | Time To Complete (Round 1)              | Online         | 45.4               | 69.4               | <=45.4            | 52                              |
| 23) Symbol Digit Substitution | Number Attempted                      | Online         | 45.4               | 69.4               | <=45.4            | 52                              |
| 22) Symbol Digit Substitution | Number Correct                  | Online         | 45.4               | 69.4               | <=45.4            | 52                              |
| 24) Symbol Digit Substitution | Time To Complete 10 Substitutions    | Online         | 45.4               | 69.4               | <=45.4            | 51                              |
| 30) Trail-making          | Time to Complete Alphanumeric Trail    | Online         | 45.4               | 69.4               | <=45.4            | 52                              |
| 29) Trail-making          | Time to Complete Numeric Trail         | Online         | 45.4               | 69.4               | <=45.4            | 57                              |
| 14) Pairs Matching        | Number Incorrect (Round 2)              | Online         | 45.5               | 69.5               | <=45.5            | 57                              |
| 16) Pairs Matching        | Time To Complete (Round 2)              | Online         | 45.5               | 69.5               | <=45.5            | 57                              |
| 32) Trail-making          | Number Of Errors In Alphanumeric Trail | Online         | 45.5               | 69.5               | <=45.5            | 58                              |
| 6) Pairs Matching         | Number Correct (Round 1)               | In Person      | 41                 | 70                 | 46                | 54                              |
| 7) Pairs Matching         | Number Correct (Round 1)               | In Person      | 41                 | 70                 | 46                | 54                              |
| 20) Symbol Digit Substitution | Number Attempted                      | In Person      | 47                 | 70                 | <=47              | 56                              |
| 21) Symbol Digit Substitution | Number Correct                  | In Person      | 47                 | 70                 | <=47              | 58                              |
|   | Task Description                                      | Group  | Mean   | SD     | Median  | Range |
|---|------------------------------------------------------|--------|--------|--------|---------|-------|
| 27) | Trail-making Time to Complete Alphanumeric Trail     | In Person | 47     | 70     | <=47    | 56    |
| 2)  | Fluid Intelligence Number Attempted                  | In Person | 41     | 70     | 48      | 70+   |
| 28) | Trail-making Number Of Errors In Alphanumeric Trail  | In Person | 47     | 70     | 49      | 58    |
| 25) | Trail-making Time to Complete Numeric Trail          | In Person | 47     | 70     | 49      | 58    |
| 1)  | Fluid Intelligence Number Correct                    | In Person | 41     | 70     | 51      | 70+   |
| 5)  | Numeric Memory Number Correct                        | Online  | 45.4   | 69.4   | 51.4    | 60    |
| 12) | Pairs Matching Number Correct (Round 1)              | Online  | 45.4   | 69.4   | 51.4    | 57    |
| 3)  | Fluid Intelligence Number Correct                    | Online  | 45.4   | 69.4   | 53.4    | 60    |
| 31) | Trail-making Number Of Errors In Numeric Trail       | Online  | 45.4   | 69.4   | 53.4    | 70+   |
| 26) | Trail-making Number Of Errors In Numeric Trail       | In Person | 47     | 70     | 55      | 61    |
| 18) | Prospective Memory 1st Or 2nd Attempt Correct        | In Person | 41     | 70     | 67      | 70+   |
| 17) | Prospective Memory 1st Attempt Correct               | In Person | 41     | 70     | 70      | 70+   |
eTable 14: Age of divergence in sensitivity analysis with cubic polynomial age term and fourth-order divergence term

| Test | Variable | Location  | Minimum Age Tested | Maximum Age Tested | Age of Divergence | Age of Statistical Significance |
|------|----------|-----------|--------------------|--------------------|------------------|--------------------------------|
| 2) Fluid Intelligence | Number Attempted | In Person | 41 | 70 | <=41 | 70+ |
| 4) Numeric Memory | Number Correct | In Person | 41 | 70 | <=41 | 70+ |
| 6) Pairs Matching | Number Correct (Round 1) | In Person | 41 | 70 | <=41 | 58 |
| 7) Pairs Matching | Number Correct (Round 2) | In Person | 41 | 70 | <=41 | 57 |
| 8) Pairs Matching | Number Incorrect (Round 1) | In Person | 41 | 70 | <=41 | 70+ |
| 9) Pairs Matching | Number Incorrect (Round 2) | In Person | 41 | 70 | <=41 | 70+ |
| 10) Pairs Matching | Time To Complete (Round 1) | In Person | 41 | 70 | <=41 | 70+ |
| 11) Pairs Matching | Time To Complete (Round 2) | In Person | 41 | 70 | <=41 | 70+ |
| 19) Reaction Time | Mean Time | In Person | 41 | 70 | <=41 | 70+ |
| 3) Fluid Intelligence | Number Correct | Online | 45.4 | 69.4 | <=45.4 | 61 |
| 5) Numeric Memory | Number Correct | Online | 45.4 | 69.4 | <=45.4 | 62 |
| 12) Pairs Matching | Number Correct (Round 1) | Online | 45.4 | 69.4 | <=45.4 | 60 |
| 13) Pairs Matching | Number Incorrect (Round 1) | Online | 45.4 | 69.4 | <=45.4 | 61 |
| 15) Pairs Matching | Time To Complete (Round 1) | Online | 45.4 | 69.4 | <=45.4 | 58 |
| 23) Symbol Digit Substitution | Number Attempted | Online | 45.4 | 69.4 | <=45.4 | 59 |
| 22) Symbol Digit Substitution | Number Correct | Online | 45.4 | 69.4 | <=45.4 | 59 |
| 24) Symbol Digit Substitution | Time To Complete 10 Substitutions | Online | 45.4 | 69.4 | <=45.4 | 58 |
| 31) Trail-making | Number Of Errors In Numeric Trail | Online | 45.4 | 69.4 | <=45.4 | 70+ |
| 30) Trail-making | Time to Complete Alphanumeric Trail | Online | 45.4 | 69.4 | <=45.4 | 59 |
|   |   |   |
|---|---|---|
| 29) Trail-making | Time to Complete Numeric Trail | Online | 45.4 | 69.4 | <=45.4 | 62 |
| 14) Pairs Matching | Number Incorrect (Round 2) | Online | 45.5 | 69.5 | <=45.5 | 62 |
| 16) Pairs Matching | Time To Complete (Round 2) | Online | 45.5 | 69.5 | <=45.5 | 63 |
| 32) Trail-making | Number Of Errors In Alphanumeric Trail | Online | 45.5 | 69.5 | <=45.5 | 64 |
| 1) Fluid Intelligence | Number Correct | In Person | 41 | 70 | <=47 | 70+ |
| 20) Symbol Digit Substitution | Number Attempted | In Person | 47 | 70 | <=47 | 63 |
| 21) Symbol Digit Substitution | Number Correct | In Person | 47 | 70 | <=47 | 65 |
| 28) Trail-making | Number Of Errors In Alphanumeric Trail | In Person | 47 | 70 | <=47 | 63 |
| 26) Trail-making | Number Of Errors In Numeric Trail | In Person | 47 | 70 | <=47 | 62 |
| 27) Trail-making | Time to Complete Alphanumeric Trail | In Person | 47 | 70 | <=47 | 63 |
| 25) Trail-making | Time to Complete Numeric Trail | In Person | 47 | 70 | <=47 | 63 |
| 17) Prospective Memory | 1st Attempt Correct | In Person | 41 | 70 | 70 | 70+ |
| 18) Prospective Memory | 1st Or 2nd Attempt Correct | In Person | 41 | 70 | 70 | 70+ |
eTable 15: Comparison of ages of divergence across different functional forms

| Test                      | Linear | Quadratic | Cubic |
|---------------------------|--------|-----------|-------|
| 6) Pairs Matching         | 46     | <=41      | <=41  |
| 9) Pairs Matching         | <=41   | <=41      | <=41  |
| 11) Pairs Matching        | <=41   | <=41      | <=41  |
| 2) Fluid Intelligence     | 48     | 42        | <=41  |
| 4) Numeric Memory         | 45     | 42        | <=41  |
| 8) Pairs Matching         | <=41   | 45        | <=41  |
| 3) Fluid Intelligence     | 53.4   | <=45.4    | <=45.4|
| 5) Numeric Memory         | 51.4   | <=45.4    | <=45.4|
| 23) Symbol Digit Substitution | <=45.4 | <=45.4    | <=45.4|
| 22) Symbol Digit Substitution | <=45.4 | <=45.4    | <=45.4|
| 30) Trail-making          | <=45.4 | <=45.4    | <=45.4|
| 29) Trail-making          | <=45.4 | <=45.4    | <=45.4|
| 16) Pairs Matching        | <=45.5 | <=45.5    | <=45.5|
| 32) Trail-making          | <=45.5 | <=45.5    | <=45.5|
| 13) Pairs Matching        | <=45.4 | 46.4      | <=45.4|
| 15) Pairs Matching        | <=45.4 | 46.4      | <=45.4|
| 20) Symbol Digit Substitution | <=47   | <=47      | <=47  |
| 21) Symbol Digit Substitution | <=47   | <=47      | <=47  |
| 27) Trail-making          | <=47   | <=47      | <=47  |
| 25) Trail-making          | 49     | <=47      | <=47  |
| 12) Pairs Matching        | 51.4   | 47.4      | <=45.4|
| 1) Fluid Intelligence     | 51     | 49        | 47    |
| 24) Symbol Digit Substitution | <=45.4 | 49.4      | <=45.4|
| Task                      | Lower Limit | Upper Limit | Percentile |
|---------------------------|-------------|-------------|------------|
| Pairs Matching            | 46          | 50          | <=41       |
| Pairs Matching            | 43          | 56          | <=41       |
| Trail-making              | 55          | 59          | <=47       |
| Trail-making              | 49          | 61          | <=47       |
| Pairs Matching            | <=45.5      | 64.5        | <=45.5     |
| Prospective Memory        | 67          | 66          | 70         |
| Reaction Time             | <=41        | 68          | <=41       |
| Trail-making              | 53.4        | 69.4        | <=45.4     |
| Prospective Memory        | 70          | 70          | 70         |
Average CV error is plotted on vertical axis, and the age of divergence for the model ($t_{\text{threshold}}$) is on the horizontal axis. The figure shows that the model with divergence in cognitive test score between low and high AD-GRS at age 59 was the best CV fit to the data based on the location of the minimum error.
eFigure 2: Divergence plots for all cognitive tests – part 1

Plots of predicted average cognition of four cognitive measures at higher (1.76) and lower (-1.22) z-scored AD-GRS. Solid vertical lines indicate threshold age at which the AD-GRS begins to influence the cognitive measure. At ages below the threshold, AD-GRS does not interact with age to influence cognition. Dashed vertical lines indicate the earliest age at which the cognitive difference in the
high and low AD-GRS groups are statistically detectable using a one-sided, two-sample t-test at (p \leq 0.05). These predictions were based on females with median values of the 10 principal components. Red lines indicate high (95th percentile) AD-GRS and blue lines indicate low (5th percentile) AD-GRS. Key: PM_nCorrect_ac_0_1: 6) Pairs Matching Number Correct (Round 1) In Person. PM_nCorrect_ac_0_2: 7) Pairs Matching Number Correct (Round 2) In Person. PM_nCorrect_ol_0_1: 12) Pairs Matching Number Correct (Round 1) Online. PM_nCorrect_ac_0_0: 4) Numeric Memory Number Correct In Person. PM_nCorrect_ol_0_0: 5) Numeric Memory Number Correct Online. RT_tMean_ac_0_0: 19) Reaction Time Mean Time In Person. FI_nAttempted_ac_0_0: 2) Fluid Intelligence Number Attempted In Person. FI_nCorrect_ac_0_0: 1) Fluid Intelligence Number Correct In Person.
Plots of predicted average cognition of four cognitive measures at higher (1.76) and lower (-1.22) z-scored AD-GRS. Solid vertical lines indicate threshold age at which the AD-GRS begins to influence the cognitive measure. At ages below the threshold, AD-GRS does not interact with age to influence cognition. Dashed vertical lines indicate the earliest age at which the cognitive difference in the high and low AD-GRS groups are statistically detectable using a one-sided, two-sample t-test at (p <= 0.05). These predictions were based on females with median values of the 10 principal components. Red lines indicate high (95th percentile) AD-GRS and blue lines...
indicate low (5th percentile) AD-GRS. Key: FI_nCorrect_ol_0_0: 3) Fluid Intelligence Number Correct Online. SD_nAttempt_ol_0_0: 23) Symbol Digit Substitution Number Attempted Online. SD_nCorrect_ol_0_0: 22) Symbol Digit Substitution Number Correct Online. SD_timeToComplete10_ol_0_0: 24) Symbol Digit Substitution Time To Complete 10 Substitutions Online. SD_nAttempt_ac_2_0: 20) Symbol Digit Substitution Number Attempted In Person. SD_nCorrect_ac_2_0: 21) Symbol Digit Substitution Number Correct In Person. TM_tAlphanumeric_ac_2_0: 27) Trail-making Time to Complete Alphanumeric Trail In Person. TM_tAlphanumeric_ol_0_0: 30) Trail-making Time to Complete Alphanumeric Trail Online. TM_tNumeric_ac_2_0: 25) Trail-making Time to Complete Numeric Trail In Person. TM_tNumeric_ol_0_0: 29) Trail-making Time to Complete Numeric Trail Online. TM_nErrorsAlphanumeric_ac_2_0: 28) Trail-making Number Of Errors In Alphanumeric Trail In Person. TM_nErrorsAlphanumeric_ol_0_0: 32) Trail-making Number Of Errors In Alphanumeric Trail Online. TM_nErrorsNumeric_ac_2_0: 26) Trail-making Number Of Errors In Numeric Trail In Person. TM_nErrorsNumeric_ol_0_0: 31) Trail-making Number Of Errors In Numeric Trail Online. ProMem1stAttemptCorrect_ac_0_0: 17) Prospective Memory 1st Attempt Correct In Person. ProMem1stOr2ndAttemptCorrect_ac_0_0: 18) Prospective Memory 1st Or 2nd Attempt Correct In Person.
eFigure 4: Mean cognitive scores by age and ADGRS, unadjusted for covariates – Part 1

Blue vertical lines indicate 5-year age group at which divergence was detected in the main analysis. Black vertical lines denote the minimum of the 5-year age group containing the blue vertical line. Red series indicates mean cognitive score among participants in the highest quartile of AD-GRS, a blue series indicates mean cognitive score among participants in the lowest quartile of AD-GRS. Key: PM_nCorrect_ac_0_1: 6) Pairs Matching Number Correct (Round 1) In Person. PM_nCorrect_ac_0_2: 7) Pairs Matching Number
Correct (Round 2) In Person. PM_nCorrect_ol_0_1: 12) Pairs Matching Number Correct (Round 1) Online. PM_nIncorrect_ac_0_1: 8) Pairs Matching Number Incorrect (Round 1) In Person. PM_nIncorrect_ac_0_2: 9) Pairs Matching Number Incorrect (Round 2) In Person. PM_nIncorrect_ol_0_1: 13) Pairs Matching Number Incorrect (Round 1) Online. PM_nIncorrect_ol_0_2: 14) Pairs Matching Number Incorrect (Round 2) Online. PM_tToComplete_ac_0_1: 10) Pairs Matching Time To Complete (Round 1) In Person. PM_tToComplete_ac_0_2: 11) Pairs Matching Time To Complete (Round 2) In Person. PM_tToComplete_ol_0_1: 15) Pairs Matching Time To Complete (Round 1) Online. PM_tToComplete_ol_0_2: 16) Pairs Matching Time To Complete (Round 2) Online. NM_nCorrect_ac_0_0: 4) Numeric Memory Number Correct In Person. NM_nCorrect_ol_0_0: 5) Numeric Memory Number Correct Online. RT_tMean_ac_0_0: 19) Reaction Time Mean Time In Person. FI_nAttempted_ac_0_0: 2) Fluid Intelligence Number Attempted In Person. FI_nCorrect_ac_0_0: 1) Fluid Intelligence Number Correct In Person.
Blue vertical lines indicate 5-year age group at which divergence was detected in the main analysis. Black vertical lines denote the minimum of the 5-year age group containing the blue vertical line. Red series indicates mean cognitive score among participants in the highest quartile of AD-GRS, a blue series indicates mean cognitive score among participants in the lowest quartile of AD-GRS. Key: FI_nCorrect_ol_0_0: 3) Fluid Intelligence Number Correct Online. SD_nAttempt_ol_0_0: 23) Symbol Digit Substitution Number Attempted Online. SD_nCorrect_ol_0_0: 22) Symbol Digit Substitution Number Correct Online. SD_timeToComplete10_ol_0_0: 24)
Symbol Digit Substitution Time To Complete 10 Substitutions Online. SD_nAttempt_ac_2_0: 20) Symbol Digit Substitution Number Attempted In Person. SD_nCorrect_ac_2_0: 21) Symbol Digit Substitution Number Correct In Person. TM_tAlphanumeric_ac_2_0: 27) Trail-making Time to Complete Alphanumeric Trail In Person. TM_tAlphanumeric_ol_0_0: 30) Trail-making Time to Complete Alphanumeric Trail Online. TM_tAlphanumeric_ac_2_0: 25) Trail-making Time to Complete Numeric Trail In Person. TM_tNumeric_ol_0_0: 29) Trail-making Time to Complete Numeric Trail Online. TM_nErrorsAlphanumeric_ac_2_0: 28) Trail-making Number Of Errors In Alphanumeric Trail In Person. TM_nErrorsAlphanumeric_ol_0_0: 32) Trail-making Number Of Errors In Alphanumeric Trail Online. TM_nErrorsNumeric_ac_2_0: 26) Trail-making Number Of Errors In Numeric Trail In Person. TM_nErrorsNumeric_ol_0_0: 31) Trail-making Number Of Errors In Numeric Trail Online. ProMem1stAttemptCorrect_ac_0_0: 17) Prospective Memory 1st Attempt Correct In Person. ProMem1stOr2ndAttemptCorrect_ac_0_0: 18) Prospective Memory 1st Or 2nd Attempt Correct In Person.
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