# Cognitive Capacity Genomewide Polygenic Scores Identify Individuals Resilient to Cognitive Decline in Aging

*Running title: Polygenic underpinning of cognitive performances and their declines*

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## Disclosures

The authors have no conflicts to declare.

## Data Availability

The data/analyses presented in the current publication have been deposited in and are available from the dbGaP database under dbGaP accession *phs001157.v1.p1.*

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**Abstract**

The genetic underpinnings of cognitive resilience in aging remains unknown. Predicting an individual's rate of cognitive decline—or cognitive resilience—using genetics will allow personalized intervention for cognitive enhancement and optimal selection of target samples in clinical trials. Here, using genome-wide polygenic scores(GPS) as the genomic indicators for variations of human intelligence, we examined the genetic liability of cognitive abilities in the behavioral/cognitive phenome to understand individual differences in cognitive capacity over time. Using the longitudinal sociogenomic data of 8,509 European-ancestry adults between the ages of mid-60s to 70s, we found that a higher cognitive GPS significantly correlated with a slower cognitive decline specifically in memory recall, but not in other cognitive domains. Linear mixed models with cognitive GPSs explained proportions of the variances in cognitive tests up to 60.4%. This study presents the novel genetic protective effects of cognitive ability on the decline of memory recall in aging population.

## Introduction

The magnitudes of cognitive decline in aging, a major health concern in contemporary society, differ substantially across individuals[1,2]. Unraveling the genetic underpinning for individual variations of cognitive decline with aging, particularly those associated with cognitive resilience, could help develop individualized interventions for cognitive decline and allow better sample selection in clinical trials in dementia research. Despite studies reporting the genetic risk factors of accelerated cognitive decline among individuals with dementia[3-5], we know little about the genetic protective factors of cognitive resilience in the normal aging population.

Genomewide Polygenic Scores (GPS) leverage the fact that most human traits are developed from the aggregated influence of many genetic variants, both common and rare[6-8]. By aggregating the miniscule effects of millions of genetic variants into a single score, GPS allows researchers to stratify individuals by their genomic propensity for a particular trait and to select individuals with extremely high or low GPS for further research. The recent large genome-wide association studies (GWAS) of educational attainment, a well-established proxy phenotype to human intelligence, identified 1,271 independent autosomal loci reaching genome-wide significance[9]. These findings suggest several biological pathways related to brain development or neuron-to-neuron communication contribute to human intelligence. While the GWAS revealed many genetic variants associated with cognitive phenotypes (such as cognitive performance, math ability, highest math class taken)[9-16], the genomic contribution to specific cognitive domains remains unknown, as does their relationship to cognitive changes with aging.

Since general cognitive ability is known to be highly heritable (50-70%) and polygenic[17,18 12,17], we utilize GPS to account for the genome-wide factors underlying cognitive capacity and its secular changes. We leverage the expansive phenotype information of a 50+ year social longitudinal database for phenomewide association studies (PheWAS). The Wisconsin Longitudinal Study (WLS), the longest-running social longitudinal study in the United States[19,20], encompasses a detailed and broad lifelog of cognition, personality, financial, health, and socioeconomic status. The sample is based on 10,317 individuals surveyed in 1957 – representing a 1/3 random sample of Wisconsin high school graduates that year – with a randomly-selected sibling empaneled later. The surveys have repeatedly administered the

same cognitive ability tests with the time interval of ~10 years in their latest survey rounds, as well as collected the genotype data of the participants, which creates a deep genotype-phenotype catalogue of an individual's cognitive and behavioral traits over their adult lives.

Herein, we hypothesize that the polygenic influence of the cognitive phenotypes can explain certain patterns of cognitive abilities and their declines in aging as well as other socio-behavioral phenotypes that might be affected by genetics of cognitive phenotypes. We tested the associations between longitudinal observations of individual cognitive/behavioral phenomes and the GPSs of four different cognitive phenotypes (educational attainment, cognitive performance, math ability, highest math class taken) with a focus on the secular changes of cognitive test scores. There are three important aspects in this approach: firstly, whether a certain cognitive domain is more impacted by polygenic influence than other cognitive domains; secondly, whether individuals with different GPS show different patterns of cognitive decline in aging; and, thirdly, the extents to which phenotypic variances of behavioral/cognitive phenotypes can be explained by genetic liability of cognitive capacities.

## Results

### *Cognitive GPS correlates with the changes in delayed recall and immediate recall*

The analysis sample includes 8,509 European-ancestry individuals, and cognitive assessments included 6 different cognitive ability tests. Among the 6 cognitive performance tests, the WLS had administered items from the WAIS Similarities[21] subtest three times over the survey period and the others twice (Immediate and Delayed Recall, Letter and Category Fluency, and Digit Ordering). The first cognitive assessments were conducted in the average age of 64-65 for original WLS participants (WLS survey round 5, 2003-2004), and the subsequent assessment in the age of 71 (WLS survey round 6, 2011). To capture the polygenic nature of general cognitive ability, a set of cognitive ability-related GPSs were constructed based on four large-scale GWASs on educational attainment (EA, n=1,131,881), cognitive performance (CP, n=257,841), self-reported math ability (MA, n=564,698), and highest-level math class taken (HM, n=430,445) from Lee et al[9]. We used linear mixed model with interaction terms to test whether the four cognitive GPSs can quantify the inherited

portions of secular cognitive test scores changes which were recorded repetitively with an 8-9-year interval. Among those GPSs, two representative cognitive GPSs of EA and CP are reported throughout the main text, and the results for MA/HM GPSs are available in **Supplementary Material**.

Results showed that higher GPS for cognitive phenotypes were significantly associated with the changes of Delayed Recall (p-value=1.82E-07 with CP GPS) and Immediate Recall test scores (p-value=3.23E-10 with CP GPS) after accounting for interaction effects with time. The patterns were consistent across all four cognitive GPSs that have been examined on Delayed and Immediate Recall tests. Compared to individuals with 1 SD standard deviation (SD) higher EA GPS (GPS mean=-0.131), individuals with 1SD lower GPS (GPS mean=-0.439) showed stronger associations in Delayed Recall score decline in their later survey round (β= -3.69E-03 versus -4.77E-02). Interestingly, significant increases were observed for Immediate Recall test scores among the individuals with high cognitive GPS. Individuals with 1SD higher GPS for cognitive phenotypes showed increased performance in the Immediate Recall test over time (β=2.50E-02, SE=5.28E-03) whereas individuals with 1SD lower GPS for cognitive phenotypes showed decreased performance in the same test (β=-2.19E-02, SE=5.28E-03) **(Table 1, Figure 1).**

***Similarities task most strongly correlates with cognitive GPS***

Without a time interaction term, the secular changes observed in the Similarities test score marked the strongest p-value significance (p-value= 1.20E-117, β=0.46) with cognitive GPS, when assuming random variances for each participant through the linear mixed model. For individual assessments of the Similarities task, the effect size (β) of GPS stayed robust, ranging from 1.26 (R5) to 1.36 (R6) **(Figure 2(a) and Figure 3(a)).** Other cognitive decline phenotypes, such as changes in Digit Ordering (β=0.33, p-value=1.00E-51, 95% CI=(0.29, 0.37)), Category Fluency (β=0.25, p-value=8.99E-46, 95% CI=(0.24, 0.31)) and Letter Fluency (β=0.27, p-value=2.24E-34, 95% CI=(0.23, 0.32)) also presented strong associations with EA GPS. Their positive effect sizes suggest that an individual who has higher EA GPS tend to show less changes in cognitive phenotypes over time.

***Polygenic Effect of Educational Attainment in the Cognitive Phenome (EA GPS PheWAS)***

The strongest phenome-wide associations with EA GPS were IQ score from a test taken as a junior or freshman in high school (β=1.96, p-value=2.68E-163, 95% CI=(1.82, 2.10)) and class rank in high school (β=1.95, p-value=6.00E-103, 95% CI=(1.78, 2.12)). Among the tested cognitive GPS-PheWAS, the years of educational attainment measure (EduYear variable) showed the strongest p-value association with EA GPS (β=1.50, p-value=1.04E-125, 95% CI=(1.36, 1.64)) **(Figure 2(a), Supplementary Table).** EA GPS explained 7.2% of the phenotypic variability of EduYear **(Table 2).**

Next, the Number Series (β=0.93, p-value=5.85E-61, 95% CI=(0.78, 1.07)), Digit Ordering (R6, β=0.50, p-value=2.64E-25, 95% CI=(0.36, 0.65)) and Letter Fluency tasks (R6, β=0.78, p-value=1.31E-23, 95% CI=(0.63, 0.94)) showed significant associations with EA GPS. WLS also includes measures of the average educational and income levels associated with one's occupation. These occupational education (β=1.09, p-value=2.28E-60, 95% CI=(0.95, 1.23)) and occupational income (β=0.86, p-value=7.34E-33, 95% CI=(0.72, 1.00)) scores showed positive relationships with EA GPS. Other leisure activities of 'watching lecture, concert, or play' (β=0.61, p-value=2.26E-23, 95% CI=(0.49, 0.73)) and 'reading books, magazines, or newspapers' (β=0.51, p-value=2.01E-21, 95% CI=(0.40, 0.61)) also reached the phenome-wide significance. Among the Big 5 personality dimensions, Openness (β=0.45, p-value=4.51E-14, 95% CI=(0.30, 0.60)) was the only personality dimension that met phenome-wide significance.

***Polygenic Effect of Cognitive Performance in the Cognitive Phenome (CP GPS PheWAS)***

Across all of our PheWAS, the association between IQ score and CP GPS had the strongest significance in terms of p-value and the variance explained ($R^2$) (β=1.48, p-value=1.12E-196, 95% CI=(1.38, 1.57)) **(Figure 2(b), 3(b) and Table 2)**. The variance of IQ scores explained by CP GPS was 11.5% (Adjusted $R^2$ 11.4%), whereas 9.8% (Adjusted $R^2$ 9.6%) of IQ variance was explained by EA GPS **(Table 2).**

The PheWAS of CP GPS in the cognitive phenome largely showed a similar pattern to the EA GPS PheWAS. Several cognitive tests were consistently and firmly associated with CP GPS: Similarities (R4, β=0.87, p-value=2.48E-65, 95% CI=(0.77, 0.97)), Number Series

(β=0.67, p-value=8.14E-73, 95% CI=(0.57, 0.77)), 'digit ordering' (R6, β=0.39, p-value=1.16E-39, 95% CI=(0.29, 0.49)), and Letter Fluency (R6, β=0.60, p-value=1.36E-28, 95% CI=(0.50, 0.71)). Among the cognitive decline phenotypes, changes in the Similarities task marked the best p-value association (β=0.29, p-value=3.00E-100), followed by the changes in Digit Ordering (β=0.28, p-value=7.33E-76). We also confirmed the strong associations of CP GPS with high school class rank (β=1.24, p-value=8.23E-87, 95% CI=(1.12, 1.36)), the years of educational attainment (β=0.79, p-value=5.72E-74, 95% CI=(0.70, 0.89)), occupational education score (β=0.55, p-value=4.12E-35, 95% CI=(0.46, 0.65)) and occupational income score (β=0.45, p-value=3.59E-20, 95% CI=(0.35, 0.55)) as we observed in EA GPS PheWAS **(Figure 2(b) and Supplementary Table).**

## Discussion

In this study, we assessed the genetic influences of general cognitive abilities on cognitive phenome using a combinational approach of GPS-based PheWAS on longitudinal observations of cognitive assessments. Our mixed-effect linear model examined the role of cognitive GPS on the changes of cognitive capacity in aging, and additional analyses tested the phenomewide associations between cognitive GPS and several cognitive/behavioral traits. In conjunction with genotype data, the availability of cognitive phenome data from the WLS enabled exploration of cognitive/behavioral phenotypes with longitudinal measurements of human cognitive ability.

In addition to the wide range of the cognitive domains correlating with the cognitive GPS, a decline of memory recall in aging correlated with the cognitive GPS but not the other cognitive domains did. Memory recall, assessed by immediate and delayed recall tests of words, is hippocampus dependent[22-24]. It is interesting that the discovered genetic protective effect exerted specifically on the hippocampus-related memory recall. There are two implications worth noting. Firstly, given the specificity of the correlations among various cognitive domains, the genetic protective factor of memory decline may be mediated via the hippocampus. Indeed, the hippocampus is the primary mediator of interventions for the cognitive wellness or dementia, such as aerobic fitness[25], diet[26], and medication[27-29]. This is

closely related to the unique role of the hippocampus in neurogenesis and synaptic plasticity[30,31]. Future research should thus test whether the hippocampus and hippocampal network underlies the genetic projective effect on memory decline, and if so seek to elucidate the mechanisms involved. Secondly, given the role of the hippocampal memory impairment in the pathophysiology of Alzheimer's disease (AD), our finding may lead to the potential link of the inherited genetic factor of cognitive resilience to the individual differences in hippocampal degeneration, as well as memory decline in AD[32,33]. Testing this link will allow better stratification of AD and monitoring the course of the disease by the individual-specific genetic profiles of cognitive resilience.

Considering that the correlations of the time-x-GPS interactions were positive **(Table 1)**, individuals with a higher cognitive GPS presented a slower trajectory of memory decline than those with a lower GPS. This result indicates that the portions of cognitive ability under genetic influence may serve as a 'buffer' against memory decline in aging. These observations align well with existing studies on the protective effect of education and intelligence on the occurrence of dementia[34]. A close relationship between early-life education and intelligence with cognitive decline have been reported for dementia and AD[35]. Even though it is not yet clear how early-life education and intelligence moderate the risk for dementia, our findings suggest that individual variations of memory decline are closely associated with polygenic influences of cognitive abilities.

Among the WLS cognitive modules, the Similarities task from WAIS and the Number Series task showed the strongest associations across the four cognitive GPSs in terms of effect size (β) and p-value, indicating its high genetic relatedness. These findings suggest that the cognitive components required to successfully complete the Similarities or Number Series tasks might strongly overlap with genetic components of cognitive abilities primarily exhibited by the domain of fluid intelligence. All the Similarities tasks performed in three different time points (R4, R5, R6) presented significant PheWAS associations following other early-life cognition measures, such as IQ scores and high school academic achievement, suggesting its high relatedness to early-life cognition. The effect sizes of the Similarities tasks were fairly consistent and robust over time (R4: 1.26, R5: 1.36, R6: 1.36 with EA GPS).

Fluid intelligence is used to think and act flexibly and quickly, and to encode new episodic memories to solve problems in novel situations without previously existing knowledge.

The series of cognitive components involved in the Similarities and Number series tasks, such as logical memory, symbol search, and reasoning, might be closely linked to early-life cognition, all of which may serve as phenomewide indicators for fluid intelligence. Our findings are backed up by the previous knowledge that fluid intelligence is considered to be more dependent on biological influences and less dependent on past learning experiences than crystalized intelligence[36].

The IQ scores of individuals were best predicted by CP GPS in terms of both p-value and effect size **(Figure 2, 3)**. The strong genetic association between cognitive ability and educational attainment has been well established in several GWAS studies on human intelligence[9,13-16]. IQ scores of the WLS respondents were derived from the Henmon-Nelson test of mental ability, which was administered to high school students in Wisconsin in the 1950s. The test is regarded as a general measure of overall intelligence, capturing both fluid and crystallized intelligence. We found the close associations between IQ score and cognitive GPS as well as its high correlations to several early-life academic achievement such as high school rank. **(Figure 2)** Those findings jointly showed that substantial variances of IQ scores could be explained by several intercorrelated phenotypes in both domains of cognitive ability and educational achievements.

Another interesting aspect of our study was the systematic examination of the relationships between cognitive GPS and behavioral phenotypes. Our PheWAS of the behavioral phenome identified several behavioral phenotypes having high genetic influences from cognitive abilities. Several cognitive GPSs significantly correlated with Openness among the Big 5 personality factors, but not with others. Another personality trait, Neuroticism, showed a significant negative correlation with the same range of cognitive GPS[37]. The finding presents an interesting cross-trait hypothesis in which the variances of cognitive abilities may be partially explained by a personality dimension. ‘Openness’ could be regarded as the attitude and tendency to explore, detect, understand, and appreciate complicated patterns of new information through both the senses and in the abstract[38]. Previous studies support our findings, concluding that an overall open-minded attitude might positively influence the long-term variances of cognitive abilities with willingness to explore [39].

No significant associations between Spouse IQ and cognitive abilities were confirmed, which indicates that the behavioral associations between assortative mating and cognitive

abilities is unclear. In addition, a strong relationship between occupational income and several cognitive GPS were found, which supports the existing studies on a strong association between general mental ability and job performance [40].

The GPS-based PheWAS found that up to 11.5% (adjusted $R^2$ 11.4%) of variances in IQ score could be explained with CP GPS. The variances in academic achievement in high school were explained as high as 6.2-9.2% across GPS of cognitive abilities. Among the WLS cognitive test modules, up to 4.8% of the Similarities task score variances was explained by EA GPS **(Table 2).** Those findings demonstrate that a substantial portion of phenotypic variances in several cognitive abilities could be explained and influenced by intelligence genetic risk variants, presented as several GPS.

Several limitations of this study should be noted. The WLS had two time points for measuring changes in their cognitive assessments with an 8-9 year interval. Adding more cognitive measurements through time will strengthen our findings by more thoroughly monitoring cognitive changes over the lifetime. Also, the unexplored impact of other sociodemographic variables such as socioeconomic status, educational environment, lifestyles, or family structure, should be considered to better connect our theorical findings with phenome-wide expression of cognitive abilities. In addition, we used European-ancestry specific summary statistics for constructing the cognitive GPSs and applied them to participants with European-ancestry. Researchers should note that the translational application to non-European individuals could be different and the results should be interpreted with caution. Future investigation is needed to elucidate heterogeneity between ancestry groups for the genetic underpinnings of cognitive abilities.

Our analytic approach combining GPS and PheWAS leverages the fact that human intelligence has a considerably polygenic and pleiotropic architecture in its phenotypic expression[12,17,41]. Through this study, we confirmed potential utility of GPS on future prediction of dementia or other neurocognitive disorders. Our findings could serve as the first cognitive-phenome map that describes the functional boundaries of human cognition from a genetic perspective, and the map could be further expanded with the advanced phenotyping of human cognition and behavior traits.

## Methods

### *WLS Study Population*

The WLS has measured 27,000+ phenotypic variables of 10,317 self-identified non-Hispanic White individuals, who graduated from Wisconsin high schools in 1957, during 6 waves of data collection over 60 years. The WLS also surveyed selected siblings and the spouse of the original participants, expanding the total number of respondents to 19,050 individuals starting from 1977. The cohort is representative of non-Hispanic White Americans who completed at least 12 years of high school education in the United States.

### *Genotype data and Quality Control process of WLS*

In 2007-2008, saliva samples were collected by mail or by home-interview, and 9,019 individuals were successfully genotyped at the Johns Hopkins University center for inherited disease research (CIDR) using the Illumina HumanOmniExpress-24 v.1.1 array. The subsequent quality control process filtered individuals with (i) genotype missingness rate > 0.05 in all chromosomes, (ii) mismatch between recorded sex and genetically determined sex, (iii) high genetic relatedness with other individual (>0.025), (iv) outlier in heterozygosity/homozygosity test, and (v) non-European ancestry outliers. Non-European individuals were identified by visually inspecting the principal component analysis (PCA) plot of the covariance matrix of the WLS genotype data with 1000 Genome populations. Additionally, SNPs with (i) genotype call rate < 0.95, (ii) Hardy-Weinberg exact test p-value < 1.0E-05, and (iii) minor allele frequency < 0.01 were excluded from the data, resulting in 607,469 autosomal SNPs in 8,527 European-ancestry individuals. The data was then imputed to the Haplotype Reference Consortium (HRC) v1.1 European reference panel[42] and resulted in 39,127,657 variants. The detailed imputation and QC report is available separately[43,44].

### *Cognitive GPS construction*

The WLS provided polygenic scores for four different cognitive traits based on GWAS MTAG summary statistics from Lee et al (REF), which were obtained from a multivariate analysis of educational attainment, cognitive performance, self-reported math ability and highest-level math class taken. GPS were calculated with PLINK 1.9 (REF) using the SNP weights adjusted

for linkage disequilibrium using LDpred software (REF). All SNP weights were obtained from cognitive GWAS discovery samples that did not contain the WLS participants (REF).

***Creation of the Cognitive Phenome***

1. Cognitive performance

The WLS administered seven types of cognitive modules over the survey periods, which were used as the key components of the cognitive phenome: Similarities (administered in Round 4/5/6), Letter/Category Fluency (R5/6), Immediate/Delayed Word Recall (R5/6), Linguistic Function (R5/6), Digit Ordering (R5/6), Number series (R6), and Health Literacy test scores. Six of the seven cognition modules were repeatedly administered to the same participants. More details of each module are illustrated in **Supplementary Material.**

2. Cognitive decline

We measured the degree of cognitive decline by comparing the two (three for similarity tests) cognition test scores taken by the same individual, with time interval as the dependent variable in the linear mixed model regression. We defined six measures of cognitive decline based on the cognitive modules: similarities, letter fluency, category fluency, immediate recall, delayed recall, and digit ordering.

3. Education
    a. IQ score: All the respondents completed the Henmon-Nelson Test of Mental Ability with 90 items during their high school junior years (1956), which measured verbal, quantitative, and spatial knowledge[45-47]. Raw scores were converted to IQ scores by standardizing to a mean of 100 based on Wisconsin centile rank (z-score).
    b. Educational attainment: The years of education were estimated from the highest degree obtained by each participant, ranging from 12 to 20 years.
    c. High School Class rank: Percentile rank information was retrieved from high school records, which is based on the mean grade taken throughout the high school courses. (100–(rank in class/(# of students in class))*100] The correlation between class grade and standardized test scores was as high as 0.90, which reduces the possibility of teacher bias on grades or ranks[48].
4. Personality

WLS administered a short-version of the Big 5 Factor Model of Personality inventory test [49] to the respondents in the 1992-1993 collection wave: extraversion, openness, neuroticism, conscientiousness, and agreeableness.

5. Leisure Activities

We investigated leisure activities of the WLS respondents to examine the genetic effects of cognition regarding how time is allocated in individual habits, social roles, and behavioral preferences. The contents of participants' leisure activities were self-reported in hours per week and illustrated in the **Supplementary Material**. In order to correct for outliers with extreme hours of certain activities, we took the natural logarithm of the reported hours for each activity and ran linear regression with the built GPS.

6. Miscellaneous

   a. Occupational Education Score: The WLS collected the first or only employment information of the respondents. The measure assigned each employment with a numeric value for their industry or class-of-worker categories based on the 1990 US Census data, which represents a percentage of persons who had at least one year of college education, ranging from 0 to 999.

   b. Occupational Income Score: For the first or only job of the respondents in the employment modules, the WLS assigned the 1990-basis occupational earning scores, which represent the percentage of persons in the 1990 US Census data in an industry or class-of-work category who earned more than $14.30/hour in 1989, ranging from 37 to 876.

   *c.* Spouse IQ: Previous literature has suggested the psychiatric hypothesis of assortative mating in academic achievements and IQ (i.e. individuals tend to select spouses similar in academic achievements and IQ to themselves) [50-54]. As spouse IQ data were available through the additional panels of WLS, we assessed the behavioral genetics of spouse concordance for IQ. We aimed to investigate if behaviors of assortative mating have pleiotropic associations with GPS of cognitive abilities.

***Phenome-wide Analysis***

Regression analyses mapped the four types of cognitive GPS (EA, CP, HM, MA) to the cognitive phenome that is created from the aforementioned normalized variables of the WLS

data. For numerical phenotypes, linear regression is used to measure each GPS prediction performance, adjusting for biological sex and the first 10 principal components (PC 1-10) of ancestry. We measured each GPS' significance (p-value), effect size (β), 95% confidence interval (CI), and proportion of variance explained ($R^2$) on cognitive phenotype prediction. For cognitive decline variables, we used linear mixed models, assuming fixed effects of each GPS and covariates, and random effects for the weight level specific to each survey round and individual. (c.f. WLS Round4 = timepoint 0, Round5= timepoint 1, Round6= timepoint 2) The analyses were performed in R 3.5.1 environment, and linear mixed model was run with lme4 package[55]. For each analysis, we excluded the respondents who had not completed all the questionnaires for each phenotype. We used *interaction* R package to visualize our regression results with interaction terms.

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**Figure 1. Interaction plots showing different slopes of time-dependent interaction effects of cognitive GPS on the cognitive assessments that were administered to 8,507European ancestry individuals between the age of mid-60s (timepoint 0) and mid-70s (timepoint 1).** Changes in five cognitive assessments (immediate recall test, category fluency test, digit ordering test, delayed recall test, and letter fluency test) and interaction effects of EA GPS (upper panel) and CP GPS (bottom panel) were shown. The X-axis indicates the timepoints of WLS survey round, while the y-axis indicates each cognitive assessment score. The three lines indicates different groups of individuals stratified by GPS. The gray area represents 95% confidence interval of each slope.

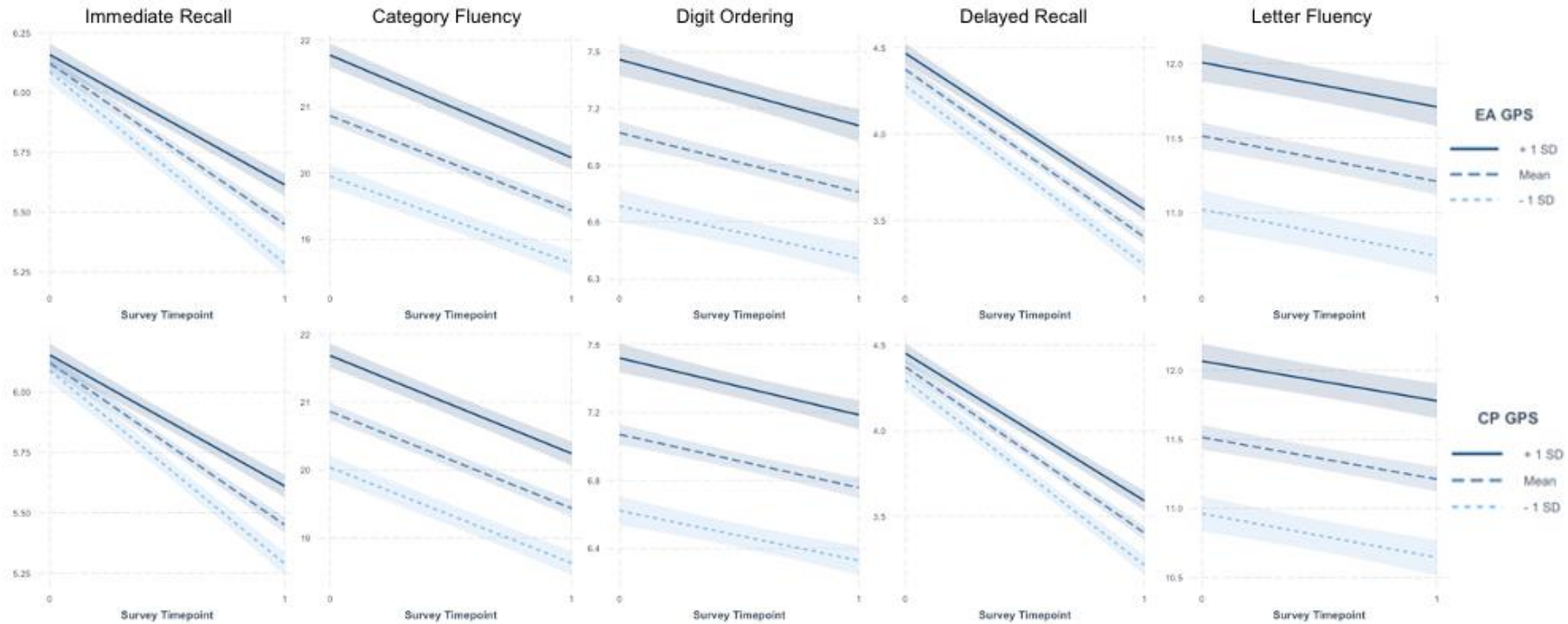
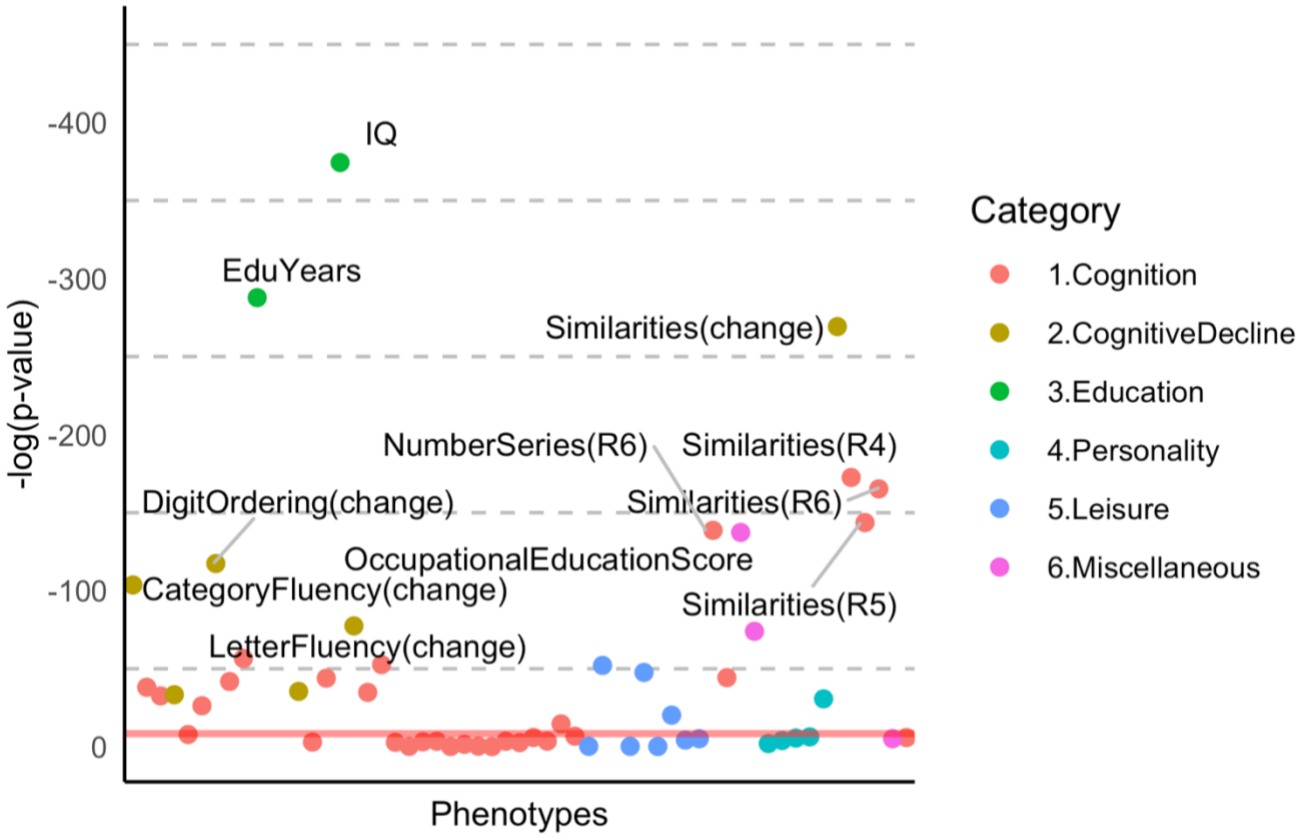


**Figure 2. PheWAS plots of (a) Educational attainment (EA), and (b) Cognitive Performance (CP) GPS in the cognitive phenome of the WLS participants.** The cognitive phenome on x-axis was created from the cognitive variables retrieved from WLS survey data, primarily from the cognition modules in the 2003-2005 and 2011-2013 waves. The red line represents the phenome-wide significance level [ $\log_{10}$ of the Bonferroni corrected p-value for multiple testing corrections (alpha = 0.05 / (58 tested phenotypes * 4 GPS) = 2.15E-04).

(a) PheWAS plot of Educational Attainment (EA) GPS



(b) PheWAS plot of Cognitive Performance (CP) GPS

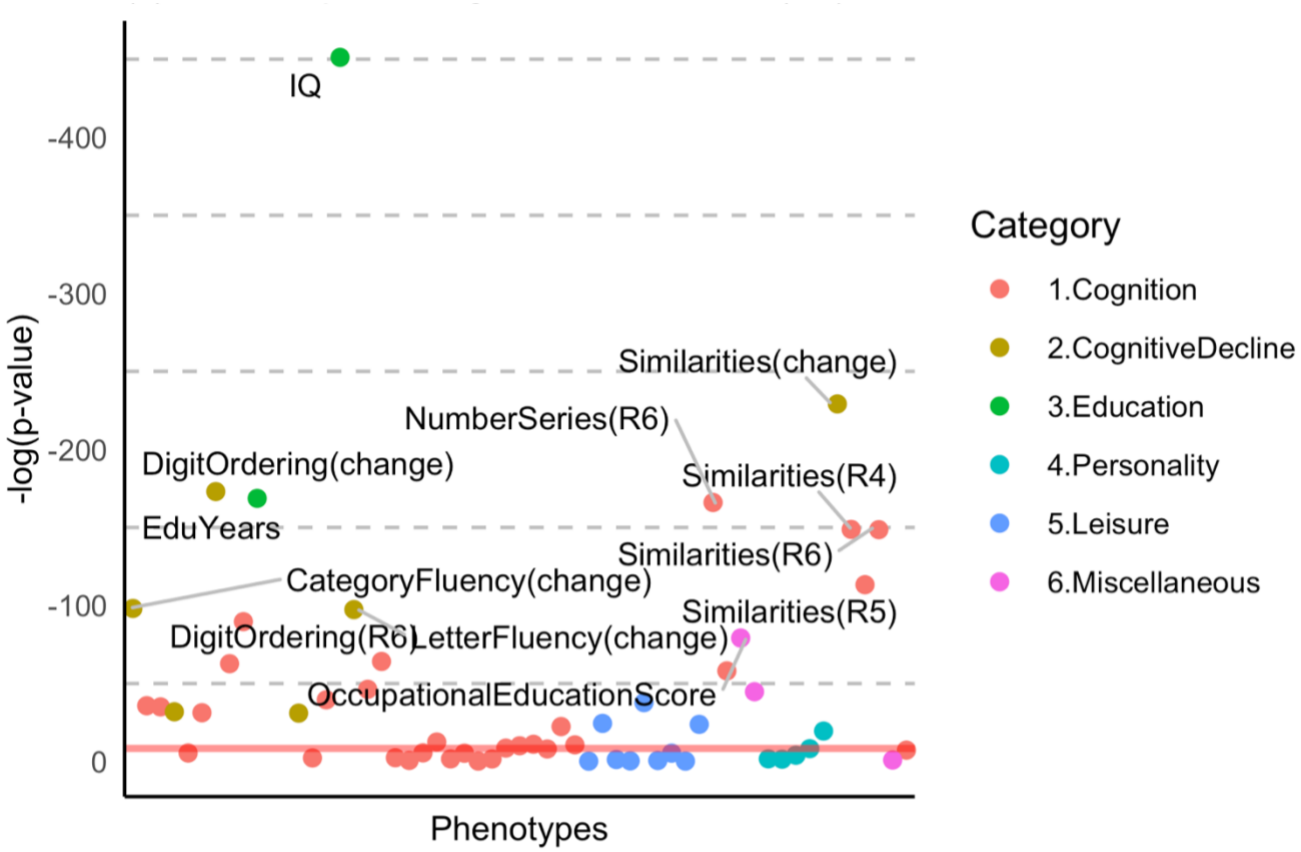
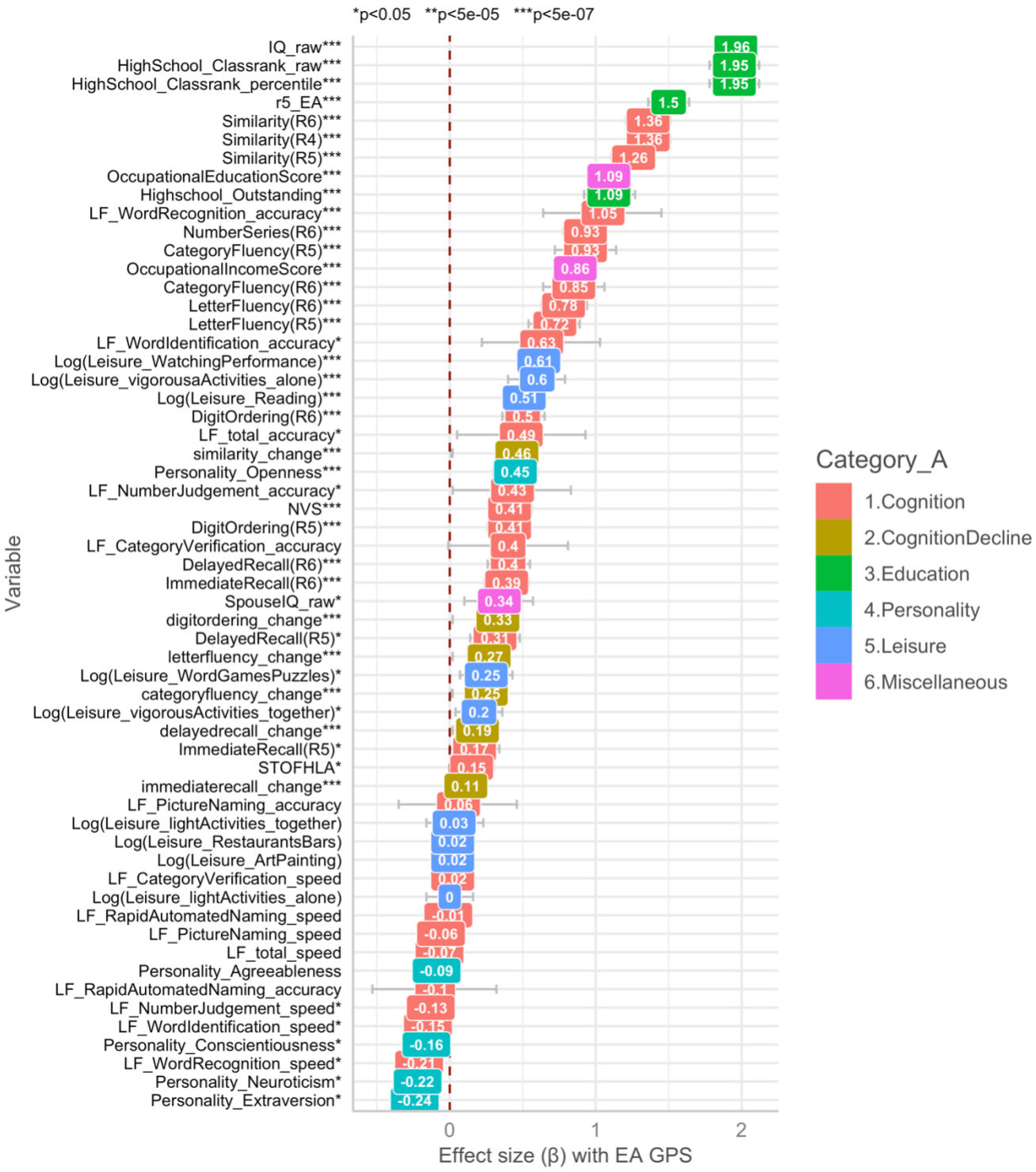


**Figure 3. Forest plots of the effect size (β) of phenome-wide associations with GPS of (a) Educational attainment (EA), (b) Cognitive Performance (CP).** Cognitive and behavioral phenotype variables are on the y-axis, and the number of asterisks (*) indicates the Bonferroni corrected significance of each phenome-wide association; * p-value of GPS-phenotype association < 0.05, ** p-value of GPS-phenotype association < 5E-05, *** p-value of GPS-phenotype association < 5E-07. The numeric value of each effect size is specified as white-colored text in the colored circle, while the grey-colored error bar around the circles indicates 95% CI of each effect size.

(a) Forest plot of the effect sizes of PheWAS with GPS of Educational Attainment (EA)



(b) Forest plot of the effect sizes of PheWAS with GPS of Cognitive Performance (CP)

**Table 1.** PheWAS results of Educational attainment (EA) and Cognitive Performance (CP) GPS in the cognitive phenome of the WLS participants.

| | | EA GPS | | | CP GPS | | |
|---|---|---|---|---|---|---|---|
| | | β | SE | P | | SE | P |
| **Similarities** | **time** | -0.015 | 0.026 | 5.56E-01 | -0.007 | 0.023 | 7.47E-01 |
| | **GPS** | 3.152 | 0.160 | 1.67E-87 | 1.970 | 0.111 | 3.37E-71 |
| | **time x GPS** | -0.063 | 0.080 | 4.36E-01 | -0.029 | 0.056 | 6.05E-01 |
| **Delayed Recall** | **time** | -0.847 | 0.057 | 4.68E-50 | -0.801 | 0.049 | 1.41E-58 |
| | **GPS** | 0.609 | 0.136 | 7.50E-06 | 0.353 | 0.094 | 1.79E-04 |
| | **time x GPS** | 0.433 | 0.175 | *1.31E-02* | 0.498 | 0.122 | *4.22E-05* |
| **Immediate Recall** | **time** | -0.434 | 0.047 | 6.22E-20 | -0.474 | 0.041 | 2.85E-30 |
| | **GPS** | 0.236 | 0.112 | 3.49E-02 | 0.146 | 0.078 | 5.96E-02 |
| | **time x GPS** | 0.834 | 0.146 | *1.22E-08* | 0.582 | 0.102 | *1.14E-08* |
| **Digit Ordering** | **time** | -0.380 | 0.075 | 4.71E-07 | -0.346 | 0.066 | 1.43E-07 |
| | **GPS** | 2.516 | 0.203 | 4.64E-35 | 2.032 | 0.140 | 3.47E-47 |
| | **time x GPS** | -0.229 | 0.232 | 3.24E-01 | -0.092 | 0.162 | 5.68E-01 |
| **Letter Fluency** | **time** | -0.291 | 0.088 | 9.27E-04 | -0.279 | 0.077 | 2.62E-04 |
| | **GPS** | 3.190 | 0.303 | 8.85E-26 | 2.500 | 0.210 | 1.26E-32 |
| | **time x GPS** | 0.045 | 0.271 | 8.69E-01 | 0.071 | 0.189 | 7.06E-01 |
| **Category Fluency** | **time** | -1.646 | 0.127 | 3.22E-38 | -1.454 | 0.110 | 3.38E-39 |
| | **GPS** | 5.929 | 0.420 | 7.20E-45 | 3.733 | 0.291 | 2.28E-37 |
| | **time x GPS** | -0.763 | 0.391 | 5.10E-02 | -0.077 | 0.272 | 7.79E-01 |

**Table 2.** Phenotypic variances ($R^2$) explained by Educational attainment (EA) and Cognitive Performance (CP) GPS in cognitive and behavioral phenomes of the WLS participants. Conditional $R^2$ were reported, taking into account both the fixed and random effects, for the changes of cognitive test scores using linear mixed models. The numbers in parentheses indicate $R^2$ adjusted for biological sex and the first 10 principal components of ancestry.

| Variable | **EA GPS $R^2$ (Adj. $R^2$)** | **CP GPS $R^2$ (Adj. $R^2$)** |
|---|---|---|
| IQ | 0.098 (0.096) | 0.115 (0.114) |
| Educational Attainment (R5) | 0.072 (0.071) | 0.050 (0.049) |
| Similarities (change) | 0.543 | 0.543 |
| Similarities test (R4) | 0.048 (0.047) | 0.042 (0.041) |
| Similarities test (R5) | 0.041 (0.040) | 0.033 (0.032) |
| Similarities test (R6) | 0.047 (0.046) | 0.043 (0.041) |
| Letter Fluency (change) | 0.605 | 0.605 |
| Letter Fluency test (R5) | 0.018 (0.016) | 0.022 (0.020) |
| Letter Fluency test (R6) | 0.021 (0.020) | 0.024 (0.023) |
| Category Fluency (change) | 0.578 | 0.578 |
| Category Fluency test (R5) | 0.025 (0.022) | 0.023 (0.020) |
| Category Fluency test (R6) | 0.022 (0.019) | 0.024 (0.021) |
| Immediate Recall (change) | 0.177 | 0.177 |
| Immediate Recall Test (R5) | 0.005 (0.003) | 0.005 (0.003) |
| Immediate Recall Test (R6) | 0.006 (0.005) | 0.006 (0.005) |
| Delayed Recall (change) | 0.216 | 0.217 |
| Delayed Recall test (R5) | 0.004 (0.002) | 0.003 (0.001) |
| Delayed Recall test (R6) | 0.006 (0.005) | 0.006 (0.005) |
| Digit Ordering (change) | 0.347 | 0.347 |
| Digit Ordering test (R6) | 0.009 (0.008) | 0.010 (0.009) |
| Digit Ordering test (R5) | 0.008 (0.006) | 0.010 (0.009) |
| Number series test (R6) | 0.023 (0.021) | 0.025 (0.023) |
| NVS test (R6) | 0.005 (0.004) | 0.006 (0.004) |
| STOFHLA test (R6) | 0.002 (0.001) | 0.003 (0.001) |
| Linguistic Function - Speed (R6) | 0.014 (0.003) | 0.027 (0.016) |
| Linguistic Function - Accuracy (R6) | 0.025 (0.014) | 0.037 (0.026) |
| Spouse IQ | 0.006 (0.003) | 0.004 (0.000) |
| Occupational Education Score | 0.036 (0.035) | 0.024 (0.023) |
| Occupational Income Score | 0.021 (0.020) | 0.014 (0.013) |
| Classrank in high school (percentile) | 0.092 (0.090) | 0.080 (0.078) |
| Outstanding Student in high school | 0.035 (0.033) | 0.028 (0.026) |