Association of genetic risk factors with cognitive decline: The PATH Through Life Project

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Abstract

We examined the association of 28 single nucleotide polymorphisms (SNPs), previously associated with dementia or cognitive performance, with tests assessing episodic memory, working memory, vocabulary and perceptual speed in 1,689 non-demented older Australians of European ancestry. In addition to testing each variant individually, we assessed the collective association of the 12 risk SNPs for Late-onset Alzheimer's disease (LOAD) using weighted and unweighted genetic risk scores (GRS). Significant associations with cognitive performance were observed for *APOE* *ϵ4 allele, *ABCA7*-rs3764650, *CR1*-rs3818361, *MS4A4E*-rs6109332, *BDNF*-rs6265, *COMT*-rs4680, *CTNNBL1*-rs6125962, *FRMD4A*-rs17314229, *FRMD4A*-rs17314229, intergenic SNP chrX-rs12007229, *PDE7A*-rs10808746, *SORL1*-rs668387 and *ZNF224*-rs3746319. Additionally, the weighted GRS was associated with worse performance on episodic memory. The identification of genetic risk factors, that act individually or collectively, may help in screening for people with elevated risk of cognitive decline and for understanding the biological pathways that underlie cognitive decline.

Keywords: Alzheimer's Disease; Cognitive Decline; SNPs; Genetic Risk Scores, Population-Based Study.

1. Introduction

Cognitive differences in the elderly consist of differences in stable, life-long cognitive traits and differences in age-associated cognitive change. For both of these there is significant inter-individual variability in the population (Wilson et al., 2002). Loss of cognitive function due to age-associated cognitive decline is associated with increased difficulties in performing tasks involving memory or rapid information processing and can have a major impact on an individual's quality of life, even in the absence of dementia (Boyle et al., 2012; Kobayashi et al., 2014; Tucker-Drob, 2011; Wilson et al., 2013; Yam and Marsiske, 2013; Zahodne et al., 2013). Identifying factors that predispose individuals to a faster rate of cognitive decline is an important step for developing intervention and treatment strategies aimed at maintaining cognitive health.

Genetic factors likely contribute to the inter-individual variability observed in cognitive decline, with common genetic variants estimated to account for between 40-50% of the variability associated with general cognitive functioning in later life and 24% of the variability in lifetime cognitive change (Davies et al., 2011; Deary et al., 2012). To date the majority of genetic research on cognitive decline has focused on candidate genes that have been previously associated with age-related disease, traits or mechanisms (Payton, 2009; Harris and Deary, 2011), and particularly with genes related to neurotransmitters, neurotrophins, cognitive function and neurodegenerative disease. Two of the most widely studied such genes are *COMT*, which encodes the neurotransmiter catechol-O-methyl transferase, and *BDNF*, which encodes the neurotrophin brain-derived neurotrophic factor. Functional variants in these genes have been primarily associated with decline in executive functioning and memory, respectively, although results are inconsistent (Payton, 2009). Late-onset Alzheimer's disease (LOAD) susceptibility genes are also good candidates for association with cognitive decline as the pathological features of LOAD progress to varying degrees in individuals without dementia or cognitive impairment and are associated with non-clinical cognitive

decline (Boyle et al., 2013b; Savva et al., 2009). This cross-over effect is exemplified by the *APOE* *ϵ4 allele, which confers the largest known genetic risk for LOAD, approximately 2-3 times and 10-12 times for heterozygotes and homozygotes respectively (Farrer et al., 1997). The *APOE* genotypes is also associated with specific effects on the cognitive domains of episodic memory, executive functioning, perceptual speed and global cognitive ability (Wisdom et al., 2011).

Despite the publication of numerous genetic associations with cognitive decline, the variants identified typically explain a very small fraction of the phenotypic variability and many remain to be replicated. Furthermore, failure to replicate an initial positive result is common due to differences in participant characteristics (e.g. baseline education, mean age, gender and ethnicity) and methodologies (e.g. sample size, duration of the study, number of follow-ups, population stratification, variation in classification and cognitive measures) (Payton, 2009).

Here we investigate the association between selected genetic risk factors with cognitive decline in a longitudinally followed community-based cohort of 1,689 older adults without dementia who have undergone comprehensive cognitive testing. First, we investigate whether 12 SNPs from the top replicated LOAD associated genes (Morgan and Carrasquillo, 2013; Supplementary Tables 1 and 2) are individually, or collectively as a genetic risk score (GRS), associated with cognitive decline. Second, we investigate whether 16 SNPs, previously associated with either dementia or cognition (Table 1 and Supplementary Table 2), are also associated with cognitive decline.

2. Methods

2.1. Participants

Participants were recruited randomly from the electoral rolls (registration is a legal requirement

for Australian Citizens) of Canberra and Queanbeyan into the Personality and Total Health (PATH) Through Life Project. PATH consists of three cohorts 20-24 (20+), 40-44 (40+) and 60-64 (60+) years at baseline, who have participated in a large longitudinal community survey of health and wellbeing in adults, the background and procedures for which have been described in detail elsewhere (Anstey et al., 2012). Written informed consent was obtained from all participants and approval for the study was obtained from the Human Research Ethics Committee of The Australian National University.

The 60+ cohort is the focus of this study. Individuals were assessed at 4-year intervals for a period of 8 years with interviews conducted in 2001-2002 (n = 2,551), 2005-2006 (n = 2,222) and 2009-2010 (n = 1,973). Individuals were excluded from further analysis based on the following criteria: attendance at only one interview (n = 309), no genomic DNA available for genotyping (n = 185), *APOE* $*\epsilon 2/*\epsilon 4$ genotype (n = 60; to avoid the conflation of $*\epsilon 2$ protective and $*\epsilon 4$ risk effect), non-European ancestry (n = 110), probable dementia at any wave (Mini Mental State Examination score < 24 (Folstein et al., 1975), self-reported medical history of epilepsy, stroke, transient ischaemic attack, brain tumour or brain infection (n = 327). Missing values, which can reduce power and result in biased estimates, were imputed for the covariate 'Education' (total years of education) using random forests via the 'missForest' package available in R (Stekhoven and Bühlmann, 2012) (n = 139). This left a final sample of 1,689 individuals. At baseline, the individuals retained in the final sample had on average of 0.69 more years of education and scored 0.74 points higher on the MMSE than those excluded (Table 1).

2.2. Cognitive Assessment

All participants were assessed at baseline and at each subsequent interview for the following five cognitive abilities: perceptual speed was assessed using the Symbol Digit Modalities Test, which asks the participant to substitute as many digits for symbols as possible in

90s (Smith, 2002); episodic memory was assessed using the immediate recall and delayed recall of the first trial of the California Verbal Learning Test, which involves recalling a list of 16 nouns (Delis et al., 1987); working memory was assessed using the Digit Span Backward from the Wechsler Memory Scale, which presents participants with series of digits increasing in length at the rate of one digit per second and asks them to repeat the digits backwards (Wechsler, 1945); and vocabulary was assessed with the Spot-the-Word Test, which asks participants to choose the real words from 60 pairs of words and nonsense words (Baddeley et al., 1993). (Supplementary Tables 5 and 6).

2.3. Genotyping

Sixty-four single nucleotide polymorphisms (SNPs) were selected for genotyping based on previous associations with dementia, cognition, neuroanatomical differences and blood pressure (Supplementary Table 2). Genomic DNA was extracted from cheek swabs (n = 4,597) using Qiagen DNA blood kits or from peripheral blood leukocytes (n = 64) using QIAamp DNA 96 DNA blood kits.

Pre-amplification of the targeted loci was performed using the TaqMan PreAmp Master Mix Kit (Life Technologies). Each reaction included 2.5 µL TaqMan PreAmp Master Mix (2×), 1.25 µL Pre-amplification Assay Pool, 0.5 µL H_20 and 1.2 µL genomic DNA. These reactions were incubated in a Biorad thermocycler for 10 min at 95°C, followed by 12 cycles of 95°C for 15 sec and 60°C for 4 min, and then incubated at 99.9°C for 10 minutes. The PreAmplified products were then held at 4°C until they were diluted 1:20 in 1× TE buffer and then stored at -20°C until use.

2.5 µL diluted pre-amplified products was mixed with 2.5 µL TaqMan OpenArray Master Mix. The resulting samples were dispensed using the OpenArray® AccuFill™ System onto OpenArray plates with each plate containing 48 samples and 64 SNP assays per sample.

The QuantStudio™ 12K Flex instrument (Applied Biosystems, Carlsbad, California) was used to perform the real time PCR reactions on the loaded OpenArray plates. The fluorescence emission results were read using the OpenArray® SNP Genotyping Analysis software v1 (Applied Biosystems) and the genotyping analysis was performed using TaqMan® Genotyper v1.3, using the autocalling feature. Participant-specific quality controls included filters for genotype success rate ($> 90\%$), genotype-derived gender concordant with reported gender and sample provenance error assessed via pairwise comparisons of genotype calls between all samples to identify samples with $> 90\%$ similarity. Samples that were flagged in the initial quality control checks were repeated, those that still failed quality control were excluded. SNP-specific filters included genotype call rate ($> 90\%$) and Hardy-Weinberg equilibrium ($p > 0.001$) assessed using an exact test with the PLINK toolkit (Purcell et al., 2007).

For this study, data for 28 of the 64 genotyped SNPs was extracted based on a priori hypotheses (Supplementary Table 1). These SNPs have being previously identified as being associated with dementia or cognition through GWAS or candidate gene studies (Supplementary Table 2) and consist of 12 SNPs that have been highly replicated as being associated with LOAD and an additional 16 SNPs whose associations are ambiguous and are in need of further replication. Genotyping of the PATH sample for *APOE* variants was performed separately and has been described previously (Jorm et al., 2007). The SNPs were in Hardy-Weinberg equilibrium and genotype frequencies are presented in Supplementary Tables 3 and 4.

2.4. Data Preparation and Statistical Analysis

Data were analysed in the R Statistical Computing environment (R Core Team, 2013). We created an index for episodic memory using the average scores of the immediate and delayed recall tasks. To allow for comparison across all cognitive tasks, the tests scores for each cognitive task at all three waves were transformed into Z scores (M = 0, SD = 1), using the baseline means and standard deviations. Higher test scores indicate better

cognitive function.

Genetic dominance was assumed for previously reported risk alleles (Bertram et al., 2007) for LOAD GWAS SNPs, and for minor alleles (alleles with the lowest frequency in the population) of the 16 additional SNPs. The *APOE* $*\epsilon 4$ and $*\epsilon 2$ alleles were assumed to be dominant to the $\epsilon 3$ allele. For *APOE* participants were classified as either APOE $*\epsilon 4+$ ($*\epsilon 4/*\epsilon 4$ + $*\epsilon 4/*\epsilon 3$), $*\epsilon 2+$ ($*\epsilon 2/*\epsilon 2$ + $*\epsilon 2/*\epsilon 3$) or $*\epsilon 3$ ($*\epsilon 3/*\epsilon 3$). Because we wanted to assess the independent contributions of $*\epsilon 4$ and $*\epsilon 2$ to cognitive decline, those with the $*\epsilon 2/*\epsilon 4$ genotype were excluded.
Three genetic risk scores (Che and Motsinger-Reif, 2013) were calculated using the LOAD GWAS SNPs: 1) a simple count genetic risk (SC-GRS): the sum of all risk alleles across all loci; 2) an odds-ratio weighted genetic risk score (OR-GRS): the sum of all risk alleles across all loci, weighted by effect size of the risk allele on AD, as reported in the AlzGene Database (Bertram et al., 2007); 3) an explained variance-weighted genetic risk score (EV-GRS): the sum of all risk alleles across all loci, weighted by minor allele frequency and effect size on AD, as reported in the AlzGene Database. For all genetic risk scores a higher value indicates greater risk. The MAF and OR used to derived the GRS are presented in Supplementary Table 1. Individuals missing any genetic data (n = 69) were excluded from the analysis.

Linear mixed effect models (LMM) with maximum likelihood estimation and subject-specific random slopes and intercepts were used to assess the effect of predictors on change in cognitive test scores over time. Age, centered on mean age at baseline, was used as an indicator of time in the study. The predictor variables included in the analysis were the individual SNPs or the three GRS's: SC-GRS, OR-GRS and EV-GRS. Covariates used in the models included, sex, education and for individual SNP models *APOE* genotype. LMM's were estimated using the R package 'lme4' (Bates et al., 2014) and F and p values were estimated using Satterthwaite-type approximation were used to determine the statistical significance

of the fixed effects. To evaluate if the random slopes were significantly different from 0 and to determine if there was residual variability in the rate of change that could be explained by predictor variables, LMM's that included random slopes were compared to models that did not include random slopes using parametric bootstrap methods where 1000 simulations of the likelihood ratio test statistic were generated (R package 'pbkrtest', Halekoh and Højsgaard, 2012). For each SNP and GRS we compared the model fit of the full model with the covariates-only model to evaluate if there was an overall effect of the SNP or GRS on cognitive decline. Model fit was assessed using a Kenward-Rodger approximation for F-tests (R package 'pbkrtest', Halekoh and Højsgaard, 2012). Two R^2 statistics were calculated to quantify, 1) the proportion of outcome variation explained by the fixed factors (marginal R^2) and 2) the amount of outcome variation explained by the fixed and random factors (conditional R^2; Johnson, 2014; Nakagawa and Schielzeth, 2013; R package 'MuMIn' Barton and Barton, 2013). Additionally, we performed a secondary analysis in which changes in the rate of cognitive decline by genotype were estimated separately for participants who were classified as cognitive impaired (CI) at wave 3 if they scored <=27 on the MMSE (n = 118) and those classified as cognitively normal (CN, n = 1340). For the secondary analysis, LMM's were performed with the inclusion of the additional terms for a time by cognitive status and separate time by genotype interactions for the CI and CN classifications. We did not adjust for multiple comparison as strong a priori evidence for all our hypothesis based on previous findings for LOAD and cognitive decline was available; a P-value < 0.05 was considered statistically significant.

3. Results

3.1. Population characteristics of the PATH cohort

General demographics of the PATH cohort are presented in 1. Linear Mixed Models 1-3 in Supplementary Table 7-9 show the average rate of change for each cognitive test. Random slopes for all cognitive tests scores were significantly different from 0, indicating that there

was sufficient variability in the rate of change between participants thus allowing potential genetic predictors of this change to be tested (bootstrap P value: Episodic Memory = 0.04; Digits backwards = 0.01; Spot-the-Word test = 0.0001; Symbol digits modalities test = 0.01). Significant change in test scores over time was observed for all cognitive tests except Digits Backwards. In model 2, participants experienced an overall decline in test scores for Episodic memory and Symbol digits Modalities Test, and an increase in test scores for Spot-the-Word. 'Time' explained 57-89% of outcome variation for the entire model. The covariates in model 3 improved the model fit for all cognitive tests and explained 7-21% of the outcome variation in the fixed effects, although they did not explain any additional random effect variation for the entire model (Supplementary Tables 9).

3.2. Main effects of LOAD GWAS SNPs

There was a significant improvement in model fit for various cognitive tests after the introduction of the *APOE*, *ABCA7*, *CR1* and *MS4A4E* SNPs into their respective models. *APOE* ϵ4+ was associated with a greater rate of decline in Episodic memory and the association remained unchanged when *APOE* ϵ3/ϵ4 heterozygotes were assessed separately from *APOE* ϵ4 homozygotes and *APOE* ϵ2 carriers; *ABCA7*-rs3764650-G was associated with a lower initial status at baseline in Episodic memory test scores; *CR1*-rs3818361-A was associated with a greater rate of decline in Episodic memory and; *MS4A4E*-rs670139-T was associated with a higher baseline Spot-the-Word Test score and a slower decline in Episodic memory test scores. The group differences resulted in a small increase in the marginal R^2 ranging from 0.001 to 0.002, though there was no increase in the conditional R^2 statistics. Table 2, Supplementary Tables 10-21.

The remaining SNPs (*BIN1*, *CD2AP*, *CD33*, *CLU*, *EPHA1*, *MS4A4A*, *MS4A6A* and *PICALM*) were not significantly associated with baseline status or rate of change for any of cognitive tests.

In the secondary analysis assessing the rate of cognitive decline separately for participants

who were classified as CI (supplementary Table 44), the *APOE* $\epsilon 4+$ was associated with a faster rate of decline in Episodic memory for CI and CN participants, with a steeper decline observed in CI participants, and a reduced rate of decline in Digits Backwards test scores in CN participants; *ABCA7*-rs3764650-G was associated with a faster rate of decline in Digits backwards tests scores in CI participants and; *EPHA1*-rs11767557-T was associated with as faster rate of decline SDMT tests in CI participants.

3.3. Effect of Genetic Risk Scores

The equally-weighted SC-GRS has an approximately normal distribution in the PATH Cohort (Figure 1; mean = 10.5; range = 3-18). The bimodal distribution and long upper tails of the weighted OR- and EV-GRS reflect the strong effect of *APOE* relative to other loci (Figure 1; mean = 1.47; range = -0.7-4.5 & mean = 0.92; range = -0.1-2.4 respectively). The SC-GRS was not significantly associated with either initial status at baseline or rate of change for any of the cognitive tests. There was a significant improvement in model fit for Episodic memory for both the OR- and EV-GRS, with higher OR- and EV-GRS being associated with a greater rate of decline in cognitive performance. These associations resulted in a small increase in the amount of explained variation in the fixed effects, in comparison to that explained by time and the covariates, of 0.001 and 0.002 for the OR-GRS and EV-GRS respectively though there was no increase in the conditional R^2 statistics. (Table 2, supplementary Tables 22-24). The OR- and EV-GRS were not associated with cognitive performance when the *APOE* allele was excluded (supplementary Tables 25-27). In the secondary analysis (supplementary Table 44), the OR- and EV-GRS were associated with a faster rate of decline in episodic memory in both CI and CN participants, with a steeper decline observed in CI participants.

3.4. Main effects of SNPs associated with dementia or cognition

Statistics for the models introducing the additional dementia and cognition SNPs are shown

in Table 3. See Supplementary Tables 28-43 for full models with random and fixed effects.

A significant improvement in model fit was observed for a number of cognitive tests after the introduction of the following SNPs: *BDNF*, *COMT*, *FRMD4A*-rs7081208, Intergenic chrX, *PDE7A* and *ZNF224* into their respective models. In these models significant parameter estimates were observed. *BDNF*-rs6265-T was associated with a lower baseline Digits Backwards tests scores while *COMT*-rs4680-A with a greater rate of decline in Episodic memory test scores. *FRMD4A*-rs7081208-A was associated with a lower baseline score as well as a slower rate of decline in Digits Backwards test scores and with higher baseline scores, but a greater rate of decline in Spot-the-Word test scores. Intergenic-rs12007229-A was associated with a greater rate of decline in Episodic memory test scores. *PDE7A*-rs10808746-A was associated with a slower rate of decline in Symbol Digits Modalities test scores; *ZNF224*-rs3746319-A associated with a higher baseline Spot-the-Word Test scores.

Statistically significant parameter estimates in the absence of improvement in model fit were also observed, with *CTNNBL1*-rs6125962-C associated with a reduced rate of decline in Episodic memory test scores; *FRMD4A*-rs17314229-T was associated with a greater rate of decline in digits backwards test scores; *PDE7A*-rs10808746-A was associated with lower digits backwards test baseline scores and a slower rate of decline in Symbol Digits Modalities test scores; *SORL1*-rs668387-T was associated with higher Spot-the-Word Test scores at baseline.

These significant associations result in a small increase in explained variation in the fixed effects ranging from 0.0003 to 0.003, though no increase in the conditional R^2.

In the secondary analysis assessing the rate of cognitive decline separately for participants who were classified as CI or CN are presented in supplementary Table 45). *BDNF*-rs6265-T, *CETP*-rs5882-G, *MTHFD1L*-rs11754661-A, *CTNNBL1*-rs6125962-C, *FRMD4A*-rs17314229-T, *PAICS*-rs11549976-A and *PED7A*-rs10808746-A were associated with rate of change in participants classifed as CI. *COMT*-rs4680-A, *FRMD4A*-rs7081208-A and Intergenic-rs12007229-A were associated with rate of change in participants who were classified as CN.

4. Discussion

In this study we investigated the association between common genetic variants that have been previously reported to be associated with LOAD, dementia or cognition with change in episodic memory, working memory, vocabulary and perceptual speed. The top LOAD GWAS SNPs were primarily associated with cognitive performance in episodic memory. This is likely indicative of their role in Alzheimer's disease, as progressive deficits in episodic memory that begin early on in the disease course are one of its defining features (Dubois et al., 2010). Associations with rate of change in cognitive performance were observed for *APOE*, *CR1*, *MS4A4E*, while *ABCA7* was associated with baseline cognitive performance. The direction of the effect for *APOE*, *CR1*, and *ABCA7* was as expected, however for the *MS4A4E* the AD risk allele was associated with a protective effect on episodic memory, and the same trend was also observed for the SNPs *MS4A6A* and *MS4A4A*, though they were not significant. However, the parameter estimates for the effect of these SNPs on change in cognitive abilities ranged from -0.9% to 0.9% over four years, while the increase in the marginal R^2 statistics after inclusion of the genetic predictors ranged from 0.001 to 0.002, emphasising that the effect of individual SNPs on cognition are extremely small.

Additionally, we constructed three genetic risk scores to investigate the combined effect of the LOAD risk SNPs on cognitive decline. An odds ratio weighted GRS and a novel combined odds ratio and minor allele frequency weighted GRS were significantly associated with steeper rate of cognitive decline in episodic memory. The EV-GRS takes into account that within the same OR disease risk can vary depending on the risk allele frequencies and has been shown to be more robust approach for identifying associations in the presence of potential genetic interactions, linkage disequilibrium and false positive predictors (Che and Motsinger-Reif, 2013). An unweighted GRS was not associated with cognitive performance. This latter score utilised a simple count of the number of risk allele per individual and does

not take into account the varying effect sizes among the LOAD risk SNPs. The lack of significant associations with the SC-GRS, in contrast to the weighted methods, indicates that the significant associations observed for the OR- and EV-GRS can be attributed to the dominant role of the *APOE* *ϵ4 allele, which was further confirmed when *APOE* was excluded from the GRS.

These results are similar to those of several comparable candidate gene (Carrasquillo et al., 2015; Engelman et al., 2013) and GWAS based (Davies et al., 2014; De Jager et al., 2012; Zhang and Pierce, 2014) studies, that reported a lack of robust associations between cognitive decline and non-*APOE* LOAD risk genes. These previous studies have only identified suggestive evidence for *CR1* (De Jager et al., 2012; Vivot et al., 2015), *CLU* (Mengel-From et al., 2013) *BIN1* (Vivot et al., 2015) and *PICALM* (Zhang and Pierce, 2014). However, when examining genetic associations with general cognitive function in middle and older age in a large meta-analysis of 31 studies (n = 53,949) no associations were observed with any of these LOAD risk genes, though two other AD related genes, *MEF2C* and *ABCG1*, were associated (Davies et al., 2015). Furthermore, when the non-*APOE* LOAD GWAS risk loci were assessed collectively as a GRS weighted by their estimated OR's, no associations were observed with cognitive decline (De Jager et al., 2012; Carrasquillo et al., 2015), though after inclusion of *APOE* the GRS did reach significance (Carrasquillo et al., 2015; Vivot et al. (2015)). An alternative approach using a polygenic risk score of all LOAD associated variants, not just the top associated loci, found no association with cognitive ability in later life or with age-related cognitive change (Harris et al., 2014). Investigating interactions between environmental and lifestyle factors and GRS may provide more promising results, with a higher GRS composed of *APOE*, *CLU*, *CR1* and *PICALM*, while not independently associated with cognitive decline was shown to exacerbate the deleterious effects of type 2 diabetes on cognitive decline (McFall et al., 2015).

Alzheimer's related genes may be associated with cognitive decline in subjects who are in the preclinical stages of dementia and who, if followed for long enough, might eventually develop dementia. We also assessed the effect of the LOAD risk SNPs separately for those who were classified as cognitively impaired according to MMSE at wave 3 and observed faster rates of decline associated with the *ABCA7* risk allele and reduced rates of decline associated with the *EPHA1* risk allele In previous studies, variants in *ABCA7*, *EPHA1* (Carrasquillo et al., 2015) and *CLU* (Thambisetty et al., 2013) have been observed to be associated with cognitive decline in subjects who eventually converted to dementia, but not in individuals who remained cognitively normal throughout the study. This also suggests that associations observed between LOAD risk genes and cognitive decline could be due to individuals who are in the preclinical stages of Alzheimer's disease and that the retrospective removal of these individuals could attenuate the observed associations (Knight et al., 2014; Davies et al., 2015). However, removing individuals who are in the preclinical stages of disease in the early analytic stages of a study is likely to be difficult due to the long and asymptomatic nature of the preclinical stages of LOAD.

The above findings, and those of previous studies, suggest that the added predictive value of the top LOAD SNPs for cognitive decline in non-demented individuals may be limited. This is consistent with polygenic models of cognitive decline indicating that there is a large number of variants with modest effects sizes rather than a few variants with large or moderate effect sizes. Additionally, this is consistent with indices of LOAD pathology (amyloid and neurofibrillary tangles) that only explain 30% of observed variance in cognitive decline, and cerebrovascular (macro and micro infarcts) and Lewy body disease neuropathologies explaining an additional 10% of variation (Boyle et al., 2013a). This is consistent with the notion that while LOAD pathology is important in the development of cognitive decline, it occurs in conjunction with other pathological features that are observed in brain ageing. As such, the cognitive deficits observed in brain ageing are unlikely to be due to an isolated

pathological feature, but the interaction between multiple neuropathologies (Keller, 2006). This highlights the need to investigate additional genetic variants in addition to those associated with AD.

For the remaining 16 SNPs investigated, which were previously associated with dementia or cognitive performance, we observed associations with a increased rate of decline in cognitive performance for the minor alleles of *COMT* and Intergenic chrX, while for *CTNNBL1* and *PDE7A* the minor alleles were associated with a reduced rate of cognitive decline. At baseline, *BDNF* and *PDE7A* minor alleles were associated with worse cognitive performance, while *SORL1* and *ZNF224* minor alleles were associated with better cognitive performance. *FRMD4A*-rs7081208 was associated with a reduced and a greater rate of decline for working memory and vocabulary respectively, though at baseline working memory was associated with worse performance while vocabulary was associated with better performance. Additionally, *FRMD4A*-rs17314229 minor allele were associated with a greater rate of decline in Working memory.

In comparison to the top AD related SNPs, the additional AD related genetic variants in *FRMD4A*, *SORL1* and *ZNF224* were associated with cognitive performance in vocabulary and working memory, potentially indicating that they may be involved in the development of atypical AD, in which the development of non-amnestic cognitive deficits occurs early on in the disease process (Dubois et al., 2010). For the cognition related genetic variants, SNPs in *COMT* and *CTNNBL1* have been associated with differences in regional brain structures and activations that are involved in episodic memory processes, potentially explaining the differential associations of these variants with episodic memory (Papassotiropoulos et al., 2013; Witte and Flöel, 2012). *BDNF* is widely expressed in the prefrontal cortex, which is associated, amongst other functions, with working memory (Galloway et al., 2008). As with the LOAD risk loci, the additional SNPs were primarily associated with cognitive decline in participants who were classified cognitively impaired. However, as with the LOAD

risk loci, the effect sizes for these SNPs were small and inclusion of the SNPs in the model resulted in a negligible increase in the amount of explained variability in cognitive performance.

The presented findings should be interpreted in conjunction with some study limitations. The sample used in this study is somewhat better educated than the population from which it was drawn. Higher education is associated with a reduced risk of cognitive decline and incident dementia. Additionally, the sample is relatively young, which in combination with a higher level of education could limit our ability to detect an effect of the genetic factor with cognitive decline. This is possibly reflected in the limited person specific variation in the rate of decline in the linear mixed models. Second, the subjects in this study are Caucasian and as such our findings need to be replicated in other ethnic groups. Third, despite excluding individuals with probable dementia at each wave, it is still possible that individuals in the preclinical phase of dementia were included in the analysis. Fourth, in concordance with the avaliable data, we have specified time as linear, however, cognitive decline may accelerate at older ages (Wilson et al., 2009) highlighting the need to investigate nonlinear cognitive trajectories (Weuve et al., 2015). Finally, although we have a strong a priori evidence for all our hypothesis, it should be noted that correcting for multiple testing using Bonferroni correction, all corrected p values would have yielded non-significant results.

Despite these limitations however, this study investigated a large community based cohort followed longitudinally for a period of eight years, with three waves of assessment that included a comprehensive cognitive assessment of different cognitive abilities. These strengths allow for a robust statistical inference about the effect the selected genetic factors have on non-clinical cognitive decline. The narrow age-cohort design also reduced the impact of age-differences influencing results.

To conclude, our findings suggest that the majority of LOAD risk genes are not individually associated with non-clinical cognitive decline in a cohort of older adults who were followed for a period of 8 years. When considered collectively as a genetic risk score, the observed associations are due to the significantly larger weight associated with *APOE* $*\epsilon 4$ allele. The PATH study is ongoing and the number of incident cases of mild cognitive impairment and dementia among participants is increasing. The work presented here thus provides an excellent basis for further investigating the effects of AD risk variants in non-pathological versus pathological decline (Knight et al., 2014), gene-gene interactions (Barral et al., 2012; Engelman et al., 2013) and gene-environment interactions (Ferencz et al., 2014) in future studies.

Acknowledgements

We thank the participants of the PATH study, Peter Butterworth, Andrew Mackinnon, Anthony Jorm, Bryan Rodgers, Helen Christensen, Patricia Jacomb, Karen Mawell and Jorge Velez. The study was supported by the Dementia Collaborative Research Centers and the National Health and Medical Research Council (NHMRC) grants 973302, 179805, 1002160. DD is funded by NHMRC Project Grant No. 1043256. NC is funded by Research Fellowship No. 12010227. KJA is funded by NHMRC Research Fellowship No. 1102694.

Disclosures

The authors have no conflict of interests to report.

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Table 1: Sample Demographics

	Excluded (n=861)	Included (n=1,689)	Degrees of Freedom	t/χ^2	p
Age†	62.46 ± 1.49	62.54 ± 1.51	1,753	-1.22	0.21
Education†	3.31 ± 3.09	14 ± 2.59	1,488	-5.62	<0.001
MMSE†	28.6 ± 2.13	29.35 ± 0.92	1010	-9.77	<0.001
Male n(%)‡	443 (51.4%)	873 (51.7%)	1	0.005	0.94
APOE Genotypes n(%)					
ϵ2/ϵ2	6 (0.70%)	13 (0.77%)			
ϵ3/ϵ3	395 (45.82%)	1048 (62%)			
ϵ4/ϵ4	20 (2.32%)	29 (1.71%)			
ϵ2/ϵ3	70 (8.12%)	204 (12.07%)			
ϵ2/ϵ4	60 (6.96%)	0 (0%)			
ϵ3/ϵ4	137 (15.89%)	395 (23.37%)			

†Unpaired 2-tailed t-test. ‡Pearson's χ^2 2-tailed test.

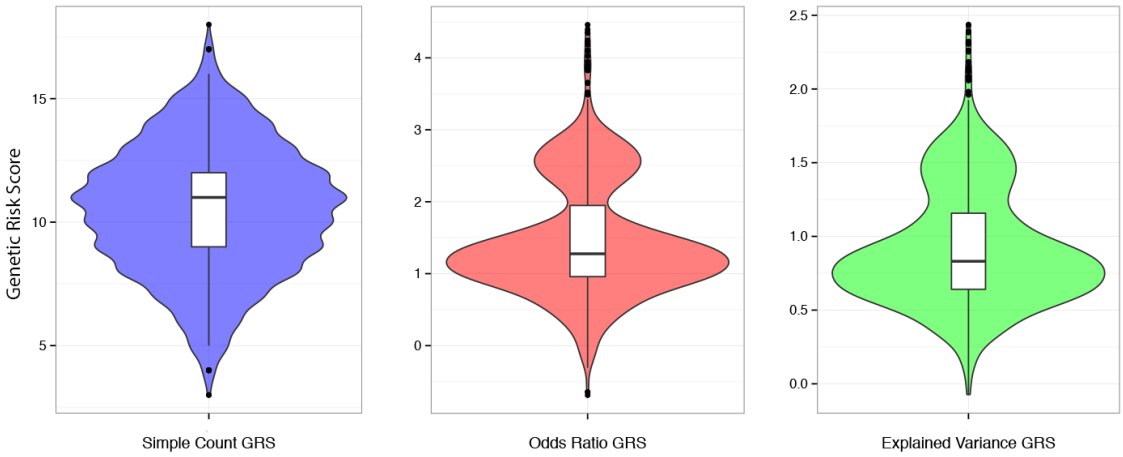

Figure 1: Distributions of the three genetic risk scores: SC-GRS (Mean = 10.5; sd = 2.58), OR-GRS (Mean = 1.47; sd = 0.8) and EV-GRS (Mean = 0.92; sd = 0.4). The variable widths of each violin plot indicate the probability density of the data at each score, with the box plots indicating the first, median and third quartile (Hintze and Nelson, 1998).

Table 2: Top LOAD risk SNPs and GRS: Parameter estimates and model fit statistics for SNP/GRS main effects

		Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
		Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
APOE ϵ2	Intercept	−0.02 (0.07)	0.01 (0.07)	0.06 (0.06)	−0.04 (0.06)
	Slope	−0.00 (0.01)	0.01 (0.01)	−0.00 (0.00)	0.01 (0.01)
APOE ϵ4	Intercept	0.03 (0.05)	0.02 (0.05)	0.02 (0.05)	−0.01 (0.05)
	Slope	−0.02 (0.01)**	0.01 (0.01)	−0.00 (0.00)	−0.01 (0.00)
	F-test	2.61*	1.78	0.30	0.80
ABCA7-rs3764650	Intercept	−0.12 (0.06)*	0.02 (0.06)	−0.05 (0.05)	−0.04 (0.06)
	Slope	−0.0003 (0.007)	0.004 (0.007)	−0.0002 (0.004)	0.01 (0.01)
	F-test	2.93	0.46	0.59	0.84
BIN1-rs744373	Intercept	−0.03 (0.04)	0.07 (0.04)	−0.00 (0.04)	0.04 (0.04)
	Slope	−0.006 (0.005)	0.0002 (0.005)	−0.002 (0.003)	−0.001 (0.004)
	F-test	1.71	1.78	0.18	0.49
CD2AP-rs9296559	Intercept	0.02 (0.04)	0.03 (0.05)	−0.02 (0.04)	0.004 (0.04)
	Slope	−0.006 (0.006)	−0.001 (0.005)	−0.003 (0.003)	−0.001 (0.004)
	F-test	0.56	0.27	0.91	0.03
CD33-rs34813869	Intercept	−0.02 (0.07)	−0.05 (0.07)	−0.07 (0.06)	0.06 (0.07)

	Slope	0.0004 (0.009)	−0.009 (0.008)	0.003 (0.005)	−0.003 (0.006)
	F-test	0.08	1.51	0.66	0.48
CLU-rs11136000	Intercept	0.03 (0.06)	0.07 (0.06)	−0.005 (0.05)	0.05 (0.06)
	Slope	0.0004 (0.007)	−0.001 (0.007)	0.003 (0.004)	0.004 (0.005)
	F-test	0.25	0.75	0.41	0.89
CR1-rs3818361	Intercept	−0.03 (0.05)	0.01 (0.05)	−0.06 (0.04)	−0.05 (0.04)
	Slope	−0.01 (0.01)	−0.01 (0.01)	0.001 (0.003)	−0.0001 (0.004)
	F-test	3.46*	0.49	1.22	0.65
EPHA1-rs11767557	Intercept	0.07 (0.12)	0.08 (0.12)	−0.13 (0.11)	−0.20 (0.11)
	Slope	−0.01 (0.01)	−0.02 (0.01)	0.01 (0.01)	0.01 (0.01)
	F-test	0.37	0.57	0.76	1.54
MS4A4A-rs4938933	Intercept	−0.06 (0.06)	−0.04 (0.06)	0.10 (0.05)	0.06 (0.06)
	Slope	0.01 (0.01)	0.01 (0.01)	0.002 (0.004)	−0.004 (0.005)
	F-test	1.20	1.28	2.90	0.68
MS4A4E-rs670139	Intercept	−0.06 (0.04)	−0.04 (0.05)	0.11 (0.04)**	0.08 (0.04)
	Slope	0.01 (0.01)*	0.01 (0.01)	0.0007 (0.003)	−0.0002 (0.004)
	F-test	3.10*	0.73	4.57*	1.71
MS4A6A-rs610932	Intercept	−0.09 (0.06)	−0.03 (0.06)	0.04 (0.05)	0.03 (0.05)
	Slope	0.01 (0.01)	0.01 (0.01)	0.006 (0.004)	−0.002 (0.005)

	F-test	1.64	1.39	2.12	0.17
PICALM-rs3851179	Intercept	0.01 (0.06)	−0.03 (0.06)	−0.02 (0.06)	0.01 (0.06)
	Slope	0.0001 (0.008)	0.006 (0.007)	0.003 (0.004)	0.009 (0.006)
	F-test	0.01	0.35	0.19	1.41
SC-GRS	Intercept	−0.01 (0.009)	−0.001 (0.009)	0.001 (0.008)	0.008 (0.008)
	Slope	−0.001 (0.001)	0.0006 (0.001)	−0.0005 (0.0006)	0.0002 (0.0008)
	F-test	1.95	0.18	0.35	0.53
OR-GRS	Intercept	−0.00001 (0.03)	−0.003 (0.03)	−0.001 (0.02)	0.007 (0.03)
	Slope	−0.009 (0.003)*	0.002 (0.003)	−0.002 (0.002)	−0.004 (0.003)
	F-test	4.20*	0.13	0.58	1.01
EV-GRS	Intercept	−0.007 (0.05)	−0.007 (0.06)	0.004 (0.05)	0.02 (0.05)
	Slope	−0.017 (0.007)*	0.004 (0.007)	−0.004 (0.004)	−0.006 (0.005)
	F-test	4.44*	0.20	0.64	0.75

*$p < .05$; **$p < .01$.; adjusted for Sex, *APOE* and Education

Table 3: Additional SNPs: Model Fit for SNP main effects

		Episodic Memeory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
		Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
BDNF-rs6265	Intercept	0.002 (0.05)	−0.1 (0.05)*	−0.02 (0.04)	0.05 (0.05)
	Slope	−0.008 (0.006)	−0.003 (0.006)	−0.005 (0.003)	0.001 (0.004)
	F-test	1.31	3.25*	1.75	0.64
CETP-rs5882	Intercept	0.005 (0.043)	−0.053 (0.045)	−0.007 (0.039)	−0.003 (0.042)
	Slope	−0.0002 (0.005)	0.01 (0.005)	−0.005 (0.003)	−0.002 (0.004)
	F-test	0.01	1.77	1.77	0.13
COMT-rs4680	Intercept	0.078 (0.050)	0.032 (0.052)	0.033 (0.045)	−0.005 (0.049)
	Slope	−0.015 (0.006)*	−0.003 (0.006)	0.004 (0.004)	−0.009 (0.005)
	F-test	3.09*	0.22	1.57	2.09
CTNNBL1-rs6125962	Intercept	−0.054 (0.067)	−0.017 (0.07)	0.024 (0.061)	−0.077 (0.065)
	Slope	0.018 (0.008)*	0.010 (0.008)	−0.002 (0.005)	0.006 (0.006)
	F-test	2.27	0.89	0.13	0.90
FRMD4A-rs17314229	Intercept	−0.022 (0.043)	0.04 (0.045)	0.037 (0.039)	−0.006 (0.042)
	Slope	0.007 (0.005)	−0.010 (0.005)*	−0.005 (0.003)	0.001 (0.004)
	F-test	0.75	1.96	1.33	0.04

FRMD4A-rs7081208	Intercept	−0.001 (0.064)	−0.142 (0.067)*	0.135 (0.058)*	−0.102 (0.062)
	Slope	−0.003 (0.008)	0.022 (0.008)**	−0.01 (0.005)*	0.001 (0.006)
	F-test	0.12	4.29*	3.63*	1.39
Intergenic-rs12007229	Intercept	0.031 (0.074)	−0.133 (0.079)	−0.055 (0.068)	0.016 (0.073)
	Slope	−0.023 (0.009)*	0.002 (0.009)	0.004 (0.005)	0.002 (0.007)
	F-test	3.56*	1.64	0.44	0.13
LGALS3-rs4644	Intercept	0.055 (0.045)	0.007 (0.047)	0.031 (0.041)	0.069 (0.044)
	Slope	−0.0003 (0.006)	0.007 (0.005)	−0.004 (0.003)	−0.004 (0.004)
	F-test	0.93	1.08	0.79	1.38
MMP12-rs12808148	Intercept	0.002 (0.048)	0.012 (0.05)	0.007 (0.043)	0.063 (0.047)
	Slope	−0.006 (0.006)	−0.010 (0.006)	−0.001 (0.003)	−0.004 (0.004)
	F-test	0.67	1.55	0.03	0.98
MTHFD1L-rs11754661	Intercept	0.025 (0.058)	−0.043 (0.061)	0.014 (0.053)	0.033 (0.057)
	Slope	−0.001 (0.007)	−0.002 (0.007)	−0.005 (0.004)	−0.005 (0.005)
	F-test	0.10	0.44	0.63	0.53
PAICS-rs11549976	Intercept	0.029 (0.066)	−0.078 (0.069)	−0.070 (0.060)	−0.084 (0.064)
	Slope	−0.009 (0.008)	0.006 (0.008)	0.004 (0.005)	0.0004 (0.006)
	F-test	0.54	0.66	0.75	0.93
PDE7A-rs10808746	Intercept	−0.039 (0.046)	−0.103 (0.048)*	−0.032 (0.042)	−0.077 (0.045)

	Slope	0.006 (0.006)	0.010 (0.006)	−0.000 (0.003)	0.009 (0.004)*
	F-test	0.69	2.60	0.35	2.76
SNTG1-rs16914781	Intercept	0.086 (0.046)	0.038 (0.048)	−0.048 (0.042)	0.008 (0.045)
	Slope	−0.008 (0.006)	−0.002 (0.006)	0.0002 (0.003)	−0.001 (0.004)
	F-test	1.94	0.31	0.74	0.06
SORL1-rs668387	Intercept	0.046 (0.047)	0.006 (0.049)	0.084 (0.043)*	0.010 (0.046)
	Slope	−0.007 (0.006)	0.007 (0.006)	−0.006 (0.003)	0.005 (0.004)
	F-test	0.85	0.94	2.73	0.92
SPON1-rs11023139	Intercept	0.058 (0.069)	−0.093 (0.072)	−0.104 (0.063)	0.009 (0.067)
	Slope	−0.009 (0.009)	0.007 (0.008)	0.007 (0.005)	−0.004 (0.006)
	F-test	0.62	0.88	1.69	0.17
ZNF224-rs3746319	Intercept	0.012 (0.046)	0.071 (0.049)	0.100 (0.042)*	0.047 (0.045)
	Slope	−0.002 (0.006)	0.007 (0.006)	−0.001 (0.003)	0.005 (0.004)
	F-test	0.06	3.43*	3.04*	1.81

*$p < .05$; **$p < .01$.; adjusted for Sex, *APOE* and Education

Supplementary Data

Table 1: SNPs used in this study

Gene	Protein	SNP	Chromosome	Alleles[†]	MAF[‡]	Odds Ratio[§]
Top Report Alzheimer's disease risk SNPs						
APOE	Apolipoprotein E	rs429358/rs7412	19	$\epsilon 2/\epsilon 3/\epsilon 4$	0.8/0.14	0.54/3.81
ABCA7	ATP-binding cassette subfamily A member 7	rs3764650	19	T/G	0.11	1.23
BIN1	Myc box-dependent-interacting protein 1	rs744373	2	A/G	0.31	1.17
CD2AP	CD2-associated protein	rs9296559	6	T/C	0.27	1.11
CD33	Myeloid cell surface antigen CD33	rs34813869	19	A/G	0.29	0.89
CLU	Clusterin	rs11136000	8	C/T	0.35	0.88
CR1	Complement receptor type 1	rs3818361	1	G/A	0.26	1.17
EPHA1	Ephrin type-A receptor 1	rs11767557	7	T/C	0.20	0.89
MS4A4A	Membrane-spanning 4-domains subfamily A member 4A	rs4938933	11	T/C	0.50	0.88
MS4A4E	Membrane-spanning 4-domains subfamily A member 4E	rs670139	11	G/T	0.34	1.08
MS4A6A	Membrane-spanning 4-domains subfamily A member 6A	rs610932	11	T/G	0.45	0.90
PICALM	Phosphatidylinositol-binding clathrin assembly protein	rs3851179	11	C/T	0.41	0.88

Additional AD, dementia and cognition SNPs

BDNF	Brain-derived neurotrophic factor	rs6265	11	C/T	0.20
CETP	Cholesteryl ester transfer protein	rs5882	16	A/G	0.36
COMT	Catechol O-methyltransferase	rs4680	22	G/A	0.48
CTNNBL1	Beta-catenin-like protein 1	rs6125962	20	T/C	0.60
FRMD4A	FERM domain-containing protein 4A	rs17314229	10	C/T	0.09
FRMD4A	FERM domain-containing protein 4A	rs7081208	10	G/A	0.29
Intergenic	-	rs12007229	X	C/A	0.12
LGALS3	Galectin-3	rs4644	14	C/A	0.49
MMP12	Macrophage metalloelastase	rs12808148	11	T/C	0.20
MTHFD1L	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	rs11754661	6	G/A	0.07
PAICS	Multifunctional protein ADE2	rs11549976	4	A/C	0.08
PDE7A	High affinity cAMP-specific 3',5'-cyclic phosphodiesterase 7A	rs10808746	8	G/A	0.48
SNTG1	Gamma-1-syntrophin	rs16914781	8	A/G	0.40
SORL1	Sortilin-related receptor	rs668387	11	C/T	0.48
SPON1	Spondin-1	rs11023139	11	G/A	0.06
ZNF224	Zinc finger protein 224	rs3746319	19	G/A	0.19

[†]Major/Minor Allele; [‡]Minor Allele Frequency: HapMap-CEU; [§]Alzegene reported OR for minor allele

Table 2: SNPs that were genotyped as part of this study

Gene	SNP	Chromsome	Alleles†	MAF‡	Association	Citations
*ABCA7**	rs3764650	19	T/G	0.11	Alzheimer's disease	Hollingworth et al. (2011)
ADRB1	rs1801253	10	C/G	0.31	Blood Pressure	Johnson et al. (2011b) Johnson et al. (2011a)
AGT	rs2004776	1	C/T	0.26	Blood Pressure	Johnson et al. (2011b) Johnson et al. (2011a)
ARHGAP42	rs633185	11	C/G	0.30	Blood Pressure	Bis et al. (2012)
ASTN2	rs7852872	9	C/G	0.39	Neuroanatomy	Bis et al. (2012)
ATP2B1	rs2681472	12	A/G	0.12	Blood Pressure	Levy et al. (2009)
BAG6	rs805303	6	G/A	0.31	Blood Pressure	Bis et al. (2012)
*BDNF**	rs6265	11	C/T	0.20	Cognition	Harris et al. (2006) Mandelman and Grigorenko (2012)
*BIN1**	rs744373	2	A/G	0.31	Alzheimer's disease	Naj et al. (2011) Seshadri S and et al (2010)
*CD2AP**	rs9296559	6	T/C	0.27	Alzheimer's disease	Naj et al. (2011) Hollingworth et al. (2011)
*CD33**	rs34813869	19	A/G	0.29	Alzheimer's disease	Naj et al. (2011) Hollingworth et al. (2011)
*CETP**	rs5882	16	A/G	0.36	Cognition	Izaks et al. (2012)
CHRNA4	rs1044396	20	G/A	0.42	Neuroanatomy	Markett et al. (2013)
*CLU**	rs11136000	8	C/T	0.35	Alzheimer's disease	Naj et al. (2011) Lambert et al. (2009)
*COMT**	rs4680	22	G/A	0.48	Cognition	Houlihan et al. (2009) Harris et al. (2005)
*CR1**	rs3818361	1	G/A	0.26	Alzheimer's disease	Naj et al. (2011) Lambert et al. (2009)
CSK	rs1378942	15	A/C	0.32	Blood Pressure	Bis et al. (2012)

*CTNNBL1**	rs6125962	20	T/C	0.60	Cognition	Papassotiropoulos et al. (2013)
CYP19A1	rs700518	15	C/T	0.42	Neuroanatomy	Bayer et al. (2013)
DPP4	rs6741949	2	G/C	0.43	Neuroanatomy	Bis et al. (2012)
DRD2	rs6277	11	A/G	0.47	Neuroanatomy	Markett et al. (2013)
*EPHA1-AS1**	rs11767557	7	T/C	0.20	Alzheimer's disease	Naj et al. (2011) Hollingworth et al. (2011)
F5	rs6703865	1	G/A	0.40	Neuroanatomy	Melville et al. (2012)
FGF5	rs1458038	4	C/T	0.27	Blood Pressure	Bis et al. (2012)
*FRMD4A**	rs17314229	10	C/T	0.09	Alzheimer's disease	Lambert et al. (2013)
FRMD4A	rs2446581				Alzheimer's disease	Lambert et al. (2013)
*FRMD4A**	rs7081208	10	G/A	0.29	Alzheimer's disease	Lambert et al. (2013)
FTO	rs3751812	16	G/T	0.46	Neuroanatomy	Ho et al. (2010)
GCFC2	rs2298948	2	T/C	0.33	Neuroanatomy	Melville et al. (2012)
GNAS-EDN3	rs6015450	20	A/G	0.07	Blood Pressure	Bis et al. (2012)
GRIN2B	rs10845840	12	C/T	0.46	Neuroanatomy	Kohannim et al. (2012)
HFE	rs1799945	6	C/G	0.18	Blood Pressure	Bis et al. (2012)
Intergenic	rs7294919	12	T/C	0.10	Neuroanatomy	Bis et al. (2012)
Intergenic	rs11139399	9	T/C	0.41	Neuroanatomy	Melville et al. (2012)
Intergenic	rs2942354	1	C/A	0.44	Neuroanatomy	Melville et al. (2012)
Intergenic*	rs12007229	X	C/A	0.12	Dementia	Schrijvers et al. (2012)

*LGALS3**	rs4644	14	C/A	0.49	Cognition	Trompet et al. (2012)
LHFP	rs9315702	13	C/A	0.43	Neuroanatomy	Melville et al. (2012)
MECP2	rs2239464	X	G/A	0.22	Neuroanatomy	Joyner et al. (2009)
*MMP12**	rs12808148	11	T/C	0.20	Dementia	Kamboh et al. (2012)
*MS4A4A**	rs4938933	11	T/C	0.50	Alzheimer's disease	Naj et al. (2011)
*MS4A4E**	rs670139	11	G/T	0.34	Alzheimer's disease	Hollingworth et al. (2011)
*MS4A6A**	rs610932	11	T/G	0.45	Alzheimer's disease	Hollingworth et al. (2011)
MSRB3	rs17178006	12	T/G	0.09	Neuroanatomy	Bis et al. (2012)
*MTHFD1L**	rs11754661	6	G/A	0.07	Alzheimer's disease	Beecham et al. (2009) Naj et al. (2011)
MTHFR	rs17367504	1	A/G	0.17	Blood Pressure	Bis et al. (2012)
NOS3	rs3918226	7	C/T	0.04	Blood Pressure	Salvi et al. (2012)
NPR3	rs1173771	5	G/A	0.49	Blood Pressure	Bis et al. (2012)
NTSR1	rs4334545	20	C/T	0.29	Neuroanatomy	Li et al. (2013)
OPRD1	rs678849	1	T/C	0.47	Neuroanatomy	Roussotte et al. (2014)
*PAICS**	rs11549976	4	A/C	0.08	Dementia	Velez et al. (2013)
PARP1	rs1136410	1	A/G	0.15	Neuroanatomy	Nho et al. (2013)
*PDE7A**	rs10808746	8	G/A	0.48	Cognition	De Jager et al. (2012)
*PICALM**	rs3851179	11	C/T	0.41	Alzheimer's disease	Naj et al. (2011) Harold et al. (2009)
SELP	rs3917836	1	T/C	0.05	Neuroanatomy	Melville et al. (2012)

*SNTG1**	rs16914781	8	A/G	0.40	Dementia	Velez et al. (2013)
*SORL1**	rs668387	11	C/T	0.48	Alzheimer's disease	Rogaeva et al. (2007)
SPON1	rs2618516	11	C/T	0.36	Neuroanatomy	Jahanshad et al. (2013)
*SPON1**	rs11023139	11	G/A	0.06	Cognition	Sherva et al. (2013)
TNF	rs1800629	6	G/A	0.17	Neuroanatomy	Baune et al. (2012)
TRIM65	rs3744028	17	T/C	0.20	Neuroanatomy	Fornage et al. (2011)
WDR41	rs163030	5	A/C	0.47	Neuroanatomy	Stein et al. (2011)
WIF1	rs6581612	12	A/C	0.25	Neuroanatomy	Bis et al. (2012)
*ZNF224**	rs3746319	19	G/A	0.19	Dementia	Shulman et al. (2010)

*SNPs included in the current analysis; †Major/Minor Allele; ‡Minor Allele Frequence: HapMap-CEU

Table 3: Frequency of top AD risk SNP genotypes and alleles at baseline

	Genotype	n (%)
APOE	e3/e3	1048 (62)
	e2+	217 (12.8)
	e4+	424 (25.1)
	NA	0 (0)
ABCA7	T/T	1394 (82.5)
	G/T	278 (16.5)
	G/G	13 (0.8)
	NA	4 (0.2)
BIN1	A/A	856 (50.7)
	A/G	683 (40.4)
	G/G	147 (8.7)
	NA	3 (0.2)
CD2AP	T/T	863 (51.1)
	C/T	667 (39.5)
	C/C	153 (9.1)
	NA	6 (0.4)
CD33	G/G	731 (43.3)
	A/G	758 (44.9)
	A/A	191 (11.3)
	NA	9 (0.5)
CLU	T/T	595 (35.2)
	C/T	814 (48.2)
	C/C	268 (15.9)
	NA	12 (0.7)
CR1	G/G	1143 (67.7)

	A/G	485 (28.7)
	A/A	50 (3)
	NA	11 (0.7)
EPHA1	C/C	1092 (64.7)
	C/T	534 (31.6)
	T/T	58 (3.4)
	NA	5 (0.3)
MS4A4A	C/C	587 (34.8)
	C/T	815 (48.3)
	T/T	283 (16.8)
	NA	4 (0.2)
MS4A4E	G/G	588 (34.8)
	G/T	789 (46.7)
	T/T	301 (17.8)
	NA	11 (0.7)
MS4A6A	T/T	562 (33.3)
	G/T	809 (47.9)
	G/G	309 (18.3)
	NA	9 (0.5)
PICALM	T/T	621 (36.8)
	C/T	824 (48.8)
	C/C	237 (14)
	NA	7 (0.4)

Table 4: Genotype Frequencies of the 16 additional SNPs

	Genotype	n (%)

BDNF	C/C	1103 (65.3)
	C/T	494 (29.2)
	T/T	50 (3)
	NA	42 (2.5)
CETP	A/A	773 (45.8)
	A/G	744 (44)
	G/G	171 (10.1)
	NA	1 (0.1)
COMT	G/G	407 (24.1)
	A/G	827 (49)
	A/A	451 (26.7)
	NA	4 (0.2)
CTNNBL1	T/T	1492 (88.3)
	C/T	188 (11.1)
	C/C	7 (0.4)
	NA	2 (0.1)
FRMD4A (1)	G/G	908 (53.8)
	A/G	646 (38.2)
	A/A	122 (7.2)
	NA	13 (0.8)
FRMD4A (2)	C/C	1462 (86.6)
	C/T	212 (12.6)
	T/T	7 (0.4)
	NA	8 (0.5)
Intergenic chrX	C/C	1524 (90.2)
	A/C	91 (5.4)

	A/A	61 (3.6)
	NA	13 (0.8)
LGALS3	C/C	585 (34.6)
	A/C	774 (45.8)
	A/A	301 (17.8)
	NA	29 (1.7)
MMP12	T/T	1218 (72.1)
	C/T	426 (25.2)
	C/C	40 (2.4)
	NA	5 (0.3)
MTHFD1L	G/G	1418 (84)
	A/G	259 (15.3)
	A/A	9 (0.5)
	NA	3 (0.2)
PAICS	A/A	1484 (87.9)
	A/C	201 (11.9)
	C/C	0 (0)
	NA	4 (0.2)
PDE7A	G/G	530 (31.4)
	A/G	790 (46.8)
	A/A	344 (20.4)
	NA	25 (1.5)
SNTG1	A/A	528 (31.3)
	A/G	823 (48.7)
	G/G	335 (19.8)
	NA	3 (0.2)
SORL1	C/C	501 (29.7)

	C/T	829 (49.1)
	T/T	334 (19.8)
	NA	25 (1.5)
SPON1	G/G	1506 (89.2)
	A/G	177 (10.5)
	A/A	4 (0.2)
	NA	2 (0.1)
ZNF224	G/G	1170 (69.3)
	A/G	469 (27.8)
	A/A	48 (2.8)
	NA	2 (0.1)

Table 5: Raw cognitive test scores (mean ± standard deviation)

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Wave 1	6.62 ± 2.30	5.05 ± 2.2	52.57 ± 5.3	51.11 ± 8.78
Wave 2	6.51 ± 2.20	5.21 ± 2.17	53.32 ± 4.92	50 ± 8.93
Wave 3	6.25 ± 2.18	5.16 ± 2.15	53.55 ± 4.86	48.28 ± 8.97

Table 6: Person correlations of wave 1 cognitive test scores

	Recall-Immediate	Recall-Delayed	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Recall-Immedite	1				
Recall-Delayed	0.84***	1			
Digits Backwards	0.24***	0.22***	1		
Spot-the-word	0.24***	0.23***	0.32***	1	
Symbol Digits Modaltiies Test	0.27***	0.28***	0.35***	0.33***	1

Table 7: Unconditional Means Models

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Intercept	−0.0004 (0.0199)	0.1033 (0.0207)***	0.1986 (0.0206)***	0.0156 (0.0205)
Individuals	1689	1689	1684	1688
Variance: Intercept	0.5364	0.6051	0.6723	0.6338
Variance: Residual	0.3732	0.3311	0.1053	0.2084
Log Likelihood	-5829.9641	-5665.0670	-3839.8119	-4938.9976

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 8: Unconditional Growth Models

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Intercept	0.1152 (0.0226)***	0.0936 (0.0232)***	0.1385 (0.0217)***	0.1643 (0.0216)***
Time	−0.0297 (0.0027)***	0.0026 (0.0026)	0.0161 (0.0015)***	−0.0390 (0.0020)***
Individuals	1689	1689	1684	1688
Variance: Intercept	0.5774	0.6460	0.7135	0.6447
Variance: Time	0.0012	0.0013	0.0008	0.0007
Variance: Residual	0.3384	0.3091	0.0891	0.1714
Log Likelihood	-5763.8218	-5660.5924	-3763.6267	-4737.9415
F-test	123.59***	1.02	112.96***	393.46***
R^2_m	0.013	0	0.004	0.023
R^2_c	0.63	0.67	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 9: Covarites

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3659 (0.1239)***	-1.1585 (0.1302)***	-2.0484 (0.1130)***	-1.2125 (0.1210)***
Gender	0.4761 (0.0432)***	-0.0550 (0.0454)	0.0060 (0.0392)	0.1087 (0.0422)**
Education	0.0894 (0.0084)***	0.0913 (0.0088)***	0.1559 (0.0076)***	0.0946 (0.0082)***
Rate of Change				
Time	-0.0174 (0.0156)	-0.0130 (0.0152)	0.0153 (0.0090)	-0.0390 (0.0115)***
Gender	0.0034 (0.0054)	-0.0051 (0.0052)	0.0021 (0.0031)	0.0045 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0002 (0.0008)
Individuals	1689	1689	1684	1688
Variance: Intercept	0.4849	0.5851	0.5525	0.5870
Variance: Time	0.0012	0.0012	0.0008	0.0008
Variance: Residual	0.3380	0.3106	0.0890	0.1709
Log Likelihood	-5638.9910	-5577.8450	-3546.1752	-4664.8600
F-test	67.07***	43.28***	123.58***	38.03***
R^2_m	0.112	0.071	0.21	0.091
R^2_c	0.629	0.669	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 10: *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3727 (0.1251)***	−1.1629 (0.1315)***	−2.0618 (0.1140)***	−1.2041 (0.1221)***
Gender	0.4762 (0.0432)***	−0.0550 (0.0454)	0.0065 (0.0392)	0.1084 (0.0422)*
Education	0.0894 (0.0084)***	0.0913 (0.0088)***	0.1559 (0.0076)***	0.0946 (0.0082)***
APOE e2	−0.0225 (0.0657)	0.0100 (0.0691)	0.0590 (0.0594)	−0.0419 (0.0640)
APOE e4	0.0346 (0.0502)	0.0151 (0.0528)	0.0217 (0.0457)	−0.0109 (0.0492)
Rate of Change				
Time	−0.0121 (0.0157)	−0.0177 (0.0153)	0.0160 (0.0091)	−0.0384 (0.0116)***
Gender	0.0033 (0.0054)	−0.0047 (0.0052)	0.0020 (0.0031)	0.0045 (0.0040)
Education	−0.0010 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0029 (0.0082)	0.0149 (0.0079)	−0.0019 (0.0046)	0.0050 (0.0060)
APOE e4	−0.0193 (0.0063)**	0.0095 (0.0061)	−0.0019 (0.0036)	−0.0056 (0.0046)
Individuals	1689	1689	1684	1688
Variance: Intercept	0.4847	0.5846	0.5521	0.5870
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3377	0.3112	0.0890	0.1708
Log Likelihood	-5633.7563	-5574.2830	-3545.5803	-4663.2460
F-test	2.61*	1.78	0.30	0.80
R^2_m	0.114	0.072	0.21	0.091
R^2_c	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 11: *ABCA7*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3615 (0.1251)***	-1.1630 (0.1318)***	-2.0545 (0.1142)***	-1.1973 (0.1223)***
Gender	0.4805 (0.0432)***	-0.0577 (0.0455)	0.0092 (0.0393)	0.1077 (0.0422)*
Education	0.0897 (0.0083)***	0.0912 (0.0088)***	0.1558 (0.0076)***	0.0947 (0.0082)***
APOE e2	-0.0184 (0.0656)	0.0092 (0.0691)	0.0608 (0.0594)	-0.0421 (0.0640)
APOE e4	0.0332 (0.0502)	0.0117 (0.0529)	0.0234 (0.0457)	-0.0133 (0.0492)
ABCA7	-0.1174 (0.0563)*	0.0198 (0.0593)	-0.0507 (0.0513)	-0.0404 (0.0551)
Rate of Change				
Time	-0.0118 (0.0157)	-0.0185 (0.0153)	0.0160 (0.0091)	-0.0390 (0.0116)***
Gender	0.0031 (0.0054)	-0.0049 (0.0052)	0.0020 (0.0031)	0.0044 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0002 (0.0008)
APOE e2	-0.0032 (0.0082)	0.0148 (0.0079)	-0.0019 (0.0046)	0.0048 (0.0060)
APOE e4	-0.0194 (0.0063)**	0.0095 (0.0061)	-0.0019 (0.0036)	-0.0054 (0.0047)
ABCA7	-0.0003 (0.0070)	0.0043 (0.0068)	-0.0002 (0.0040)	0.0064 (0.0051)
Individuals	1685	1685	1680	1684
Variance: Intercept	0.4816	0.5845	0.5515	0.5853
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3378	0.3111	0.0891	0.1710
Log Likelihood	-5618.7534	-5562.8453	-3539.6808	-4652.9621
F-test	2.93	0.46	0.59	0.84
R_m^2	0.116	0.072	0.211	0.092
R_c^2	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 12: *BIN1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3524 (0.1261)***	−1.1802 (0.1325)***	−2.0679 (0.1151)***	−1.2134 (0.1231)***
Gender	0.4753 (0.0432)***	−0.0593 (0.0454)	0.0066 (0.0393)	0.1056 (0.0423)*
Education	0.0889 (0.0084)***	0.0900 (0.0088)***	0.1563 (0.0076)***	0.0938 (0.0082)***
APOE e2	−0.0207 (0.0657)	0.0126 (0.0691)	0.0585 (0.0595)	−0.0403 (0.0640)
APOE e4	0.0361 (0.0503)	0.0114 (0.0529)	0.0234 (0.0458)	−0.0126 (0.0492)
BIN1	−0.0298 (0.0427)	0.0739 (0.0449)	−0.0002 (0.0388)	0.0409 (0.0418)
Rate of Change				
Time	−0.0105 (0.0158)	−0.0186 (0.0154)	0.0170 (0.0091)	−0.0386 (0.0117)***
Gender	0.0036 (0.0054)	−0.0044 (0.0052)	0.0021 (0.0031)	0.0047 (0.0040)
Education	−0.0009 (0.0010)	0.0014 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0030 (0.0082)	0.0146 (0.0079)	−0.0019 (0.0046)	0.0048 (0.0060)
APOE e4	−0.0190 (0.0063)**	0.0093 (0.0061)	−0.0020 (0.0036)	−0.0057 (0.0047)
BIN1	−0.0061 (0.0053)	0.0002 (0.0052)	−0.0017 (0.0030)	−0.0007 (0.0039)
Individuals	1686	1686	1681	1685
Variance: Intercept	0.4838	0.5832	0.5526	0.5867
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3380	0.3117	0.0889	0.1708
Log Likelihood	-5624.9056	-5564.5501	-3540.2586	-4655.9700
F-test	1.71	1.78	0.18	0.49
R_m^2	0.113	0.073	0.211	0.091
R_c^2	0.629	0.667	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 13: *CD2AP*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3860 (0.1259)***	-1.1727 (0.1323)***	-2.0579 (0.1148)***	-1.2124 (0.1228)***
Gender	0.4749 (0.0433)***	-0.0579 (0.0455)	0.0047 (0.0393)	0.1092 (0.0423)**
Education	0.0898 (0.0084)***	0.0909 (0.0088)***	0.1562 (0.0076)***	0.0949 (0.0082)***
APOE e2	-0.0247 (0.0659)	0.0011 (0.0692)	0.0530 (0.0596)	-0.0480 (0.0641)
APOE e4	0.0328 (0.0504)	0.0134 (0.0530)	0.0213 (0.0459)	-0.0081 (0.0493)
CD2AP	0.0182 (0.0429)	0.0322 (0.0451)	-0.0162 (0.0390)	0.0048 (0.0419)
Rate of Change				
Time	-0.0114 (0.0158)	-0.0173 (0.0154)	0.0165 (0.0091)	-0.0385 (0.0117)***
Gender	0.0037 (0.0054)	-0.0047 (0.0053)	0.0024 (0.0031)	0.0048 (0.0040)
Education	-0.0009 (0.0010)	0.0013 (0.0010)	0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0030 (0.0082)	0.0150 (0.0080)	-0.0018 (0.0047)	0.0059 (0.0060)
APOE e4	-0.0188 (0.0063)**	0.0096 (0.0062)	-0.0013 (0.0036)	-0.0057 (0.0047)
CD2AP	-0.0057 (0.0054)	-0.0009 (0.0052)	-0.0032 (0.0031)	-0.0010 (0.0040)
Individuals	1683	1683	1678	1682
Variance: Intercept	0.4863	0.5841	0.5529	0.5858
Variance: Time	0.0012	0.0012	0.0008	0.0008
Variance: Residual	0.3355	0.3107	0.0887	0.1711
Log Likelihood	-5605.3421	-5554.3613	-3533.6684	-4646.5940
F-test	0.56	0.27	0.91	0.03
R_m^2	0.115	0.072	0.211	0.092
R_c^2	0.632	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 14: CD33

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3509 (0.1398)***	-1.1070 (0.1471)***	-1.9917 (0.1273)***	-1.2592 (0.1369)***
Gender	0.4794 (0.0432)***	-0.0590 (0.0455)	0.0022 (0.0393)	0.1076 (0.0424)*
Education	0.0892 (0.0084)***	0.0911 (0.0088)***	0.1555 (0.0076)***	0.0946 (0.0082)***
APOE e2	-0.0226 (0.0657)	0.0047 (0.0691)	0.0567 (0.0594)	-0.0431 (0.0642)
APOE e4	0.0370 (0.0503)	0.0162 (0.0529)	0.0200 (0.0458)	-0.0157 (0.0494)
CD33	-0.0242 (0.0669)	-0.0531 (0.0704)	-0.0697 (0.0609)	0.0638 (0.0657)
Rate of Change				
Time	-0.0125 (0.0176)	-0.0112 (0.0172)	0.0126 (0.0101)	-0.0359 (0.0130)**
Gender	0.0030 (0.0054)	-0.0047 (0.0052)	0.0020 (0.0031)	0.0042 (0.0040)
Education	-0.0010 (0.0010)	0.0014 (0.0010)	0.0001 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0030 (0.0082)	0.0146 (0.0079)	-0.0019 (0.0046)	0.0052 (0.0060)
APOE e4	-0.0190 (0.0063)**	0.0094 (0.0061)	-0.0016 (0.0036)	-0.0056 (0.0047)
CD33	0.0004 (0.0085)	-0.0086 (0.0082)	0.0026 (0.0048)	-0.0029 (0.0062)
Individuals	1680	1680	1675	1679
Variance: Intercept	0.4829	0.5822	0.5513	0.5892
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3382	0.3121	0.0891	0.1713
Log Likelihood	-5604.7889	-5543.8680	-3526.3746	-4643.3035
F-test	0.08	1.51	0.66	0.48
R^2_m	0.114	0.073	0.211	0.091
R^2_c	0.629	0.667	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 15: *CLU*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.4076 (0.1343)***	-1.2214 (0.1416)***	-2.0821 (0.1198)***	-1.2448 (0.1315)***
Gender	0.4820 (0.0433)***	-0.0581 (0.0456)	0.0035 (0.0385)	0.1032 (0.0424)*
Education	0.0896 (0.0084)***	0.0914 (0.0088)***	0.1576 (0.0075)***	0.0947 (0.0082)***
APOE e2	-0.0235 (0.0659)	0.0052 (0.0694)	0.0585 (0.0583)	-0.0435 (0.0643)
APOE e4	0.0330 (0.0505)	0.0217 (0.0532)	0.0394 (0.0449)	-0.0104 (0.0495)
CLU	0.0343 (0.0585)	0.0710 (0.0616)	-0.0047 (0.0519)	0.0506 (0.0572)
Rate of Change				
Time	-0.0125 (0.0169)	-0.0169 (0.0164)	0.0164 (0.0090)	-0.0418 (0.0125)***
Gender	0.0023 (0.0054)	-0.0055 (0.0053)	0.0027 (0.0029)	0.0047 (0.0040)
Education	-0.0010 (0.0010)	0.0014 (0.0010)	-0.0003 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0024 (0.0082)	0.0150 (0.0080)	-0.0018 (0.0043)	0.0055 (0.0060)
APOE e4	-0.0182 (0.0063)**	0.0086 (0.0062)	-0.0044 (0.0034)	-0.0052 (0.0047)
CLU	0.0004 (0.0072)	-0.0013 (0.0070)	0.0034 (0.0038)	0.0035 (0.0053)
Individuals	1677	1677	1672	1676
Variance: Intercept	0.4833	0.5868	0.5301	0.5895
Variance: Time	0.0012	0.0011	0.0004	0.0008
Variance: Residual	0.3384	0.3112	0.0841	0.1712
Log Likelihood	-5594.4717	-5535.4866	-3361.6835	-4636.9077
F-test	0.25	0.75	0.41	0.89
R^2_m	0.115	0.073	0.215	0.092
R^2_c	0.63	0.669	0.89	0.799

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 16: *CR1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3531 (0.1266)***	-1.1660 (0.1333)***	-2.0363 (0.1155)***	-1.1752 (0.1235)***
Gender	0.4772 (0.0433)***	-0.0508 (0.0456)	0.0058 (0.0394)	0.1134 (0.0423)**
Education	0.0888 (0.0084)***	0.0913 (0.0088)***	0.1556 (0.0076)***	0.0934 (0.0082)***
APOE e2	-0.0303 (0.0661)	0.0188 (0.0696)	0.0663 (0.0598)	-0.0403 (0.0643)
APOE e4	0.0256 (0.0504)	0.0105 (0.0530)	0.0196 (0.0459)	-0.0147 (0.0492)
CR1	-0.0313 (0.0459)	0.0067 (0.0483)	-0.0647 (0.0417)	-0.0481 (0.0448)
Rate of Change				
Time	-0.0084 (0.0159)	-0.0153 (0.0155)	0.0145 (0.0092)	-0.0386 (0.0118)**
Gender	0.0028 (0.0054)	-0.0053 (0.0052)	0.0024 (0.0031)	0.0043 (0.0040)
Education	-0.0010 (0.0010)	0.0012 (0.0010)	0.0001 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0032 (0.0082)	0.0143 (0.0080)	-0.0028 (0.0047)	0.0055 (0.0061)
APOE e4	-0.0190 (0.0063)**	0.0103 (0.0061)	-0.0020 (0.0036)	-0.0055 (0.0047)
CR1	-0.0107 (0.0057)	-0.0052 (0.0056)	0.0013 (0.0033)	-0.0001 (0.0042)
Individuals	1678	1678	1673	1677
Variance: Intercept	0.4830	0.5866	0.5530	0.5844
Variance: Time	0.0011	0.0012	0.0008	0.0008
Variance: Residual	0.3383	0.3099	0.0889	0.1711
Log Likelihood	-5595.6655	-5539.2700	-3522.9848	-4635.0873
F-test	3.46*	0.49	1.22	0.65
R^2_m	0.115	0.072	0.212	0.091
R^2_c	0.629	0.67	0.885	0.797

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 17: *EPHA1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.4503 (0.1732)***	-1.2446 (0.1824)***	-1.9318 (0.1576)***	-1.0002 (0.1694)***
Gender	0.4776 (0.0432)***	-0.0518 (0.0455)	0.0042 (0.0393)	0.1052 (0.0423)*
Education	0.0898 (0.0084)***	0.0915 (0.0088)***	0.1557 (0.0076)***	0.0939 (0.0082)***
APOE e2	-0.0210 (0.0657)	0.0126 (0.0692)	0.0545 (0.0595)	-0.0460 (0.0641)
APOE e4	0.0303 (0.0502)	0.0176 (0.0529)	0.0199 (0.0458)	-0.0129 (0.0493)
EPHA1	0.0740 (0.1172)	0.0789 (0.1233)	-0.1289 (0.1063)	-0.1990 (0.1147)
Rate of Change				
Time	-0.0004 (0.0216)	-0.0020 (0.0211)	0.0102 (0.0124)	-0.0476 (0.0161)**
Gender	0.0031 (0.0054)	-0.0051 (0.0052)	0.0020 (0.0031)	0.0046 (0.0040)
Education	-0.0010 (0.0010)	0.0012 (0.0010)	0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0037 (0.0082)	0.0147 (0.0079)	-0.0019 (0.0046)	0.0053 (0.0060)
APOE e4	-0.0196 (0.0063)**	0.0094 (0.0061)	-0.0020 (0.0036)	-0.0054 (0.0047)
EPHA1	-0.0120 (0.0145)	-0.0151 (0.0142)	0.0055 (0.0083)	0.0091 (0.0109)
Individuals	1684	1684	1679	1683
Variance: Intercept	0.4823	0.5851	0.5522	0.5873
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3379	0.3115	0.0889	0.1706
Log Likelihood	-5614.3431	-5561.8987	-3531.5628	-4651.0877
F-test	0.37	0.57	0.76	1.54
R^2_m	0.114	0.072	0.212	0.092
R^2_c	0.629	0.668	0.885	0.799

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 18: *MS4A4A*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3130 (0.1346)***	−1.1293 (0.1415)***	−2.1357 (0.1225)***	−1.2538 (0.1312)***
Gender	0.4738 (0.0432)***	−0.0535 (0.0455)	0.0040 (0.0392)	0.1058 (0.0422)*
Education	0.0891 (0.0084)***	0.0910 (0.0088)***	0.1555 (0.0076)***	0.0946 (0.0082)***
APOE e2	−0.0191 (0.0659)	0.0142 (0.0692)	0.0543 (0.0595)	−0.0337 (0.0641)
APOE e4	0.0374 (0.0503)	0.0149 (0.0529)	0.0174 (0.0457)	−0.0088 (0.0492)
MS4A4A	−0.0650 (0.0572)	−0.0378 (0.0601)	0.0997 (0.0518)	0.0604 (0.0558)
Rate of Change				
Time	−0.0212 (0.0168)	−0.0272 (0.0163)	0.0134 (0.0097)	−0.0348 (0.0124)**
Gender	0.0036 (0.0054)	−0.0050 (0.0052)	0.0021 (0.0031)	0.0048 (0.0040)
Education	−0.0010 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0002 (0.0008)
APOE e2	−0.0032 (0.0082)	0.0146 (0.0079)	−0.0010 (0.0046)	0.0048 (0.0060)
APOE e4	−0.0200 (0.0063)**	0.0097 (0.0061)	−0.0018 (0.0036)	−0.0060 (0.0046)
MS4A4A	0.0105 (0.0071)	0.0110 (0.0069)	0.0025 (0.0040)	−0.0041 (0.0052)
Individuals	1685	1685	1680	1684
Variance: Intercept	0.4846	0.5845	0.5509	0.5855
Variance: Time	0.0011	0.0011	0.0008	0.0007
Variance: Residual	0.3376	0.3115	0.0885	0.1711
Log Likelihood	-5620.2648	-5562.5626	-3527.4762	-4652.2710
F-test	1.20	1.28	2.90	0.68
R_m^2	0.114	0.072	0.211	0.092
R_c^2	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 19: *MS4A4E*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3285 (0.1285)***	-1.1390 (0.1357)***	-2.1359 (0.1175)***	-1.2635 (0.1254)***
Gender	0.4804 (0.0432)***	-0.0541 (0.0456)	0.0093 (0.0393)	0.1104 (0.0422)**
Education	0.0891 (0.0084)***	0.0914 (0.0088)***	0.1559 (0.0076)***	0.0954 (0.0082)***
APOE e2	-0.0424 (0.0661)	-0.0026 (0.0697)	0.0589 (0.0599)	-0.0621 (0.0643)
APOE e4	0.0357 (0.0503)	0.0168 (0.0531)	0.0166 (0.0458)	-0.0179 (0.0492)
MS4A4E	-0.0602 (0.0447)	-0.0372 (0.0472)	0.1107 (0.0407)**	0.0773 (0.0437)
Rate of Change				
Time	-0.0207 (0.0161)	-0.0216 (0.0157)	0.0159 (0.0094)	-0.0375 (0.0120)**
Gender	0.0029 (0.0054)	-0.0048 (0.0052)	0.0021 (0.0031)	0.0046 (0.0040)
Education	-0.0011 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0002 (0.0008)
APOE e2	-0.0017 (0.0082)	0.0163 (0.0080)*	-0.0024 (0.0047)	0.0066 (0.0061)
APOE e4	-0.0194 (0.0063)**	0.0093 (0.0061)	-0.0018 (0.0036)	-0.0054 (0.0047)
MS4A4E	0.0139 (0.0056)*	0.0064 (0.0054)	0.0007 (0.0032)	-0.0002 (0.0041)
Individuals	1678	1678	1673	1677
Variance: Intercept	0.4810	0.5874	0.5517	0.5815
Variance: Time	0.0011	0.0012	0.0008	0.0008
Variance: Residual	0.3371	0.3105	0.0895	0.1714
Log Likelihood	-5590.2460	-5537.5490	-3528.4349	-4632.2743
F-test	3.10*	0.73	4.57*	1.71
R^2_m	0.115	0.072	0.212	0.094
R^2_c	0.631	0.669	0.884	0.797

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 20: *MS4A6A*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3035 (0.1337)***	-1.1283 (0.1407)***	-2.0948 (0.1222)***	-1.2260 (0.1306)***
Gender	0.4703 (0.0432)***	-0.0585 (0.0455)	0.0062 (0.0394)	0.1129 (0.0423)**
Education	0.0898 (0.0084)***	0.0908 (0.0088)***	0.1561 (0.0076)***	0.0944 (0.0082)***
APOE e2	-0.0279 (0.0660)	-0.0029 (0.0694)	0.0569 (0.0598)	-0.0400 (0.0643)
APOE e4	0.0287 (0.0503)	0.0111 (0.0530)	0.0197 (0.0459)	-0.0175 (0.0493)
MS4A6A	-0.0855 (0.0552)	-0.0299 (0.0580)	0.0374 (0.0502)	0.0290 (0.0539)
Rate of Change				
Time	-0.0200 (0.0167)	-0.0265 (0.0163)	0.0110 (0.0097)	-0.0373 (0.0124)**
Gender	0.0038 (0.0054)	-0.0046 (0.0052)	0.0021 (0.0031)	0.0042 (0.0040)
Education	-0.0011 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0026 (0.0082)	0.0153 (0.0080)	-0.0019 (0.0047)	0.0052 (0.0061)
APOE e4	-0.0186 (0.0063)**	0.0099 (0.0061)	-0.0018 (0.0036)	-0.0056 (0.0047)
MS4A6A	0.0109 (0.0069)	0.0110 (0.0067)	0.0059 (0.0039)	-0.0019 (0.0051)
Individuals	1680	1680	1675	1679
Variance: Intercept	0.4844	0.5856	0.5541	0.5864
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3366	0.3110	0.0894	0.1709
Log Likelihood	-5599.0620	-5543.4736	-3533.2931	-4640.1869
F-test	1.64	1.39	2.12	0.17
R_m^2	0.114	0.072	0.211	0.092
R_c^2	0.631	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 21: *PICALM*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3845 (0.1384)***	-1.1445 (0.1454)***	-2.0514 (0.1262)***	-1.2231 (0.1355)***
Gender	0.4813 (0.0432)***	-0.0600 (0.0454)	0.0061 (0.0393)	0.1099 (0.0423)**
Education	0.0896 (0.0084)***	0.0920 (0.0088)***	0.1561 (0.0076)***	0.0954 (0.0082)***
APOE e2	-0.0211 (0.0657)	0.0096 (0.0690)	0.0578 (0.0595)	-0.0438 (0.0641)
APOE e4	0.0364 (0.0503)	0.0148 (0.0528)	0.0146 (0.0458)	-0.0151 (0.0493)
PICALM	0.0071 (0.0613)	-0.0311 (0.0644)	-0.0151 (0.0557)	0.0112 (0.0601)
Rate of Change				
Time	-0.0113 (0.0175)	-0.0229 (0.0169)	0.0128 (0.0101)	-0.0464 (0.0129)***
Gender	0.0031 (0.0054)	-0.0040 (0.0052)	0.0021 (0.0031)	0.0046 (0.0040)
Education	-0.0011 (0.0010)	0.0013 (0.0010)	0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0030 (0.0082)	0.0154 (0.0079)	-0.0017 (0.0046)	0.0058 (0.0060)
APOE e4	-0.0191 (0.0063)**	0.0095 (0.0061)	-0.0018 (0.0036)	-0.0051 (0.0046)
PICALM	0.0001 (0.0076)	0.0061 (0.0074)	0.0027 (0.0044)	0.0085 (0.0056)
Individuals	1682	1682	1677	1681
Variance: Intercept	0.4822	0.5806	0.5514	0.5868
Variance: Time	0.0012	0.0011	0.0008	0.0007
Variance: Residual	0.3383	0.3105	0.0892	0.1713
Log Likelihood	-5612.1574	-5543.3580	-3532.6002	-4644.9827
F-test	0.01	0.35	0.19	1.41
R_m^2	0.115	0.073	0.212	0.093
R_c^2	0.629	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 22: SC-GRS with *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.2860 (0.1547)***	-1.1407 (0.1634)***	-2.0800 (0.1389)***	-1.2928 (0.1513)***
Gender	0.4821 (0.0438)***	-0.0640 (0.0463)	-0.0068 (0.0394)	0.1070 (0.0430)*
Education	0.0900 (0.0085)***	0.0914 (0.0089)***	0.1578 (0.0076)***	0.0950 (0.0083)***
SC-GRS	-0.0090 (0.0085)	-0.0013 (0.0089)	0.0015 (0.0076)	0.0073 (0.0083)
Rate of Change				
Time	-0.0058 (0.0195)	-0.0202 (0.0190)	0.0203 (0.0104)	-0.0403 (0.0144)**
Gender	0.0029 (0.0055)	-0.0055 (0.0054)	0.0037 (0.0029)	0.0046 (0.0041)
Education	-0.0011 (0.0011)	0.0014 (0.0010)	-0.0001 (0.0006)	-0.0002 (0.0008)
SC-GRS	-0.0010 (0.0011)	0.0006 (0.0010)	-0.0005 (0.0006)	0.0002 (0.0008)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4759	0.5857	0.5359	0.5815
Variance: Time	0.0012	0.0013	0.0004	0.0008
Variance: Residual	0.3388	0.3096	0.0844	0.1733
Log Likelihood	-5405.8773	-5354.5581	-3259.1441	-4491.7073
F-test	1.95	0.18	0.35	0.53
R^2_m	0.115	0.072	0.216	0.092
R^2_c	0.628	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 23: OR-GRS with *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3818 (0.1312)***	−1.1511 (0.1388)***	−2.0627 (0.1183)***	−1.2258 (0.1285)***
Gender	0.4805 (0.0438)***	−0.0642 (0.0463)	−0.0064 (0.0393)	0.1084 (0.0430)*
Education	0.0901 (0.0085)***	0.0914 (0.0089)***	0.1578 (0.0076)***	0.0948 (0.0083)***
OR-GRS	−0.00001 (0.0271)	−0.0027 (0.0287)	−0.0010 (0.0243)	0.0075 (0.0266)
Rate of Change				
Time	−0.0039 (0.0165)	−0.0162 (0.0161)	0.0179 (0.0089)*	−0.0335 (0.0122)**
Gender	0.0031 (0.0055)	−0.0054 (0.0054)	0.0037 (0.0029)	0.0048 (0.0041)
Education	−0.0011 (0.0011)	0.0014 (0.0010)	−0.0001 (0.0006)	−0.0002 (0.0008)
OR-GRS	−0.0086 (0.0034)*	0.0016 (0.0033)	−0.0018 (0.0018)	−0.0036 (0.0025)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4764	0.5857	0.5359	0.5820
Variance: Time	0.0012	0.0013	0.0004	0.0007
Variance: Residual	0.3387	0.3097	0.0844	0.1732
Log Likelihood	-5403.6228	-5354.6026	-3258.9115	-4491.2292
F-test	4.20*	0.13	0.58	1.01
R^2_m	0.116	0.072	0.216	0.092
R^2_c	0.628	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 24: EV-GRS with *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3751 (0.1346)***	−1.1487 (0.1424)***	−2.0676 (0.1213)***	−1.2333 (0.1318)***
Gender	0.4807 (0.0438)***	−0.0642 (0.0463)	−0.0065 (0.0393)	0.1082 (0.0430)*
Education	0.0901 (0.0085)***	0.0914 (0.0089)***	0.1578 (0.0076)***	0.0949 (0.0083)***
EV-GRS	−0.0075 (0.0539)	−0.0068 (0.0570)	0.0037 (0.0483)	0.0200 (0.0528)
Rate of Change				
Time	−0.0007 (0.0170)	−0.0175 (0.0165)	0.0189 (0.0091)*	−0.0329 (0.0126)**
Gender	0.0031 (0.0055)	−0.0054 (0.0054)	0.0037 (0.0029)	0.0048 (0.0041)
Education	−0.0011 (0.0011)	0.0014 (0.0010)	−0.0001 (0.0006)	−0.0002 (0.0008)
EV-GRS	−0.0171 (0.0068)*	0.0040 (0.0066)	−0.0039 (0.0036)	−0.0062 (0.0050)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4764	0.5856	0.5359	0.5819
Variance: Time	0.0012	0.0013	0.0004	0.0007
Variance: Residual	0.3387	0.3097	0.0844	0.1733
Log Likelihood	-5403.3829	-5354.5325	-3258.8489	-4491.4865
F-test	4.44*	0.20	0.64	0.75
R^2_m	0.116	0.072	0.216	0.092
R^2_c	0.628	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 25: SC-GRS without *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.2759 (0.1548)***	-1.1455 (0.1635)***	-2.0759 (0.1390)***	-1.3005 (0.1514)***
Gender	0.4823 (0.0438)***	-0.0641 (0.0463)	-0.0067 (0.0394)	0.1069 (0.0430)*
Education	0.0899 (0.0085)***	0.0914 (0.0089)***	0.1578 (0.0076)***	0.0950 (0.0083)***
SC-GRS	-0.0101 (0.0087)	-0.0009 (0.0092)	0.0011 (0.0077)	0.0082 (0.0085)
Rate of Change				
Time	-0.0116 (0.0195)	-0.0182 (0.0190)	0.0192 (0.0104)	-0.0428 (0.0144)**
Gender	0.0028 (0.0055)	-0.0054 (0.0054)	0.0037 (0.0029)	0.0045 (0.0041)
Education	-0.0011 (0.0011)	0.0014 (0.0010)	-0.0001 (0.0006)	-0.0002 (0.0008)
SC-GRS	-0.0004 (0.0011)	0.0004 (0.0011)	-0.0004 (0.0006)	0.0004 (0.0008)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4758	0.5858	0.5359	0.5814
Variance: Time	0.0012	0.0013	0.0004	0.0008
Variance: Residual	0.3388	0.3096	0.0844	0.1733
Log Likelihood	-5406.4959	-5354.6540	-3259.2813	-4491.3769
F-test	1.33	0.08	0.21	0.86
R^2_m	0.115	0.072	0.216	0.092
R^2_c	0.628	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 26: OR-GRS without *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.2465 (0.1542)***	-1.1698 (0.1630)***	-2.0526 (0.1385)***	-1.2770 (0.1509)***
Gender	0.4834 (0.0438)***	-0.0646 (0.0463)	-0.0062 (0.0394)	0.1070 (0.0430)*
Education	0.0900 (0.0085)***	0.0914 (0.0089)***	0.1577 (0.0076)***	0.0949 (0.0083)***
OR-GRS	-0.1116 (0.0740)	0.0123 (0.0781)	-0.0096 (0.0661)	0.0513 (0.0723)
Rate of Change				
Time	-0.0074 (0.0195)	-0.0172 (0.0190)	0.0196 (0.0104)	-0.0451 (0.0144)**
Gender	0.0030 (0.0055)	-0.0054 (0.0054)	0.0037 (0.0029)	0.0044 (0.0041)
Education	-0.0011 (0.0011)	0.0014 (0.0010)	-0.0001 (0.0006)	-0.0002 (0.0008)
OR-GRS	-0.0072 (0.0093)	0.0027 (0.0091)	-0.0035 (0.0049)	0.0054 (0.0069)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4754	0.5858	0.5359	0.5816
Variance: Time	0.0012	0.0013	0.0004	0.0007
Variance: Residual	0.3389	0.3096	0.0844	0.1733
Log Likelihood	-5405.1357	-5354.6316	-3259.1612	-4491.3982
F-test	2.69	0.10	0.33	0.84
R^2_m	0.116	0.072	0.216	0.092
R^2_c	0.627	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 27: EV-GRS without *APOE*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.2639 (0.1542)***	-1.1630 (0.1630)***	-2.0674 (0.1385)***	-1.2921 (0.1509)***
Gender	0.4828 (0.0438)***	-0.0644 (0.0463)	-0.0065 (0.0394)	0.1068 (0.0430)*
Education	0.0900 (0.0085)***	0.0914 (0.0089)***	0.1578 (0.0076)***	0.0950 (0.0083)***
EV-GRS	-0.1485 (0.1130)	0.0102 (0.1194)	0.0040 (0.1009)	0.0972 (0.1105)
Rate of Change				
Time	-0.0081 (0.0195)	-0.0171 (0.0190)	0.0196 (0.0104)	-0.0442 (0.0144)**
Gender	0.0029 (0.0055)	-0.0054 (0.0054)	0.0037 (0.0029)	0.0045 (0.0041)
Education	-0.0011 (0.0011)	0.0014 (0.0010)	-0.0001 (0.0006)	-0.0002 (0.0008)
EV-GRS	-0.0102 (0.0143)	0.0041 (0.0139)	-0.0054 (0.0075)	0.0073 (0.0105)
Individuals	1620	1620	1615	1619
Variance: Intercept	0.4756	0.5858	0.5359	0.5815
Variance: Time	0.0012	0.0013	0.0004	0.0007
Variance: Residual	0.3389	0.3096	0.0844	0.1733
Log Likelihood	-5405.7147	-5354.6601	-3259.2109	-4491.3083
F-test	2.11	0.07	0.28	0.93
R^2_m	0.116	0.072	0.216	0.092
R^2_c	0.628	0.671	0.89	0.796

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 28: *BDNF*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3631 (0.1266)***	−1.1842 (0.1325)***	−2.0707 (0.1161)***	−1.2047 (0.1235)***
Gender	0.4702 (0.0436)***	−0.0546 (0.0456)	−0.0022 (0.0398)	0.1019 (0.0425)*
Education	0.0886 (0.0084)***	0.0943 (0.0088)***	0.1569 (0.0077)***	0.0938 (0.0082)***
APOE e2	−0.0256 (0.0668)	−0.0015 (0.0698)	0.0689 (0.0607)	−0.0600 (0.0649)
APOE e4	0.0404 (0.0508)	0.0348 (0.0531)	0.0232 (0.0464)	−0.0187 (0.0496)
BDNF	0.0019 (0.0460)	−0.0951 (0.0481)*	−0.0213 (0.0418)	0.0451 (0.0448)
Rate of Change				
Time	−0.0117 (0.0160)	−0.0132 (0.0155)	0.0171 (0.0093)	−0.0427 (0.0118)***
Gender	0.0032 (0.0055)	−0.0042 (0.0053)	0.0019 (0.0031)	0.0052 (0.0040)
Education	−0.0008 (0.0011)	0.0011 (0.0010)	0.0000 (0.0006)	0.0001 (0.0008)
APOE e2	−0.0015 (0.0083)	0.0156 (0.0081)	−0.0033 (0.0047)	0.0058 (0.0061)
APOE e4	−0.0197 (0.0064)**	0.0076 (0.0062)	−0.0016 (0.0037)	−0.0059 (0.0047)
BDNF	−0.0082 (0.0058)	−0.0028 (0.0056)	−0.0048 (0.0033)	0.0006 (0.0042)
Individuals	1647	1647	1642	1646
Variance: Intercept	0.4789	0.5723	0.5538	0.5802
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3392	0.3108	0.0903	0.1711
Log Likelihood	-5495.2052	-5422.6478	-3473.1845	-4545.2925
F-test	1.31	3.25*	1.75	0.64
R_m^2	0.113	0.077	0.214	0.093
R_c^2	0.626	0.668	0.884	0.797

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 29: *CETP*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3743 (0.1270)***	-1.1364 (0.1335)***	-2.0560 (0.1158)***	-1.2032 (0.1240)***
Gender	0.4757 (0.0432)***	-0.0548 (0.0454)	0.0055 (0.0392)	0.1087 (0.0422)*
Education	0.0893 (0.0084)***	0.0914 (0.0088)***	0.1557 (0.0076)***	0.0946 (0.0082)***
APOE e2	-0.0221 (0.0658)	0.0089 (0.0691)	0.0600 (0.0594)	-0.0420 (0.0641)
APOE e4	0.0347 (0.0503)	0.0166 (0.0528)	0.0225 (0.0457)	-0.0110 (0.0492)
CETP	0.0052 (0.0428)	-0.0527 (0.0450)	-0.0073 (0.0389)	-0.0029 (0.0419)
Rate of Change				
Time	-0.0124 (0.0159)	-0.0225 (0.0155)	0.0186 (0.0092)*	-0.0375 (0.0118)**
Gender	0.0035 (0.0054)	-0.0046 (0.0052)	0.0020 (0.0031)	0.0045 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0031 (0.0082)	0.0148 (0.0079)	-0.0019 (0.0046)	0.0050 (0.0060)
APOE e4	-0.0194 (0.0063)**	0.0092 (0.0061)	-0.0017 (0.0036)	-0.0056 (0.0047)
CETP	-0.0002 (0.0053)	0.0096 (0.0052)	-0.0051 (0.0030)	-0.0018 (0.0039)
Individuals	1688	1688	1683	1687
Variance: Intercept	0.4850	0.5842	0.5523	0.5874
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3377	0.3112	0.0890	0.1707
Log Likelihood	-5631.4349	-5570.7825	-3542.5441	-4661.8838
F-test	0.01	1.77	1.77	0.13
R^2_m	0.114	0.072	0.21	0.091
R^2_c	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 30: *COMT*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.4256 (0.1304)***	-1.1862 (0.1371)***	-2.0834 (0.1189)***	-1.1931 (0.1273)***
Gender	0.4748 (0.0432)***	-0.0591 (0.0454)	0.0070 (0.0393)	0.1073 (0.0422)*
Education	0.0891 (0.0084)***	0.0914 (0.0088)***	0.1556 (0.0076)***	0.0941 (0.0082)***
APOE e2	-0.0236 (0.0657)	0.0099 (0.0691)	0.0583 (0.0595)	-0.0414 (0.0640)
APOE e4	0.0345 (0.0503)	0.0221 (0.0529)	0.0188 (0.0458)	-0.0093 (0.0493)
COMT	0.0778 (0.0498)	0.0320 (0.0524)	0.0329 (0.0453)	-0.0054 (0.0488)
Rate of Change				
Time	-0.0005 (0.0164)	-0.0150 (0.0159)	0.0129 (0.0094)	-0.0320 (0.0121)**
Gender	0.0035 (0.0054)	-0.0044 (0.0052)	0.0019 (0.0031)	0.0048 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0029 (0.0082)	0.0149 (0.0079)	-0.0019 (0.0046)	0.0050 (0.0060)
APOE e4	-0.0191 (0.0063)**	0.0091 (0.0061)	-0.0019 (0.0036)	-0.0058 (0.0047)
COMT	-0.0153 (0.0062)*	-0.0032 (0.0061)	0.0044 (0.0036)	-0.0087 (0.0046)
Individuals	1685	1685	1680	1684
Variance: Intercept	0.4852	0.5844	0.5530	0.5861
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3368	0.3110	0.0891	0.1712
Log Likelihood	-5619.1436	-5562.8753	-3539.5246	-4653.1232
F-test	3.09*	0.22	1.57	2.09
R^2_m	0.114	0.072	0.21	0.091
R^2_c	0.631	0.668	0.885	0.797

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 31: *CTNNBL1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3654 (0.1257)***	-1.1679 (0.1320)***	-2.0683 (0.1146)***	-1.1903 (0.1227)***
Gender	0.4737 (0.0432)***	-0.0588 (0.0454)	0.0061 (0.0392)	0.1072 (0.0422)*
Education	0.0894 (0.0084)***	0.0918 (0.0088)***	0.1561 (0.0076)***	0.0943 (0.0082)***
APOE e2	-0.0247 (0.0658)	0.0107 (0.0691)	0.0608 (0.0596)	-0.0461 (0.0642)
APOE e4	0.0345 (0.0503)	0.0198 (0.0529)	0.0237 (0.0458)	-0.0146 (0.0493)
CTNNBL1	-0.0540 (0.0668)	-0.0175 (0.0701)	0.0237 (0.0607)	-0.0770 (0.0653)
Rate of Change				
Time	-0.0154 (0.0158)	-0.0196 (0.0154)	0.0162 (0.0091)	-0.0396 (0.0117)***
Gender	0.0035 (0.0054)	-0.0046 (0.0052)	0.0019 (0.0031)	0.0046 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0017 (0.0082)	0.0157 (0.0080)*	-0.0021 (0.0046)	0.0054 (0.0060)
APOE e4	-0.0184 (0.0063)**	0.0099 (0.0061)	-0.0017 (0.0036)	-0.0053 (0.0047)
CTNNBL1	0.0176 (0.0083)*	0.0103 (0.0081)	-0.0021 (0.0047)	0.0061 (0.0061)
Individuals	1687	1687	1682	1686
Variance: Intercept	0.4847	0.5826	0.5525	0.5872
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3379	0.3112	0.0891	0.1708
Log Likelihood	-5627.8502	-5565.1423	-3542.1389	-4659.1763
F-test	2.27	0.89	0.13	0.90
R^2_m	0.114	0.073	0.211	0.092
R^2_c	0.63	0.667	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 32: *FRMD4A* (1)

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3767 (0.1262)***	−1.1723 (0.1333)***	−2.0843 (0.1155)***	−1.2074 (0.1235)***
Gender	0.4761 (0.0433)***	−0.0550 (0.0457)	0.0112 (0.0394)	0.1130 (0.0424)**
Education	0.0903 (0.0084)***	0.0907 (0.0088)***	0.1558 (0.0076)***	0.0948 (0.0082)***
APOE e2	−0.0320 (0.0661)	−0.0017 (0.0697)	0.0644 (0.0599)	−0.0438 (0.0644)
APOE e4	0.0378 (0.0503)	0.0143 (0.0531)	0.0280 (0.0459)	−0.0112 (0.0493)
*FRMD4A*_1	−0.0223 (0.0429)	0.0396 (0.0453)	0.0370 (0.0391)	−0.0065 (0.0420)
Rate of Change				
Time	−0.0134 (0.0159)	−0.0130 (0.0155)	0.0184 (0.0092)*	−0.0396 (0.0118)***
Gender	0.0034 (0.0054)	−0.0054 (0.0053)	0.0015 (0.0031)	0.0048 (0.0040)
Education	−0.0011 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0023 (0.0082)	0.0150 (0.0080)	−0.0021 (0.0047)	0.0052 (0.0061)
APOE e4	−0.0194 (0.0063)**	0.0093 (0.0061)	−0.0024 (0.0036)	−0.0052 (0.0047)
*FRMD4A*_1	0.0066 (0.0054)	−0.0103 (0.0052)*	−0.0048 (0.0030)	0.0011 (0.0040)
Individuals	1676	1676	1671	1675
Variance: Intercept	0.4790	0.5870	0.5534	0.5854
Variance: Time	0.0011	0.0012	0.0008	0.0008
Variance: Residual	0.3395	0.3106	0.0893	0.1708
Log Likelihood	-5595.0460	-5534.3969	-3521.7654	-4629.2447
F-test	0.75	1.96	1.33	0.04
R_m^2	0.114	0.072	0.211	0.092
R_c^2	0.628	0.669	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 33: *FRMD4A* (2)

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3894 (0.1262)***	−1.1436 (0.1323)***	−2.0971 (0.1148)***	−1.1988 (0.1228)***
Gender	0.4762 (0.0434)***	−0.0488 (0.0455)	0.0059 (0.0393)	0.1127 (0.0423)**
Education	0.0905 (0.0084)***	0.0911 (0.0088)***	0.1571 (0.0077)***	0.0951 (0.0082)***
APOE e2	−0.0181 (0.0659)	0.0130 (0.0691)	0.0593 (0.0595)	−0.0384 (0.0640)
APOE e4	0.0384 (0.0505)	0.0165 (0.0529)	0.0218 (0.0458)	−0.0043 (0.0492)
*FRMD4A*_2	−0.0014 (0.0637)	−0.1417 (0.0668)*	0.1348 (0.0578)*	−0.1019 (0.0620)
Rate of Change				
Time	−0.0093 (0.0158)	−0.0228 (0.0154)	0.0177 (0.0091)	−0.0384 (0.0117)**
Gender	0.0035 (0.0054)	−0.0055 (0.0052)	0.0023 (0.0031)	0.0045 (0.0040)
Education	−0.0012 (0.0011)	0.0015 (0.0010)	−0.0001 (0.0006)	−0.0002 (0.0008)
APOE e2	−0.0030 (0.0082)	0.0143 (0.0079)	−0.0018 (0.0047)	0.0046 (0.0060)
APOE e4	−0.0199 (0.0063)**	0.0096 (0.0061)	−0.0019 (0.0036)	−0.0064 (0.0047)
*FRMD4A*_2	−0.0032 (0.0080)	0.0215 (0.0077)**	−0.0097 (0.0045)*	0.0014 (0.0059)
Individuals	1681	1681	1676	1680
Variance: Intercept	0.4861	0.5809	0.5504	0.5838
Variance: Time	0.0012	0.0010	0.0008	0.0007
Variance: Residual	0.3378	0.3128	0.0892	0.1710
Log Likelihood	-5610.6513	-5548.6451	-3530.1780	-4638.1688
F-test	0.12	4.29*	3.63*	1.39
R^2_m	0.114	0.073	0.213	0.093
R^2_c	0.63	0.666	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 34: Intergenic ChrX

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3726 (0.1253)***	−1.1694 (0.1317)***	−2.0589 (0.1147)***	−1.1957 (0.1229)***
Gender	0.4785 (0.0434)***	−0.0430 (0.0456)	0.0069 (0.0396)	0.1068 (0.0426)*
Education	0.0892 (0.0084)***	0.0922 (0.0088)***	0.1560 (0.0077)***	0.0940 (0.0082)***
APOE e2	−0.0260 (0.0657)	0.0135 (0.0690)	0.0576 (0.0596)	−0.0440 (0.0643)
APOE e4	0.0311 (0.0502)	0.0175 (0.0528)	0.0197 (0.0459)	−0.0090 (0.0494)
inter_x	0.0310 (0.0745)	−0.1325 (0.0785)	−0.0547 (0.0679)	0.0160 (0.0733)
Rate of Change				
Time	−0.0128 (0.0157)	−0.0169 (0.0153)	0.0155 (0.0091)	−0.0385 (0.0117)**
Gender	0.0038 (0.0054)	−0.0052 (0.0053)	0.0018 (0.0031)	0.0040 (0.0040)
Education	−0.0009 (0.0010)	0.0012 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0030 (0.0081)	0.0145 (0.0079)	−0.0016 (0.0047)	0.0051 (0.0060)
APOE e4	−0.0192 (0.0063)**	0.0097 (0.0061)	−0.0018 (0.0036)	−0.0059 (0.0047)
inter_x	−0.0232 (0.0092)*	0.0018 (0.0090)	0.0040 (0.0053)	0.0024 (0.0068)
Individuals	1676	1676	1671	1675
Variance: Intercept	0.4768	0.5774	0.5517	0.5884
Variance: Time	0.0009	0.0011	0.0008	0.0008
Variance: Residual	0.3402	0.3113	0.0892	0.1709
Log Likelihood	-5586.0617	-5525.8787	-3524.9632	-4633.4901
F-test	3.56*	1.64	0.44	0.13
R_m^2	0.115	0.073	0.21	0.091
R_c^2	0.627	0.667	0.884	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 35: *LGALS3*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3815 (0.1289)***	−1.1281 (0.1360)***	−2.0538 (0.1173)***	−1.2265 (0.1264)***
Gender	0.4734 (0.0435)***	−0.0590 (0.0459)	0.0053 (0.0394)	0.1085 (0.0427)*
Education	0.0871 (0.0084)***	0.0886 (0.0089)***	0.1544 (0.0077)***	0.0931 (0.0083)***
APOE e2	−0.0234 (0.0659)	0.0147 (0.0695)	0.0554 (0.0594)	−0.0440 (0.0645)
APOE e4	0.0435 (0.0507)	0.0265 (0.0535)	0.0135 (0.0460)	−0.0166 (0.0498)
LGALS3	0.0546 (0.0449)	0.0071 (0.0474)	0.0309 (0.0407)	0.0694 (0.0441)
Rate of Change				
Time	−0.0138 (0.0162)	−0.0233 (0.0158)	0.0187 (0.0094)*	−0.0362 (0.0120)**
Gender	0.0036 (0.0054)	−0.0042 (0.0053)	0.0021 (0.0031)	0.0051 (0.0040)
Education	−0.0008 (0.0011)	0.0014 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0044 (0.0082)	0.0140 (0.0080)	−0.0023 (0.0047)	0.0044 (0.0060)
APOE e4	−0.0208 (0.0064)**	0.0078 (0.0062)	−0.0016 (0.0036)	−0.0063 (0.0047)
LGALS3	−0.0003 (0.0056)	0.0067 (0.0055)	−0.0039 (0.0032)	−0.0043 (0.0042)
Individuals	1660	1660	1655	1659
Variance: Intercept	0.4820	0.5878	0.5481	0.5903
Variance: Time	0.0012	0.0012	0.0008	0.0008
Variance: Residual	0.3384	0.3115	0.0882	0.1717
Log Likelihood	-5537.1793	-5482.1017	-3469.2748	-4592.2776
F-test	0.93	1.08	0.79	1.38
R^2_m	0.112	0.069	0.208	0.09
R^2_c	0.628	0.667	0.884	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 36: *MMP12*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3700 (0.1264)***	-1.1614 (0.1326)***	-2.0653 (0.1152)***	-1.2239 (0.1231)***
Gender	0.4739 (0.0433)***	-0.0543 (0.0454)	0.0085 (0.0393)	0.1087 (0.0422)*
Education	0.0891 (0.0084)***	0.0911 (0.0088)***	0.1560 (0.0076)***	0.0948 (0.0082)***
APOE e2	-0.0210 (0.0660)	-0.0005 (0.0692)	0.0559 (0.0597)	-0.0477 (0.0642)
APOE e4	0.0365 (0.0503)	0.0128 (0.0528)	0.0196 (0.0458)	-0.0135 (0.0491)
MMP12	0.0020 (0.0479)	0.0116 (0.0501)	0.0067 (0.0434)	0.0632 (0.0466)
Rate of Change				
Time	-0.0096 (0.0159)	-0.0146 (0.0155)	0.0167 (0.0092)	-0.0378 (0.0117)**
Gender	0.0033 (0.0054)	-0.0047 (0.0052)	0.0020 (0.0031)	0.0046 (0.0040)
Education	-0.0011 (0.0010)	0.0013 (0.0010)	-0.0001 (0.0006)	-0.0001 (0.0008)
APOE e2	-0.0044 (0.0082)	0.0143 (0.0080)	-0.0021 (0.0047)	0.0051 (0.0061)
APOE e4	-0.0194 (0.0063)**	0.0096 (0.0061)	-0.0017 (0.0036)	-0.0057 (0.0047)
MMP12	-0.0061 (0.0059)	-0.0095 (0.0058)	-0.0007 (0.0034)	-0.0035 (0.0044)
Individuals	1684	1684	1679	1683
Variance: Intercept	0.4865	0.5815	0.5532	0.5850
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3372	0.3113	0.0888	0.1699
Log Likelihood	-5616.3168	-5554.7791	-3532.8400	-4644.0230
F-test	0.67	1.55	0.03	0.98
R_m^2	0.113	0.072	0.21	0.092
R_c^2	0.63	0.667	0.885	0.799

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 37: *MTHFD1L*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3803 (0.1255)***	−1.1555 (0.1321)***	−2.0649 (0.1146)***	−1.2129 (0.1227)***
Gender	0.4761 (0.0432)***	−0.0578 (0.0454)	0.0070 (0.0392)	0.1073 (0.0422)*
Education	0.0895 (0.0084)***	0.0912 (0.0088)***	0.1558 (0.0076)***	0.0948 (0.0082)***
APOE e2	−0.0209 (0.0657)	0.0121 (0.0691)	0.0602 (0.0595)	−0.0410 (0.0641)
APOE e4	0.0361 (0.0502)	0.0174 (0.0528)	0.0229 (0.0457)	−0.0100 (0.0492)
MTHFD1L	0.0249 (0.0583)	−0.0431 (0.0613)	0.0136 (0.0529)	0.0332 (0.0570)
Rate of Change				
Time	−0.0115 (0.0157)	−0.0172 (0.0154)	0.0171 (0.0091)	−0.0371 (0.0116)**
Gender	0.0031 (0.0054)	−0.0045 (0.0052)	0.0020 (0.0031)	0.0042 (0.0040)
Education	−0.0010 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0002 (0.0008)
APOE e2	−0.0029 (0.0081)	0.0147 (0.0079)	−0.0019 (0.0046)	0.0052 (0.0060)
APOE e4	−0.0192 (0.0063)**	0.0094 (0.0061)	−0.0018 (0.0036)	−0.0054 (0.0046)
MTHFD1L	−0.0006 (0.0073)	−0.0016 (0.0070)	−0.0046 (0.0041)	−0.0053 (0.0054)
Individuals	1686	1686	1681	1685
Variance: Intercept	0.4828	0.5840	0.5524	0.5869
Variance: Time	0.0011	0.0011	0.0008	0.0007
Variance: Residual	0.3379	0.3116	0.0892	0.1710
Log Likelihood	-5621.4661	-5565.9494	-3541.6760	-4653.5998
F-test	0.10	0.44	0.63	0.53
R_m^2	0.114	0.072	0.21	0.092
R_c^2	0.629	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 38: *PAICS*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3733 (0.1253)***	-1.1482 (0.1319)***	-2.0499 (0.1142)***	-1.1990 (0.1224)***
Gender	0.4777 (0.0432)***	-0.0567 (0.0455)	0.0052 (0.0392)	0.1113 (0.0423)**
Education	0.0891 (0.0084)***	0.0910 (0.0088)***	0.1556 (0.0076)***	0.0949 (0.0082)***
APOE e2	-0.0203 (0.0658)	0.0065 (0.0692)	0.0569 (0.0595)	-0.0460 (0.0642)
APOE e4	0.0378 (0.0503)	0.0167 (0.0529)	0.0255 (0.0457)	-0.0131 (0.0493)
PAICS	0.0289 (0.0655)	-0.0777 (0.0690)	-0.0698 (0.0596)	-0.0840 (0.0642)
Rate of Change				
Time	-0.0099 (0.0157)	-0.0180 (0.0153)	0.0158 (0.0091)	-0.0375 (0.0116)**
Gender	0.0030 (0.0054)	-0.0049 (0.0052)	0.0020 (0.0031)	0.0045 (0.0040)
Education	-0.0011 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0002 (0.0008)
APOE e2	-0.0034 (0.0082)	0.0152 (0.0080)	-0.0018 (0.0047)	0.0049 (0.0060)
APOE e4	-0.0194 (0.0063)**	0.0095 (0.0061)	-0.0017 (0.0036)	-0.0059 (0.0047)
PAICS	-0.0087 (0.0083)	0.0060 (0.0081)	0.0036 (0.0047)	0.0004 (0.0062)
Individuals	1685	1685	1680	1684
Variance: Intercept	0.4829	0.5861	0.5510	0.5873
Variance: Time	0.0011	0.0012	0.0008	0.0008
Variance: Residual	0.3385	0.3102	0.0886	0.1709
Log Likelihood	-5619.0860	-5559.5847	-3531.2662	-4652.2568
F-test	0.54	0.66	0.75	0.93
R_m^2	0.113	0.072	0.211	0.092
R_c^2	0.628	0.669	0.885	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 39: *PDE7A*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3419 (0.1300)***	−1.0930 (0.1358)***	−2.0376 (0.1179)***	−1.1544 (0.1264)***
Gender	0.4720 (0.0435)***	−0.0553 (0.0455)	−0.0009 (0.0393)	0.0998 (0.0424)*
Education	0.0893 (0.0084)***	0.0913 (0.0088)***	0.1562 (0.0076)***	0.0947 (0.0082)***
APOE e2	−0.0143 (0.0663)	0.0131 (0.0692)	0.0608 (0.0596)	−0.0325 (0.0643)
APOE e4	0.0358 (0.0506)	0.0102 (0.0528)	0.0206 (0.0458)	−0.0132 (0.0493)
PDE7A	−0.0393 (0.0460)	−0.1028 (0.0481)*	−0.0320 (0.0416)	−0.0771 (0.0449)
Rate of Change				
Time	−0.0147 (0.0163)	−0.0236 (0.0159)	0.0160 (0.0094)	−0.0421 (0.0120)***
Gender	0.0030 (0.0054)	−0.0041 (0.0053)	0.0019 (0.0031)	0.0044 (0.0040)
Education	−0.0011 (0.0011)	0.0012 (0.0010)	−0.0000 (0.0006)	−0.0003 (0.0008)
APOE e2	−0.0030 (0.0082)	0.0139 (0.0080)	−0.0025 (0.0047)	0.0039 (0.0060)
APOE e4	−0.0206 (0.0063)**	0.0105 (0.0062)	−0.0023 (0.0036)	−0.0058 (0.0047)
PDE7A	0.0065 (0.0058)	0.0096 (0.0056)	−0.0001 (0.0033)	0.0089 (0.0042)*
Individuals	1664	1664	1659	1663
Variance: Intercept	0.4846	0.5766	0.5470	0.5816
Variance: Time	0.0011	0.0012	0.0008	0.0007
Variance: Residual	0.3396	0.3098	0.0893	0.1712
Log Likelihood	-5551.9141	-5480.8181	-3490.5474	-4584.1715
F-test	0.69	2.60	0.35	2.76
R_m^2	0.113	0.073	0.213	0.092
R_c^2	0.627	0.668	0.884	0.796

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 40: *SNTG1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.4248 (0.1281)***	−1.1881 (0.1348)***	−2.0312 (0.1166)***	−1.2098 (0.1251)***
Gender	0.4757 (0.0432)***	−0.0531 (0.0455)	0.0112 (0.0391)	0.1103 (0.0422)**
Education	0.0888 (0.0084)***	0.0912 (0.0088)***	0.1560 (0.0076)***	0.0946 (0.0082)***
APOE e2	−0.0210 (0.0658)	0.0052 (0.0693)	0.0623 (0.0594)	−0.0417 (0.0641)
APOE e4	0.0371 (0.0502)	0.0155 (0.0528)	0.0196 (0.0455)	−0.0126 (0.0491)
SNTG1	0.0864 (0.0460)	0.0378 (0.0484)	−0.0480 (0.0417)	0.0079 (0.0450)
Rate of Change				
Time	−0.0068 (0.0161)	−0.0158 (0.0157)	0.0158 (0.0093)	−0.0375 (0.0119)**
Gender	0.0032 (0.0054)	−0.0051 (0.0052)	0.0020 (0.0031)	0.0045 (0.0040)
Education	−0.0010 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0001 (0.0008)
APOE e2	−0.0028 (0.0082)	0.0158 (0.0079)*	−0.0024 (0.0046)	0.0047 (0.0060)
APOE e4	−0.0195 (0.0063)**	0.0094 (0.0061)	−0.0018 (0.0036)	−0.0056 (0.0047)
SNTG1	−0.0084 (0.0057)	−0.0025 (0.0056)	0.0002 (0.0033)	−0.0015 (0.0042)
Individuals	1686	1686	1681	1685
Variance: Intercept	0.4832	0.5842	0.5478	0.5858
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3376	0.3117	0.0891	0.1710
Log Likelihood	-5622.8872	-5565.5717	-3534.8577	-4656.2925
F-test	1.94	0.31	0.74	0.06
R_m^2	0.115	0.072	0.212	0.092
R_c^2	0.63	0.667	0.884	0.798

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 41: *SORL1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3745 (0.1299)***	−1.1530 (0.1363)***	−2.1243 (0.1184)***	−1.2185 (0.1267)***
Gender	0.4770 (0.0435)***	−0.0509 (0.0457)	0.0067 (0.0395)	0.1129 (0.0425)**
Education	0.0873 (0.0084)***	0.0900 (0.0088)***	0.1559 (0.0077)***	0.0951 (0.0082)***
APOE e2	−0.0406 (0.0666)	−0.0087 (0.0698)	0.0613 (0.0602)	−0.0436 (0.0648)
APOE e4	0.0303 (0.0507)	0.0240 (0.0532)	0.0228 (0.0461)	−0.0165 (0.0496)
SORL1	0.0461 (0.0468)	0.0056 (0.0492)	0.0836 (0.0426)*	0.0103 (0.0458)
Rate of Change				
Time	−0.0104 (0.0163)	−0.0226 (0.0158)	0.0210 (0.0094)*	−0.0407 (0.0120)***
Gender	0.0023 (0.0054)	−0.0056 (0.0053)	0.0023 (0.0031)	0.0049 (0.0040)
Education	−0.0007 (0.0011)	0.0013 (0.0010)	−0.0001 (0.0006)	−0.0002 (0.0008)
APOE e2	−0.0018 (0.0083)	0.0149 (0.0080)	−0.0031 (0.0047)	0.0037 (0.0061)
APOE e4	−0.0190 (0.0064)**	0.0095 (0.0062)	−0.0018 (0.0036)	−0.0059 (0.0047)
SORL1	−0.0072 (0.0059)	0.0065 (0.0057)	−0.0064 (0.0033)	0.0051 (0.0043)
Individuals	1664	1664	1659	1663
Variance: Intercept	0.4856	0.5803	0.5528	0.5863
Variance: Time	0.0012	0.0010	0.0008	0.0007
Variance: Residual	0.3378	0.3138	0.0895	0.1723
Log Likelihood	-5550.1301	-5491.1402	-3503.0898	-4592.4832
F-test	0.85	0.94	2.73	0.92
R_m^2	0.113	0.071	0.21	0.092
R_c^2	0.63	0.663	0.884	0.796

F-test with Kenward-Roger approximation

R_m^2: Marginal R^2 statistics; R_c^2: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 42: *SPON1*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	−1.3728 (0.1252)***	−1.1560 (0.1316)***	−2.0536 (0.1140)***	−1.2059 (0.1223)***
Gender	0.4776 (0.0432)***	−0.0547 (0.0454)	0.0068 (0.0392)	0.1078 (0.0422)*
Education	0.0890 (0.0084)***	0.0914 (0.0088)***	0.1560 (0.0076)***	0.0946 (0.0082)***
APOE e2	−0.0246 (0.0658)	0.0121 (0.0691)	0.0611 (0.0594)	−0.0420 (0.0641)
APOE e4	0.0310 (0.0503)	0.0164 (0.0529)	0.0229 (0.0457)	−0.0102 (0.0493)
SPON1	0.0585 (0.0687)	−0.0930 (0.0722)	−0.1037 (0.0626)	0.0093 (0.0673)
Rate of Change				
Time	−0.0116 (0.0157)	−0.0180 (0.0153)	0.0155 (0.0091)	−0.0380 (0.0116)**
Gender	0.0032 (0.0054)	−0.0048 (0.0052)	0.0020 (0.0031)	0.0046 (0.0040)
Education	−0.0010 (0.0010)	0.0013 (0.0010)	−0.0000 (0.0006)	−0.0002 (0.0008)
APOE e2	−0.0028 (0.0082)	0.0147 (0.0079)	−0.0020 (0.0046)	0.0051 (0.0060)
APOE e4	−0.0190 (0.0063)**	0.0094 (0.0061)	−0.0021 (0.0036)	−0.0058 (0.0047)
SPON1	−0.0091 (0.0087)	0.0075 (0.0084)	0.0067 (0.0050)	−0.0037 (0.0064)
Individuals	1687	1687	1682	1686
Variance: Intercept	0.4846	0.5843	0.5513	0.5876
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3377	0.3114	0.0890	0.1710
Log Likelihood	-5627.9148	-5568.9914	-3541.2258	-4659.6870
F-test	0.62	0.88	1.69	0.17
R^2_m	0.114	0.072	0.211	0.091
R^2_c	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 43: *ZNF224*

	Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
Initial Status				
Intercept	-1.3761 (0.1260)***	-1.1897 (0.1323)***	-2.0947 (0.1147)***	-1.2192 (0.1230)***
Gender	0.4755 (0.0432)***	-0.0547 (0.0454)	0.0080 (0.0392)	0.1101 (0.0422)**
Education	0.0894 (0.0084)***	0.0917 (0.0088)***	0.1561 (0.0076)***	0.0946 (0.0082)***
APOE e2	-0.0229 (0.0658)	0.0074 (0.0690)	0.0552 (0.0594)	-0.0436 (0.0641)
APOE e4	0.0364 (0.0503)	0.0156 (0.0529)	0.0192 (0.0457)	-0.0140 (0.0493)
ZNF224	0.0121 (0.0464)	0.0706 (0.0487)	0.1001 (0.0420)*	0.0468 (0.0453)
Rate of Change				
Time	-0.0117 (0.0158)	-0.0197 (0.0154)	0.0163 (0.0091)	-0.0398 (0.0117)***
Gender	0.0033 (0.0054)	-0.0046 (0.0052)	0.0019 (0.0031)	0.0045 (0.0040)
Education	-0.0010 (0.0010)	0.0013 (0.0010)	-0.0000 (0.0006)	-0.0002 (0.0008)
APOE e2	-0.0029 (0.0082)	0.0146 (0.0079)	-0.0019 (0.0046)	0.0048 (0.0060)
APOE e4	-0.0193 (0.0063)**	0.0089 (0.0061)	-0.0016 (0.0036)	-0.0057 (0.0047)
ZNF224	-0.0019 (0.0058)	0.0069 (0.0056)	-0.0009 (0.0033)	0.0050 (0.0043)
Individuals	1687	1687	1682	1686
Variance: Intercept	0.4851	0.5828	0.5506	0.5871
Variance: Time	0.0012	0.0011	0.0008	0.0008
Variance: Residual	0.3378	0.3112	0.0891	0.1709
Log Likelihood	-5629.1238	-5562.5897	-3539.3767	-4658.0289
F-test	0.06	3.43*	3.04*	1.81
R^2_m	0.114	0.075	0.213	0.093
R^2_c	0.63	0.668	0.885	0.798

F-test with Kenward-Roger approximation

R^2_m: Marginal R^2 statistics; R^2_c: Conditional R^2 statistic

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 44: Top LOAD risk SNPs and GRS: Parameter estimates and model fit statistics for SNP/GRS main effects according to last diagnosis

		Episodic Memory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
		Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
APOE ϵ2	Intercept	−0.032 (0.071)	0.037 (0.074)	0.039 (0.064)	−0.028 (0.069)
	Slope - CN	−0.002 (0.009)	0.016 (0.009)	0.000 (0.005)	0.002 (0.006)
	Slope - CI	0.007 (0.024)	0.035 (0.025)	−0.017 (0.015)	0.021 (0.020)
APOE ϵ4	Intercept	0.044 (0.054)	0.011 (0.057)	0.028 (0.049)	−0.010 (0.053)
	Slope - CN	−0.015 (0.007)*	0.013 (0.007)*	0.000 (0.004)	−0.007 (0.005)
	Slope - CI	−0.050 (0.020)*	0.004 (0.021)	−0.017 (0.013)	−0.002 (0.016)
	F-test	1.93	1.96	0.50	0.67
ABCA7-rs3764650	Intercept	−0.173 (0.059)**	0.021 (0.063)	−0.040 (0.054)	−0.053 (0.058)
	Slope - CN	0.004 (0.007)	0.007 (0.007)	−0.000 (0.004)	0.008 (0.005)
	Slope - CI	−0.026 (0.020)	−0.041 (0.021)*	−0.004 (0.013)	−0.029 (0.016)
	F-test	4.32**	1.81	0.27	1.99
BIN1-rs744373	Intercept	−0.034 (0.046)	0.079 (0.048)	−0.015 (0.041)	0.043 (0.044)
	Slope - CN	−0.008 (0.006)	−0.002 (0.006)	−0.003 (0.003)	−0.004 (0.004)
	Slope - CI	0.016 (0.017)	0.003 (0.017)	0.014 (0.011)	0.024 (0.014)

	F-test	1.73	1.01	0.97	1.62
CD2AP-rs9296559	Intercept	0.046 (0.046)	0.040 (0.048)	−0.010 (0.042)	0.011 (0.045)
	Slope - CN	−0.007 (0.006)	−0.001 (0.006)	−0.003 (0.003)	−0.000 (0.004)
	Slope - CI	−0.003 (0.016)	0.013 (0.017)	0.009 (0.010)	−0.002 (0.013)
	F-test	0.59	0.53	0.62	0.03
CD33-rs34813869	Intercept	0.000 (0.072)	−0.056 (0.076)	−0.041 (0.065)	0.086 (0.070)
	Slope - CN	−0.000 (0.009)	−0.004 (0.009)	0.002 (0.005)	−0.006 (0.007)
	Slope - CI	−0.034 (0.026)	−0.033 (0.026)	−0.008 (0.016)	0.002 (0.021)
	F-test	0.55	1.09	0.25	0.57
CLU-rs11136000	Intercept	0.016 (0.062)	0.060 (0.065)	0.013 (0.055)	0.055 (0.060)
	Slope - CN	0.005 (0.008)	0.002 (0.008)	0.004 (0.004)	0.005 (0.006)
	Slope - CI	−0.012 (0.021)	−0.008 (0.021)	−0.012 (0.013)	−0.025 (0.017)
	F-test	0.37	0.54	0.74	1.52
CR1-rs3818361	Intercept	−0.029 (0.049)	0.018 (0.052)	−0.054 (0.044)	−0.032 (0.048)
	Slope - CN	−0.010 (0.006)	−0.003 (0.006)	0.001 (0.003)	0.000 (0.005)
	Slope - CI	−0.011 (0.016)	−0.023 (0.017)	0.004 (0.010)	0.003 (0.013)
	F-test	2.07	0.72	0.50	0.17
EPHA1-rs11767557	Intercept	0.071 (0.128)	0.113 (0.135)	−0.078 (0.116)	−0.267 (0.125)*
	Slope - CN	−0.019 (0.016)	−0.026 (0.015)	0.004 (0.009)	0.005 (0.012)

	Slope - CI	0.061 (0.052)	0.064 (0.053)	−0.021 (0.032)	0.086 (0.043)*
	F-test	1.07	1.55	0.35	2.60
MS4A4A-rs4938933	Intercept	−0.080 (0.061)	−0.043 (0.064)	0.093 (0.055)	0.058 (0.059)
	Slope - CN	0.008 (0.008)	0.008 (0.007)	0.003 (0.004)	−0.006 (0.006)
	Slope - CI	−0.000 (0.019)	0.014 (0.020)	−0.003 (0.012)	−0.013 (0.016)
	F-test	0.68	0.48	1.63	0.68
MS4A4E-rs670139	Intercept	−0.045 (0.048)	−0.044 (0.050)	0.133 (0.043)**	0.055 (0.046)
	Slope - CN	0.010 (0.006)	0.004 (0.006)	−0.001 (0.003)	−0.002 (0.004)
	Slope - CI	0.006 (0.016)	0.013 (0.017)	0.005 (0.010)	0.014 (0.013)
	F-test kr	0.44	0.65	4.06**	2.35
MS4A6A-rs610932	Intercept	−0.091 (0.059)	−0.029 (0.062)	0.042 (0.053)	0.035 (0.057)
	Slope - CN	0.007 (0.007)	0.007 (0.007)	0.003 (0.004)	−0.003 (0.005)
	Slope - CI	0.004 (0.019)	0.019 (0.019)	0.017 (0.012)	−0.009 (0.015)
	F-test	0.83	0.59	1.28	0.26
PICALM-rs3851179	Intercept	0.029 (0.065)	0.010 (0.069)	0.049 (0.059)	0.041 (0.064)
	Slope - CN	−0.005 (0.008)	0.002 (0.008)	0.002 (0.005)	0.006 (0.006)
	Slope - CI	−0.021 (0.023)	0.006 (0.023)	−0.016 (0.014)	−0.007 (0.018)
	F-test	0.37	0.06	0.74	0.72
SC-GRS	Intercept	−0.008 (0.009)	0.003 (0.010)	0.008 (0.008)	0.009 (0.009)

	Slope - CN	−0.001 (0.001)	−0.000 (0.001)	−0.001 (0.001)	−0.001 (0.001)
	Slope - CI	−0.004 (0.003)	0.001 (0.004)	0.002 (0.002)	0.001 (0.003)
	F-test	2.10	0.09	1.28	0.38
OR-GRS	Intercept	0.011 (0.029)	0.006 (0.031)	0.014 (0.026)	0.009 (0.029)
	Slope - CN	−0.008 (0.004)*	0.002 (0.004)	−0.002 (0.002)	−0.004 (0.003)
	Slope - CI	−0.025 (0.010)*	−0.008 (0.011)	−0.002 (0.006)	−0.010 (0.008)
	F-test	3.57*	0.35	0.32	1.13
EV-GRS	Intercept	0.015 (0.058)	0.013 (0.062)	0.036 (0.052)	0.025 (0.057)
	Slope - CN	−0.016 (0.007)*	0.004 (0.007)	−0.004 (0.004)	−0.008 (0.005)
	Slope - CI	−0.050 (0.021)*	−0.010 (0.022)	−0.003 (0.012)	−0.016 (0.017)
	F-test	3.79*	0.27	0.45	0.96

*$p < .05$; **$p < .01$.; adjusted for Sex, *APOE* and Education

Table 45: Additional SNPs: Parameter estimates and model fit for SNP main effects according last diagnosis

		Episodic Memeory	Digits Backwards	Spot-the-Word	Symbol Digits Modalities Test
		Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
BDNF-rs6265	Intercept	−0.016 (0.049)	−0.103 (0.052)*	−0.008 (0.045)	0.042 (0.048)
	Slope - CN	−0.005 (0.006)	−0.003 (0.006)	−0.004 (0.003)	−0.002 (0.005)
	Slope - CI	−0.030 (0.017)	0.027 (0.018)	−0.022 (0.011)*	0.013 (0.014)
	F-test	1.58	2.60	2.11	0.60
CETP-rs5882	Intercept	−0.020 (0.046)	−0.068 (0.048)	−0.009 (0.041)	−0.001 (0.045)
	Slope - CN	0.002 (0.006)	0.010 (0.006)	−0.004 (0.003)	0.001 (0.004)
	Slope - CI	−0.029 (0.016)	0.000 (0.017)	−0.024 (0.010)*	−0.013 (0.013)
	F-test	1.22	1.19	2.49	0.33
COMT-rs4680	Intercept	0.104 (0.053)	0.033 (0.056)	0.022 (0.048)	−0.016 (0.052)
	Slope - CN	−0.015 (0.007)*	−0.004 (0.007)	0.004 (0.004)	−0.008 (0.005)
	Slope - CI	−0.009 (0.017)	−0.008 (0.018)	0.001 (0.011)	−0.005 (0.014)
	F-test	1.97	0.21	0.61	1.20
CTNNBL1-rs6125962	Intercept	−0.059 (0.070)	−0.021 (0.074)	0.001 (0.064)	−0.089 (0.068)
	Slope - CN	0.015 (0.009)	0.006 (0.009)	−0.005 (0.005)	0.002 (0.007)
	Slope - CI	0.055 (0.022)*	0.058 (0.022)**	0.030 (0.014)*	0.032 (0.017)

	F-test	2.91*	2.47	1.95	1.56
FRMD4A-rs17314229	Intercept	−0.052 (0.046)	0.043 (0.048)	0.025 (0.042)	−0.025 (0.045)
	Slope - CN	0.011 (0.006)	−0.010 (0.006)	−0.002 (0.003)	0.002 (0.004)
	Slope - CI	−0.002 (0.016)	−0.019 (0.017)	−0.023 (0.010)*	−0.028 (0.013)*
	F-test	1.30	1.33	1.75	1.74
FRMD4A-rs7081208	Intercept	0.022 (0.069)	−0.117 (0.072)	0.097 (0.062)	−0.112 (0.066)
	Slope - CN	−0.009 (0.008)	0.020 (0.008)*	−0.009 (0.005)	−0.001 (0.006)
	Slope - CI	0.027 (0.031)	0.055 (0.031)	−0.003 (0.020)	0.031 (0.025)
	F-test	0.68	2.91*	1.49	1.56
Intergenic-rs12007229	Intercept	0.008 (0.078)	−0.196 (0.082)*	−0.081 (0.071)	0.008 (0.076)
	Slope - CN	−0.024 (0.010)*	0.002 (0.010)	0.005 (0.005)	0.002 (0.007)
	Slope - CI	−0.020 (0.028)	0.022 (0.028)	0.003 (0.018)	0.027 (0.023)
	F-test	2.87*	2.31	0.53	0.52
LGALS3-rs4644	Intercept	0.043 (0.048)	0.024 (0.051)	0.040 (0.043)	0.083 (0.047)
	Slope - CN	0.001 (0.006)	0.008 (0.006)	−0.003 (0.003)	−0.004 (0.004)
	Slope - CI	−0.019 (0.017)	−0.008 (0.017)	−0.020 (0.010)	−0.013 (0.013)
	F-test	0.73	1.20	1.41	1.27
MMP12-rs12808148	Intercept	−0.022 (0.051)	−0.034 (0.054)	0.007 (0.046)	0.043 (0.049)
	Slope - CN	−0.004 (0.006)	−0.007 (0.006)	−0.002 (0.004)	−0.004 (0.005)

	Slope - CI	0.006 (0.018)	−0.011 (0.018)	0.020 (0.011)	0.001 (0.014)
	F-test	0.45	1.11	1.09	0.34
MTHFD1L-rs11754661	Intercept	0.063 (0.062)	−0.047 (0.065)	0.009 (0.056)	0.072 (0.060)
	Slope - CN	0.002 (0.008)	−0.003 (0.008)	−0.004 (0.004)	−0.004 (0.006)
	Slope - CI	−0.028 (0.020)	0.014 (0.020)	−0.024 (0.012)*	−0.008 (0.016)
	F-test	1.13	0.51	1.52	0.55
PAICS-rs11549976	Intercept	0.042 (0.071)	−0.057 (0.075)	−0.078 (0.065)	−0.090 (0.070)
	Slope - CN	−0.011 (0.009)	0.005 (0.009)	0.002 (0.005)	0.003 (0.007)
	Slope - CI	0.026 (0.026)	0.018 (0.027)	0.037 (0.016)*	0.003 (0.021)
	F-test	0.89	0.31	2.16	0.56
PDE7A-rs10808746	Intercept	−0.021 (0.049)	−0.109 (0.052)*	−0.019 (0.045)	−0.049 (0.048)
	Slope - CN	0.003 (0.006)	0.010 (0.006)	0.000 (0.003)	0.008 (0.005)
	Slope - CI	0.033 (0.018)	0.004 (0.019)	−0.008 (0.012)	0.036 (0.015)*
	F-test	1.12	1.70	0.27	3.06*
SNTG1-rs16914781	Intercept	0.062 (0.049)	0.036 (0.052)	−0.029 (0.045)	0.008 (0.048)
	Slope - CN	−0.007 (0.006)	−0.002 (0.006)	−0.003 (0.003)	−0.001 (0.005)
	Slope - CI	−0.023 (0.018)	−0.020 (0.018)	0.006 (0.011)	−0.012 (0.014)
	F-test	1.02	0.48	0.64	0.26
SORL1-rs668387	Intercept	0.034 (0.050)	0.010 (0.053)	0.091 (0.045)*	0.017 (0.049)

	Slope - CN	−0.008 (0.006)	0.004 (0.006)	−0.004 (0.004)	0.003 (0.005)
	Slope - CI	−0.010 (0.017)	−0.002 (0.017)	−0.017 (0.011)	0.000 (0.014)
	F-test	0.57	0.27	2.02	0.27
SPON1-rs11023139	Intercept	0.084 (0.075)	−0.093 (0.079)	−0.096 (0.068)	0.033 (0.074)
	Slope - CN	−0.012 (0.009)	0.006 (0.009)	0.004 (0.005)	−0.005 (0.007)
	Slope - CI	−0.009 (0.028)	0.023 (0.028)	−0.014 (0.018)	0.008 (0.023)
	F-test	0.63	0.60	0.97	0.24
ZNF224-rs3746319	Intercept	0.025 (0.050)	0.097 (0.053)	0.096 (0.045)*	0.056 (0.049)
	Slope - CN	−0.005 (0.006)	0.004 (0.006)	0.001 (0.003)	0.002 (0.005)
	Slope - CI	−0.018 (0.019)	0.004 (0.019)	−0.007 (0.012)	0.020 (0.015)
	F-test	0.33	2.58	2.45	1.29

*$p < .05$; **$p < .01$.; adjusted for Sex, *APOE* and Education

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