Cognitive Function in People With Familial Risk of Depression

Cognitive Function in People with Familial Risk of Depression: Evidence from Four Cohorts Across the Lifespan

Breda Cullen, PhD[1]*; Marc J. Gameroff, PhD[2,3]; Joey Ward, PhD[1]; Mark E.S. Bailey, PhD[4]; Donald M. Lyall, PhD[1]; Laura M. Lyall, PhD[1]; Niamh MacSweeney, BA[5,6]; Eleanor Murphy, PhD[2,3]; Natasha Sangha, MSc[1]; Xueyi Shen, PhD[5]; Rona J. Strawbridge, PhD[1,7]; Milenna T. van Dijk, PhD[2,3]; Xingxing Zhu, MSc[1]; Daniel J. Smith, MD[5,6]; Ardesheer Talati, PhD[2,3]; Heather C. Whalley, PhD[5,6]; Jonathan Cavanagh, MD[8]; Myrna M. Weissman, PhD[2,3,9]

[1]School of Health and Wellbeing, University of Glasgow, Glasgow, UK

[2]Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

[3]Division of Translational Epidemiology, New York State Psychiatric Institute, NY, USA

[4]School of Molecular Biosciences, University of Glasgow, Glasgow, UK

[5]Division of Psychiatry, University of Edinburgh, Edinburgh, UK

[6]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

[7]Department of Medicine Solna, Karolinska Institute, Stockholm, Sweden

[8]School of Infection and Immunity, University of Glasgow, Glasgow, UK

[9]Mailman School of Public Health, Columbia University, New York, NY, USA

*Correspondence:

Dr Breda Cullen

School of Health and Wellbeing

University of Glasgow

Administration Building

Gartnavel Royal Hospital

1055 Great Western Road

Glasgow, G12 0XH, UK

Telephone: +44 (0)141 211 3912

Email: Breda.Cullen@glasgow.ac.uk

Word count main text: 3,500

Tables/figures: 5

References: 23

Date of revision: January 18, 2023

Key Points

Questions: Are hypothesized associations between familial risk of depression and lower cognitive performance evident across the lifespan, for both family history and genetic risk measures?

Findings: In three younger cohorts (TGS, ABCD, and Add Health; age range 6-42y), family history of depression was primarily associated with lower performance in the memory domain, whereas in the older UK Biobank cohort (age range 44-83y) the associations were stronger for processing speed, attention and executive function; effect sizes were largest in the deeply-phenotyped TGS cohort. Associations were similar in the polygenic risk score analyses and were evident even in participants who had never been depressed themselves but had a family history of depression.

Meaning: Whether assessed by family history or genetic data, there is evidence that depression in prior generations is associated with lower cognitive performance in offspring, which has important implications for understanding and addressing potentially modifiable risk factors.

Abstract

Importance: Cognitive impairment in depression is poorly understood. Family history of depression is a potentially useful risk marker for cognitive impairment, facilitating early identification and targeted intervention in those at highest risk, even if they do not themselves have depression. Several research cohorts have emerged recently which enable findings to be compared according to varying depth of family history phenotyping, in some cases also with genetic data, across the lifespan.

Objective: To investigate associations between familial risk of depression and lower cognitive performance in four independent cohorts with varied depth of assessment, using both family history and genetic risk measures.

Design: Longitudinal or cross-sectional analyses conducted in March-June 2022, of data from the 'Three Generations' family study (TGS; data collected 1982-2015) and three large population cohorts: ABCD (2016-2021), Add Health (1994-2018), and UK Biobank (2006-2022).

Setting: Family and population-based research cohorts.

Participants: Children and adults with or without familial risk of depression.

Exposures: Family history (across one or two prior generations) and polygenic risk of depression.

Main Outcome(s) and Measure(s): Neurocognitive tests at follow-up. Regression models were adjusted for confounders and corrected for multiple comparisons.

Results: The sample sizes for analysis were 87 in TGS (mean age 19.71y, SD 6.55; 48% female), 10,258 in ABCD (mean age 12.00y, SD 0.66; 48% female), 1,064 in Add Health (mean age 37.75y, SD 1.88; 49% female), and 45,899 in UK Biobank (mean age 63.99y, SD 7.71; 51% female). In the younger cohorts (TGS, ABCD, and Add Health), family history of depression was primarily associated with lower performance in the memory domain and there

were indications that this may be partly related to educational and socioeconomic factors. In the older UK Biobank cohort, the associations were stronger for processing speed, attention, and executive function, with little evidence of education or socioeconomic influences. These associations were evident even in participants who had never been depressed themselves. Effect sizes were largest in TGS: largest standardized mean differences in primary analyses were -0.55, 95% CI -1.49 to 0.38 (TGS); -0.09, 95% CI -0.15 to -0.03 (ABCD); -0.16, 95% CI -0.31 to -0.01 (Add Health); -0.10, 95% CI -0.13 to -0.06 (UK Biobank). Results were generally similar in the polygenic risk score analyses. In UK Biobank, several tasks showed statistically significant associations in the polygenic risk score analysis that were not evident in the family history models.

Conclusions and Relevance: Whether assessed by family history or genetic data, there is evidence that depression in prior generations is associated with lower cognitive performance in offspring. There are opportunities to generate hypotheses about how this arises through genetic and environmental determinants and moderators of brain development and brain aging, and potentially modifiable social and lifestyle factors across the lifespan.

Introduction

Cognitive impairment is a key cause of disability in adults with depression. It is evident at the first depressive episode[1] and persists even after remission[2] leading to worse functioning[3] and lower quality of life.[4] Cognitive impairment in depression is poorly understood, but likely involves a complex interplay between background risk factors for both depression and cognitive dysfunction, and other factors that operate further downstream after depression onset.

Background risk can be elucidated by studying biological relatives of people with depression. A meta-analysis of studies of never-depressed first-degree relatives of people with major depressive disorder[5] showed consistent effect sizes across all cognitive domains (standardized mean difference -0.2), which were statistically significant for intelligence, memory, and language but not attention, speed, or executive function. Family history of depression therefore has potential to be a clinically useful risk marker, opening the possibility of early identification and targeted prevention or intervention for cognitive dysfunction in those at highest risk.

There are challenges with studying familial risk of depression. Retrospective reporting of family history is liable to missingness and recall bias, but direct prospective assessment is resource-intensive and difficult to implement at scale. The family study known as 'Three Generations at High and Low Risk of Depression Followed Longitudinally'[6] (hereon, Three Generations, TGS) offers a unique opportunity to investigate family history and cognitive function using gold-standard methods. Prospective clinical assessment of depression by trained clinical interviewers has been undertaken on multiple occasions across more than 30 years, together with high quality cognitive testing and neuroimaging. The inclusion of multiple generations enables family risk to be characterized in greater detail than the majority of studies to date, which have included only first-degree relatives. We have

shown that there is a 'dose' effect in this cohort whereby offspring with both a parent and grandparent with major depression were at highest risk for developing depression themselves.[6] No study to date has investigated whether a dose effect is also present for offspring cognitive outcomes. If that were found to be the case, it would enable better targeting of early intervention on the basis of number of prior generations affected.

Although the TGS cohort is uniquely well-placed to enable this research, it is essential that findings are replicable and generalizable to the wider population, especially where direct assessment of relatives is not feasible. We have demonstrated that a dose effect on offspring depression outcomes is also evident in the general population-based Adolescent Brain Cognitive Development study (ABCD Study®),[7,8] which relied on family history reported retrospectively by a single informant, and similar research is needed on cognitive outcomes.

It is also important to include cohorts with different age ranges; there are indications that processing speed deficits are less prominent (compared with deficits in other domains) in unaffected relatives[5] and emerge later in life in those with depression,[2] implicating downstream effects of depressive illness or differential aspects of brain aging. A further advantage of studying large population cohorts such as ABCD is that many include genotyping data, enabling the derivation of polygenic risk scores (PRS). Polygenic risk for depression represents genetic aspects of familial depression risk based on common genotypic variants, and has been shown to be associated with a wide range of phenotypes relating to mental and physical health and brain structure in independent cohorts.[9] Socially diverse population cohorts can also shed light on non-genetic aspects of familial risk; for example, lower socioeconomic resources in families affected by depression may reduce opportunities for cognitive development in offspring,[5,10] as well as modifying genetic risk in an interactive manner.[9]

In this study we quantified the association of familial risk of depression with cognitive outcomes, in TGS and in three general population cohorts spanning childhood to old age: ABCD,[7] the National Longitudinal Study of Adolescent to Adult Health ('Add Health'),[11] and UK Biobank.[12] Our aims were to ascertain whether the hypothesized associations with lower cognitive performance were evident in all cohorts and for both family history and genetic data, and to elucidate the patterns of association across cognitive domains and across the lifespan.

Method

This study used a cohort design within TGS, ABCD, and UK Biobank, with family history data collected at one assessment wave and cognitive outcomes measured at a later wave. In Add Health the family history data and cognitive data were only available at the same wave, and so these analyses were cross-sectional. Reporting follows STROBE guidelines.[13]

Participants

Each cohort's study procedures were approved by the relevant Institutional Review Board or Ethics Committee and participants gave written informed consent. Full details regarding the design and composition of each cohort are provide in eMethods in the Supplement.

Familial Risk Exposures

Familial risk of depression was measured using two sources of data: reported/assessed biological family history and PRS.

Family History of Depression

TGS was the only cohort in which depression was directly assessed in all generations by direct interview with the subject. In the other cohorts, family history was ascertained from retrospective reporting by the participant or their parent. The cohorts varied in how depression was defined (details in eMethods): TGS used a best-estimate major depressive disorder diagnosis with an additional requirement of impaired functioning; ABCD asked about "depression, that is, have they felt so low for a period of at least two weeks that they hardly ate or slept or couldn't work or do whatever they usually do?"; Add Health asked about "depression" (not further defined); and UK Biobank asked about "severe depression" (not further defined). The primary family history measure used in the main analyses was a binary variable based on lifetime parental history (at least one biological parent with depression versus no parent with depression); this is in keeping with the previous meta-analysis, in which parental history was the exposure in most studies.[5] Three of the cohorts (not UK Biobank) also collected data on biological grandparent history, enabling the creation of secondary exposure measures: (i) binary variable for at least one parent/grandparent with depression versus no parent/grandparent with depression and (ii) four-category dose variable[8] representing the number of prior generations with depression (both generations; parent only; grandparent only; neither generation).

Polygenic Risk for Depression

This was available in three cohorts (not TGS). In ABCD, we created LDpred PRS[14] based on a 2019 genome-wide association study (GWAS) meta-analysis of various depression phenotypes (self-reported or clinically confirmed).[15] Details are provided in eMethods. The Add Health PRS was created centrally by the Add Health team[16] based on the same 2019 meta-analysis. The UK Biobank PRS was not created from the 2019 meta-analysis because UK Biobank was a discovery cohort in that GWAS. We instead created the UK Biobank

LDpred PRS from a 2018 GWAS of various depression phenotypes,[17] using summary statistics that excluded UK Biobank participants. Details are provided in eMethods. All PRS were standardized as z-scores (mean 0, SD 1) within each analysis sample.

Cognitive Outcome Measures

In each cohort, all available tests of neurocognition were analyzed (details in eMethods). TGS Wave 6 follow-up included a detailed battery of assessor-administered gold-standard tests of speed, reasoning/intelligence, attention, executive function, and memory. This was administered only to participants who were assessed in person. ABCD Year 2 follow-up included assessor-administered brief computerized tests of vocabulary, speed, attention/executive function, and memory, using a mix of in person and videoconferencing assessment. Add Health Wave V follow-up included three assessor-administered brief bespoke measures of attention/executive function and memory, administered only to a representative subsample who were assessed in person. The UK Biobank imaging visit follow-up (in person) included self-administered brief computerized touchscreen tests of speed, reasoning, attention, executive function, and memory. Composite scores (representing the mean performance across tests within a cognitive domain) were also analyzed.

Covariates

Age, sex, ethnicity, country of birth (as an indicator of linguistic/cultural variation which may affect performance on US/UK-designed cognitive tests), and duration between exposure and outcome waves were analyzed as potential confounders. We also extracted data on highest level of educational qualifications (except in ABCD, where all participants were still in education) and socioeconomic status (SES); these may act as mediators rather than confounders (i.e. if they are influenced by parental/grandparental depression and in turn

affect opportunities for cognitive development in offspring), and their potential role was evaluated by adding them as additional covariates in sensitivity analyses. For the purpose of secondary analyses, we classified participants according to whether they had a lifetime history of depression or of neurological disorders that may affect cognitive performance (see eMethods).

Statistical Analyses

Analyses were conducted in Stata[18] v15 or v17 and took account of complex survey structure and relatedness in the datasets using weighting and cluster standard errors. Descriptive statistics are reported for the whole sample and split by family history status. The validity of the familial risk exposure measures was checked by examining their association with lifetime history of depression in the analysis sample. Analyses of the association between familial risk of depression and cognitive outcome were conducted using unadjusted and adjusted regression models. All but one of the cognitive outcome measures were z-scores, so these were analyzed in linear models and the coefficients can be interpreted as standardized mean differences in cognitive score per unit of the exposure. The Prospective Memory score in UK Biobank was binary, so this was analyzed in a logistic model with results expressed as the odds ratio (OR) for a correct response per unit of the exposure. We report 95% confidence intervals (CI), and two-tailed *P* values are reported with and without correction for multiple comparisons (false discovery rate [FDR] maintained at .05). Full details of all models are provided in the eMethods.

Results

Characteristics of the Samples

Demographic, health, and family history characteristics in each cohort are summarized in Table 1. Further descriptive statistics for all measures, stratified by family history status, are provided in eTables 1-4. The validity of the family history and PRS exposures was demonstrated by their clear associations with lifetime depression history in each analysis sample (see eResults).

Association Between Family History of Depression and Cognitive Outcomes

Three Generations

Sample sizes were small and so estimates have relatively wide confidence intervals and should be interpreted with caution. In the primary adjusted models (parental history of depression; Figure 1), the only task with an estimate tending towards lower performance was dual-task decrement, with an effect size of medium magnitude. Additional adjustment for SES showed similar results on most tasks, but shifted the results for IQ in a positive direction (eFigure 1(C) in Supplement). Using the dose exposure measure, the specific contrast analysis between the subgroups with both versus neither prior generations affected was strongest for dual-task decrement (eFigure 2(B)). The exclusion of individuals with depression attenuated some estimates towards the null, with the exception of the visual delayed memory task (eFigure 3(A)). After taking account of missing data, results again suggested possibly lower performance on some attention/executive tasks (eFigure 4). It was not possible to conduct sensitivity analyses in an unrelated subgroup due to very small sample sizes.

ABCD

The primary adjusted models (parental history; Figure 2(A)) showed that performance on the picture memory task was lower in the group with a family history of depression, with verbal

memory, the memory composite score, and processing speed also suggestive of slightly lower performance. Effect sizes were very small. These differences attenuated towards the null after additional adjustment for SES (eFigure 5(B) in Supplement). Participants with a family history of depression showed relatively higher performance on vocabulary tasks in the unadjusted model and in the adjusted model including SES (eFigure 5). Compared with the primary models, the pattern of results across cognitive domains was similar in models that took into account grandparental as well as parental history, that excluded participants with depression or neurological disorders, that were restricted to unrelated participants, and that took account of missing data (eFigures 6-8).

Add Health

Delayed memory and the memory composite score showed suggestive evidence of lower performance in those with a family history (primary adjusted analysis for parental history, Figure 3(A)), with small effect sizes. This attenuated slightly after additional adjustment for education and SES (eFigure 9 in Supplement). Results were similar in secondary models taking into account grandparental history (eFigure 10), in models that excluded people with depression or neurological conditions (eFigure 11), and after accounting for missing data (eFigure 12(B)). In models restricted to unrelated participants, all estimates shifted towards the null or positive direction (eFigure 12(A)).

UK Biobank

Figure 4(A) shows associations in the primary adjusted analyses between family (parental) history and lower performance on tests of processing speed, attention and executive function. Effect sizes were very small. Results were essentially the same after additional adjustment for education and SES (eFigure 13 in Supplement). Results attenuated after excluding people

with depression (though still showed lower performance) but there was little or no evidence of attenuation after excluding those with neurological conditions (eFigure 14), or restricting to unrelated participants (eFigure 15(A)). Results were the same after accounting for missing data (eFigure 15(B)).

Association Between Polygenic Risk for Depression and Cognitive Outcomes

ABCD

Primary adjusted models in the White subgroup (Figure 2(B)) showed lower performance on picture memory, similar to the family history models, but also showed lower performance on picture vocabulary and a tendency towards lower performance on other tasks except verbal memory. Effect sizes were very small. After additional adjustment for SES (eFigure 16(B) in Supplement), the picture memory result was essentially unchanged but the vocabulary estimates attenuated towards the null. Results were virtually the same in the larger multi-ancestry sample (eFigure 17). Compared with the primary models, results were almost the same in models that excluded participants with depression or neurological disorders, that were restricted to unrelated participants, and that took account of missing data (eFigures 18 and 19).

Add Health

Primary adjusted models in the European subgroup (Figure 3(B)) showed no association with memory performance, but there was a positive association of small magnitude on the attention task (digit span) that had not been evident in the family history analyses. This remained evident after additional adjustment for education and SES (eFigure 20 in Supplement), and was also seen in the larger multi-ancestry sample (eFigure 21). Excluding participants with depression or neurological disorders, restricting to unrelated participants,

and taking account of missing data did not make any appreciable difference to the results (eFigures 22 and 23).

UK Biobank

Lower performance was seen on all but two of the cognitive tests in the primary adjusted models (Figure 4(B)). The general pattern of performance across domains was quite similar compared with the family history results, with similarly small effect sizes, but several tasks showed statistically significant associations in the PRS analysis only (reasoning, digit span, memory). Additional adjustment for education and SES did not change the results (eFigure 24 in Supplement); nor did excluding participants with depression or neurological disorders (eFigure 25), restricting to unrelated participants (eFigure 26(A)) or accounting for missing data (eFigure 26(B)).

Discussion

This study provides evidence for lower cognitive performance in people with familial risk of depression, which appears to manifest differently across the lifespan. In the younger cohorts (primarily ABCD and Add Health), family history of depression was associated with lower performance in the memory domain, albeit inconsistently, and there were indications that this may be partly related to educational and socioeconomic factors. In contrast, family history in the older UK Biobank cohort was associated with lower performance in the domains of processing speed, attention and executive function, but not memory, and there was little evidence of an influence of education or SES. Although there was a dose effect for depression itself, with participants with two prior generations affected showing greater odds of depression, this effect was not clearly evident with regard to the strength of association with cognitive performance.

The largest effect sizes were found in TGS, albeit with wider confidence intervals due to the small sample size. Effect sizes in the other cohorts were smaller than in TGS and the previous systematic review.[5] Larger effect sizes in TGS may reflect the gold-standard assessments used for both family history and cognitive testing, which increases measurement reliability, as well as the strict eligibility criteria in the first generation at cohort inception. The other cohorts had broader inclusion criteria and relied on responses from the participant or their parent to retrospective questions about family history; similarly, the PRS were created from GWAS of a broad depression phenotype. These factors may have biased associations towards the null, although the large sample sizes nevertheless enabled weaker associations to be detected from less reliable measures. This demonstrates the value of using population cohorts for this type of research, where gold-standard phenotyping is not feasible at such a large scale. A major strength of our study is that we have used small-scale, carefully phenotyped data alongside big datasets with less detailed phenotyping. Using only the former may mean that results might not be replicable, while using only the latter risks generating large numbers of statistically significant yet trivial results that are not clinically meaningful.

This study is the first to examine both polygenic risk and family history of depression in multiple cohorts: we found that both exposures showed similar results, although the PRS models tended to show associations with lower performance on a greater number of cognitive tests. An exception was the digit span test in Add Health, on which higher PRS was associated with better performance. We did not directly compare the contribution of family history and polygenic risk in the same models, and so we cannot infer the relative strength of their distinct associations with cognitive outcome. This would require detailed multivariate modelling to take account of the mediating paths between genetic and non-genetic aspects of family history, and their interactions.

The memory domain findings in the younger cohorts are congruent with neuroimaging markers in depression that also underpin memory function: hippocampal volumes are lower on average[19] and cortical gray matter is thinner on average in various regions including the temporal lobes[20] in people with depression, and we have previously shown in TGS that family history of depression is associated with hippocampal microstructure differences,[21] cortical thinning,[22] and default mode network hyperconnectivity.[23] The speed, attention, and executive function findings in the older UK Biobank cohort may point to differences in brain aging (e.g. white matter disease), even in never-depressed participants, although evidence is currently lacking on neuroimaging in older people with high familial risk of depression and this should be investigated in future UK Biobank analyses. It should also be borne in mind that the different pattern of results in UK Biobank may not be fully attributable to older age, but rather to the other differences in the methods used in this cohort, including the use of a bespoke test battery with an emphasis on timed and executive function tasks.

There was little impact on the results after excluding participants who themselves had depression. Only UK Biobank showed clear evidence of attenuation in those models, but not enough to negate the findings. This suggests that lifetime experience of depression may have some influence on cognitive outcomes, especially in older participants, but other factors must be at play.

Education and SES may explain some of the association: this was evident in the three younger cohorts and may reflect a mediating role of household/neighborhood environment, resource access and opportunities, in influencing cognitive development and reserve, in families affected by parental or multi-generational depression. This warrants further research within a mediation framework, with important implications for early intervention on potentially modifiable intermediate risk factors.

Limitations

The four cohorts we analyzed have various strengths and limitations with regard to sample size, representativeness, and depth and completeness of measures, which means that it is difficult to disentangle age-related and generational effects from methodological differences when interpreting the patterns of findings. TGS was the only cohort with clinically confirmed depression diagnoses in all generations, but PRS data are not available at present in this cohort. We focused on biological family history and so have not captured the influence of non-biological relatives, such as step-parents, in the household. It would also be of interest to analyze the number of affected biological relatives in detail (e.g. whether one or both parents had a depression history), but this was not feasible owing to the amount of missing data. We aimed to analyze exposures and outcomes from different assessment waves (to reduce the possibility of reverse causality and allow for future mediation analyses to examine intermediate measures such as brain imaging) but data from different waves were not available in Add Health.

Conclusions

Whether assessed by family history or genetic data, there is evidence that depression in prior generations is associated with lower cognitive performance in offspring. The next challenge is to elucidate the pathways by which this arises, which may include genetic and environmental determinants and moderators of brain development and brain aging, and potentially modifiable social and lifestyle factors at play across the lifespan. These and other cohorts enable such research at a scale and depth never before possible, opening new research directions for prevention and early intervention in at-risk individuals.

Acknowledgements

Conflicts of Interest

M.M. Weissman in the last three years has received research funding from NIMH, Brain and Behavior Foundation, and Templeton Foundation, and has received book royalties from Perseus Press, Oxford Press, and APA Publishing, and receives royalties on the Social Adjustment Scale from Multihealth Systems; none of these represent a conflict of interest. All other authors declare that they have no conflicts of interest.

Author Contributions

Dr Cullen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cullen, van Dijk, Weissman.

Acquisition, analysis, or interpretation of data: All authors.

Statistical analysis: Cullen.

Drafting of the manuscript: Cullen.

Critical revision of the manuscript for important intellectual content: All authors.

Approval of final version: All authors.

Obtained funding: Cullen, Weissman.

Administrative, technical, or material support: Ward, Gameroff.

Funding/Support

This work was supported in part by grant DTF/14/03 from the Scottish Executive Chief Scientist Office (PI: B. Cullen), and grant R01MH036197 from the National Institute of Mental Health (PI: M.M. Weissman). L.M. Lyall is supported by a JMAS Sim Fellowship from the Royal College of Physicians of Edinburgh and a Lord Kelvin Adam Smith

Fellowship from the University of Glasgow. N. MacSweeney is supported by a Mental Health Research UK PhD Studentship. R.J. Strawbridge is supported by a UK Research and Innovation Health Data Research-UK Fellowship MR/S003061/1 and a Lord Kelvin Adam Smith Fellowship from the University of Glasgow. M.T. van Dijk is funded by National Institute of Mental Health K99MH129611 and AFSP Young Investigator Award YIG-R-001-19.

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information

ABCD

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development[SM] (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete

listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from Annual Release 4.0 (study number 1299). NIMH Data Archive Digital Object Identifier (DOI) http://dx.doi.org/10.15154/1528043.

Add Health

Add Health is directed by Robert A. Hummer and funded by the National Institute on Aging cooperative agreements U01 AG071448 (Hummer) and U01 AG071450 (Aiello and Hummer) at the University of North Carolina at Chapel Hill. Waves I-V data are from the Add Health Program Project, grant P01 HD31921 (Harris) from Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), with cooperative funding from 23 other federal agencies and foundations. Add Health was designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill.

UK Biobank

This research has been conducted using the UK Biobank Resource under Application Number 11332 (PI: Cullen). UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government, and the Northwest Regional Development Agency. It has also had funding from the Welsh Government, British Heart Foundation, Cancer Research UK, and Diabetes UK.

Data Availability

Data from the Three Generations cohort are not yet available for sharing as the study is still ongoing; these data will become available after 2023. ABCD is an open access resource and access procedures are described at https://abcdstudy.org/scientists/data-sharing/. Add Health is an open access resource and access procedures are described at https://addhealth.cpc.unc.edu/data/. UK Biobank is an open access resource and access procedures are described at https://www.ukbiobank.ac.uk/enable-your-research. The statistical analysis code for the ABCD, Add Health and UK Biobank analyses in this study is available at https://osf.io/tngqh/.

References

1. Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J Affect Disord.* 2012;140(2):113-124.

2. Bora E, Harrison BJ, Yucel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med.* 2013;43(10):2017-2026.

3. Cambridge OR, Knight MJ, Mills N, Baune BT. The clinical relationship between cognitive impairment and psychosocial functioning in major depressive disorder: A systematic review. *Psychiatry Res.* 2018;269:157-171.

4. Evans VC, Iverson GL, Yatham LN, Lam RW. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. *J Clin Psychiatry.* 2014;75(12):1359-1370.

5. MacKenzie LE, Uher R, Pavlova B. Cognitive Performance in First-Degree Relatives of Individuals With vs Without Major Depressive Disorder: A Meta-analysis. *JAMA Psychiatry.* 2019;76(3):297-305.

6. Weissman MM, Berry OO, Warner V, et al. A 30-Year Study of 3 Generations at High Risk and Low Risk for Depression. *JAMA Psychiatry.* 2016;73(9):970-977.

7. Garavan H, Bartsch H, Conway K, et al. Recruiting the ABCD sample: Design considerations and procedures. *Dev Cogn Neurosci.* 2018;32:16-22.

8. van Dijk MT, Murphy E, Posner JE, Talati A, Weissman MM. Association of Multigenerational Family History of Depression With Lifetime Depressive and Other

519 Psychiatric Disorders in Children: Results from the Adolescent Brain Cognitive
520 Development (ABCD) Study. *JAMA Psychiatry.* 2021;78(7):778-787.

521 9. Shen X, Howard DM, Adams MJ, et al. A phenome-wide association and Mendelian
522 Randomisation study of polygenic risk for depression in UK Biobank. *Nat Commun.*
523 2020;11(1):2301.

524 10. Tomasi D, Volkow ND. Associations of family income with cognition and brain
525 structure in USA children: prevention implications. *Mol Psychiatry.*
526 2021;26(11):6619-6629.

527 11. Harris KM, Halpern CT, Whitsel EA, et al. Cohort Profile: The National Longitudinal
528 Study of Adolescent to Adult Health (Add Health). *Int J Epidemiol.* 2019;48(5):1415-
529 1415k.

530 12. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for
531 identifying the causes of a wide range of complex diseases of middle and old age.
532 *PLoS Med.* 2015;12(3):e1001779.

533 13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of
534 Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting
535 observational studies. *Ann Intern Med.* 2007;147(8):573-577.

536 14. Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium
537 Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet.* 2015;97(4):576-592.

538 15. Howard DM, Adams MJ, Clarke TK, et al. Genome-wide meta-analysis of depression
539 identifies 102 independent variants and highlights the importance of the prefrontal
540 brain regions. *Nat Neurosci.* 2019;22(3):343-352.

16. Braudt D, Harris KM. Polygenic Scores (PGSs) in the National Longitudinal Study of Adolescent to Adult Health (Add Health) – Release 2. https://addhealth.cpc.unc.edu/wp-content/uploads/docs/user_guides/WaveIVPGSRelease2UserGuide.pdf. Published 2020. Accessed June 5, 2022.

17. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet.* 2018;50(5):668-681.

18. StataCorp. *Stata Statistical Software.* College Station, TX: StataCorp LLC; 2021.

19. Schmaal L, Veltman DJ, van Erp TG, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry.* 2016;21(6):806-812.

20. Schmaal L, Hibar DP, Samann PG, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. *Mol Psychiatry.* 2017;22(6):900-909.

21. van Dijk MT, Cha J, Semanek D, et al. Altered Dentate Gyrus Microstructure in Individuals at High Familial Risk for Depression Predicts Future Symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2021;6(1):50-58.

22. Hao X, Talati A, Shankman SA, et al. Stability of Cortical Thinning in Persons at Increased Familial Risk for Major Depressive Disorder Across 8 Years. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2017;2(7):619-625.

563 23. Posner J, Cha J, Wang Z, et al. Increased Default Mode Network Connectivity in
564 Individuals at High Familial Risk for Depression. *Neuropsychopharmacology.*
565 2016;41(7):1759-1767.
566

567

Figure Legends

Figure 1. Association Between Familial Risk of Depression and Cognitive Function in the Three Generations Cohort (age 6-38y)

Primary family history exposure (at least one parent with depression versus none), adjusted for age, sex, ethnicity, and duration between exposure and outcome measurement.

Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. FDR correction was applied across the set of *P* values within the forest plot.

Abbreviations: Attn/Exec, Attention & Executive; Aud/Ver, Auditory/Verbal; CI, confidence interval; Comm. Err., commission errors; comp., composite; CPT, Continuous Performance Test; C-W Interf., color-word interference; Decr., decrement; FDR, false discovery rate; Immed., immediate; IQ, intelligence quotient; RT, reaction time.

Figure 2. Association Between Familial Risk of Depression and Cognitive Function in the ABCD Cohort (age 10-13y)

(A) Primary family history exposure (at least one parent with depression versus none), adjusted for age, sex, ethnicity, birth country, duration between exposure and outcome measurement, and mode of cognitive test administration (in-person or remote). (B) Polygenic risk score for depression, in the White subgroup, adjusted for age, sex, birth country, mode of cognitive test administration, and first 10 genetic principal components.

Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. FDR correction was applied across the set of *P* values within each forest plot. *P* values reported as 0.000 in the figure should be taken as $P<.001$.

Abbreviations: CI, confidence interval; comp., composite; FDR, false discovery rate; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

Figure 3. Association Between Familial Risk of Depression and Cognitive Function in the Add Health Cohort (age 32-42y)

(A) Primary family history exposure (at least one parent with depression versus none), adjusted for age, sex, ethnicity, and birth country. (B) Polygenic risk score for depression, in the European subgroup, adjusted for age, sex, birth country, and first 10 genetic principal components.

Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. FDR correction was applied across the set of *P* values within each forest plot.

Abbreviations: CI, confidence interval; FDR, false discovery rate; immed., immediate.

Figure 4. Association Between Familial Risk of Depression and Cognitive Function in the UK Biobank Cohort (age 44-83y)

(A) Primary family history exposure (at least one parent with depression versus none), adjusted for age, sex, ethnicity, birth country, and duration between exposure and outcome measurement. (B) Polygenic risk score for depression, in the White British subgroup, adjusted for age, sex, birth country, first 10 genetic principal components, and batch.

Some tests were added to the battery part-way through the assessment wave and so sample sizes vary. The 8-pair version of the Visual Memory task was only administered to participants who had made ≤2 errors on the 6-pair version. Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. FDR correction was applied across

the set of *P* values within each forest plot as well as the Prospective Memory results. *P* values reported as 0.000 in the figure should be taken as $P<.001$. Prospective Memory results are not shown in plots as these are expressed as odds ratios for a correct response: family history OR 1.01 (95% CI 0.93 to 1.10, $P=.79$, $P_{FDR}=.91$); polygenic risk score OR 0.95 (95% CI 0.92 to 0.97, $P<.001$, $P_{FDR}<.001$).

Abbreviations: assoc., associates; Attn/Exec, Attention & Executive; CI, confidence interval; comp., composite; FDR, false discovery rate; Proc., Processing.

Table 1. Demographic, Health, and Family History Characteristics in Each Cohort

	Three Generations (n=87)[a]	ABCD (n=10,258)[a]	Add Health (n=1,064)[a,b]	UK Biobank (n=45,899)[a]
Demographics				
Age at baseline				
No. missing	27[c]	0	NA	0
Mean (SD), y	14.22 (4.98)	9.92 (0.63)	NA	55.02 (7.55)
Age at follow-up				
No. missing	0	0	0	0
Mean (SD), y	19.71 (6.55)	12.00 (0.66)	37.75 (1.88)	63.99 (7.71)
Duration from baseline to follow-up				
No. missing	27	0	NA	0
Mean (SD), y	7.84 (1.69)	2.08 (0.22)	NA	8.97 (1.78)
Sex, No. (%)				
No. missing	0	0	0	0
Female	42 (48)	4,899 (48)	584 (49)	23,605 (51)
Male	45 (52)	5,359 (52)	480 (51)	22,294 (49)
College degree, No. (%)				
No. missing	35[d]	NA	0	747
Yes	11 (21)	NA	415 (36)	21,154 (47)
Health Status				
Lifetime depression, No. (%)				
No. missing	0	184	2	0
Yes	18 (21)	662 (7)	347 (24)	5,507 (12)
Lifetime neurological condition, No. (%)				
No. missing	0	0	0	0
Yes	12 (14)	1,558 (15)	17 (2)	2,212 (5)
Family History of Depression				
Parental history, No. (%)				
No. missing	12	566	185	4,415
At least one parent with depression	21 (28)	3,059 (32)	344 (41)	4,401 (11)
Multi-generation history, No. (%)				
No. missing	6	570	293	NA
At least one parent or grandparent with depression	53 (65)	4,447 (46)	392 (54)	NA
Multi-generation 'dose', No. (%)				
No. missing	12	901	427	NA
Neither generation	28 (37)	5,241 (56)	379 (56)	NA
Grandparent only	26 (35)	1,324 (14)	34 (5)	NA
Parent only	8 (11)	1,026 (11)	122 (23)	NA
Both generations	13 (17)	1,766 (19)	102 (16)	NA

Abbreviations: ABCD, Adolescent Brain Cognitive Development study; Add Health, National Longitudinal Study of Adolescent to Adult Health; NA, not applicable; No., number; SD, standard deviation.

Note: Ethnic categories, birth country categories, socioeconomic status measures, and cognitive measures were different in each cohort and so are presented separately in eTables 1-4 in the Supplement. Descriptive statistics for polygenic scores are also provided in the eTables.

a. Total sample size refers to participants with data on at least one cognitive test. Within that, sample sizes available for analysis varied from model to model, depending on which exposure measures and covariates were being analyzed.

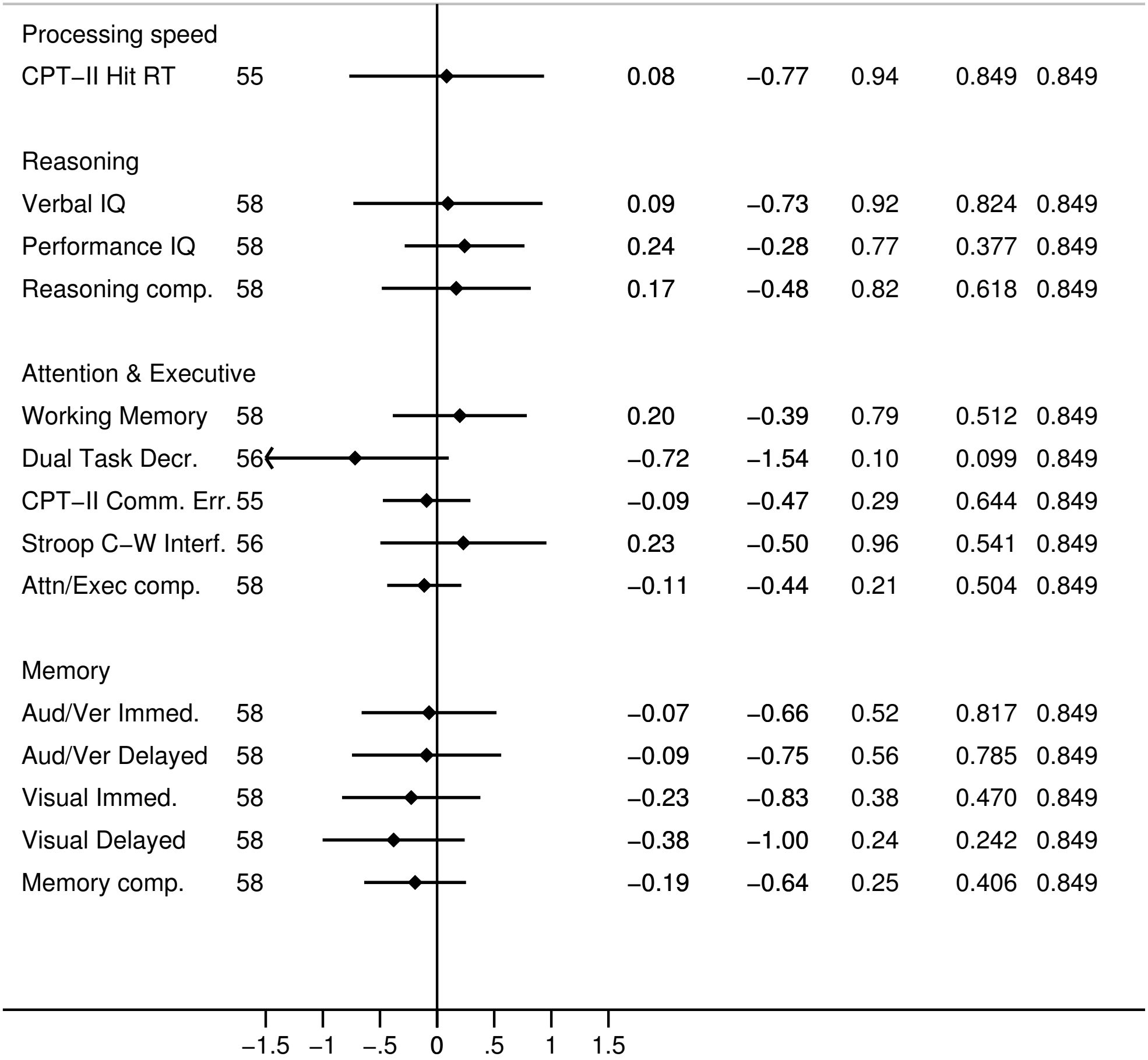
b. Summary statistics (%, mean, SD) are weighted using svy commands in Stata. Sample sizes are reported as observed (unweighted).

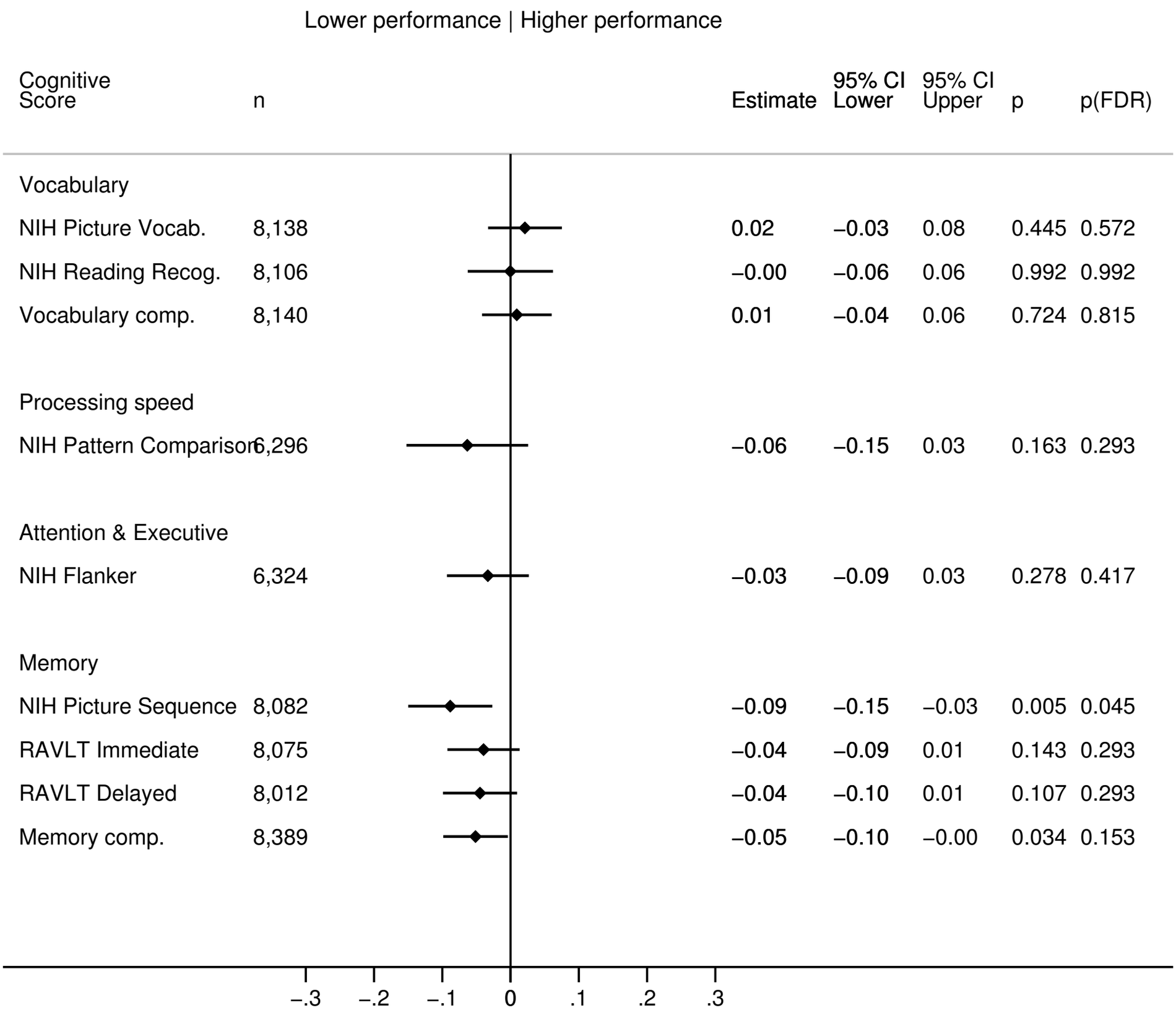
c. Some participants did not attend Wave 5 themselves but did have family history data from their relatives at Wave 5 and so were included in the analysis sample.

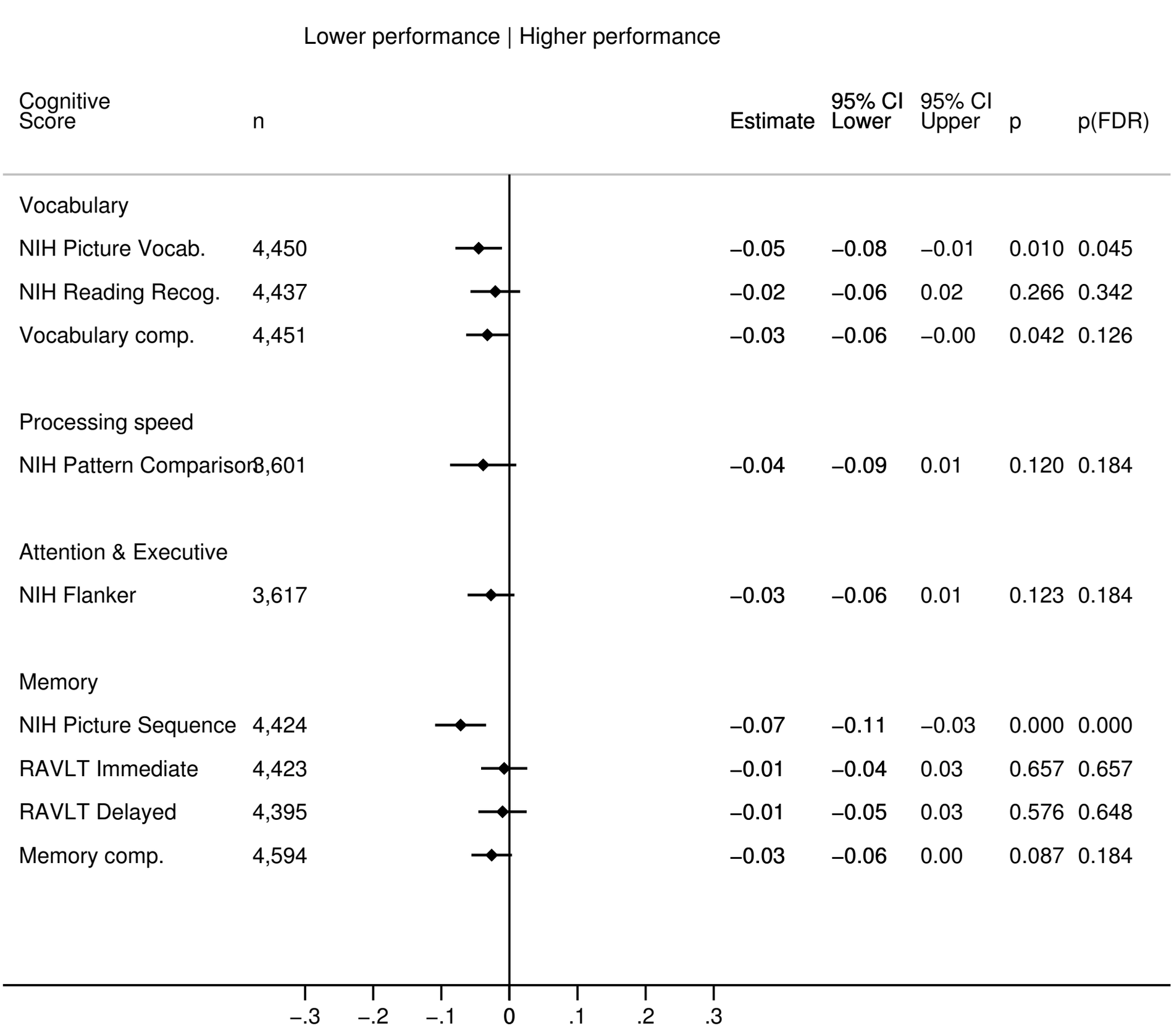
d. Only available for adult participants.

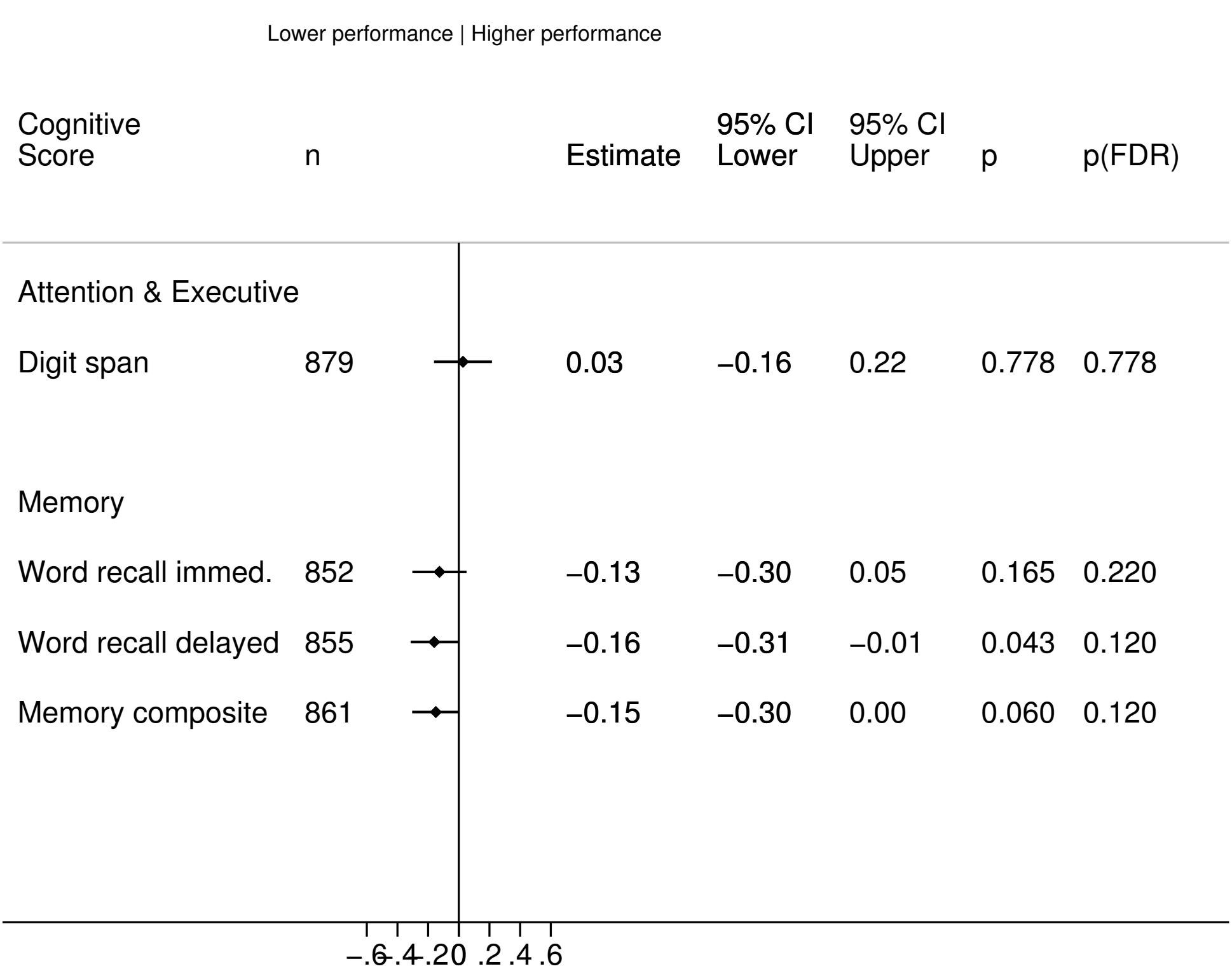
Lower performance | Higher performance

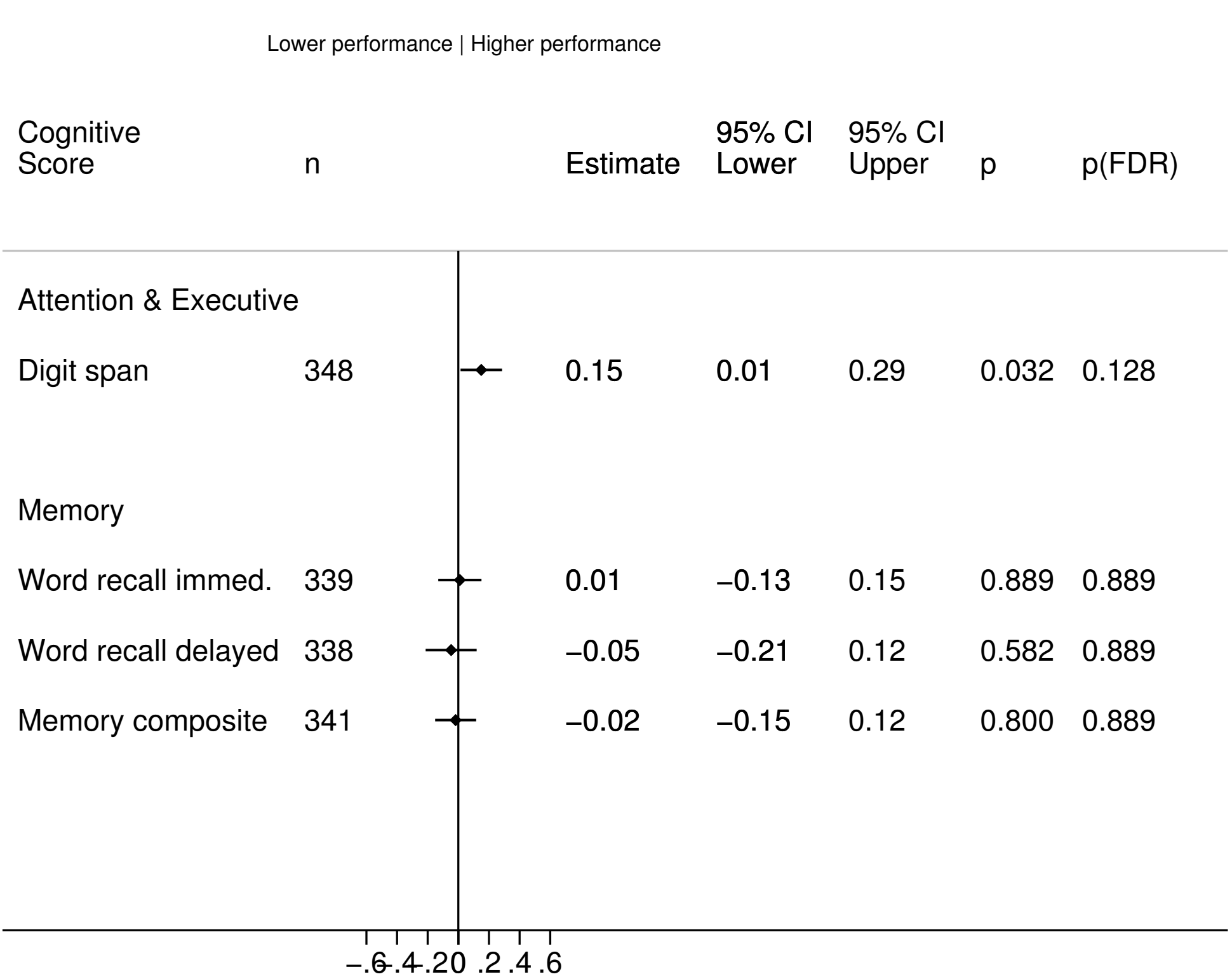
Cognitive Score	n	Estimate	95% CI Lower	95% CI Upper	p	p(FDR)
Processing speed						
CPT−II Hit RT	55	0.08	−0.77	0.94	0.849	0.849
Reasoning						
Verbal IQ	58	0.09	−0.73	0.92	0.824	0.849
Performance IQ	58	0.24	−0.28	0.77	0.377	0.849
Reasoning comp.	58	0.17	−0.48	0.82	0.618	0.849
Attention & Executive						
Working Memory	58	0.20	−0.39	0.79	0.512	0.849
Dual Task Decr.	56	−0.72	−1.54	0.10	0.099	0.849
CPT−II Comm. Err.	55	−0.09	−0.47	0.29	0.644	0.849
Stroop C−W Interf.	56	0.23	−0.50	0.96	0.541	0.849
Attn/Exec comp.	58	−0.11	−0.44	0.21	0.504	0.849
Memory						
Aud/Ver Immed.	58	−0.07	−0.66	0.52	0.817	0.849
Aud/Ver Delayed	58	−0.09	−0.75	0.56	0.785	0.849
Visual Immed.	58	−0.23	−0.83	0.38	0.470	0.849
Visual Delayed	58	−0.38	−1.00	0.24	0.242	0.849
Memory comp.	58	−0.19	−0.64	0.25	0.406	0.849




Lower performance | Higher performance
Cognitive Score
n
Estimate
95% CI Lower
95% CI Upper
p
p(FDR)
Vocabulary
NIH Picture Vocab. 8,138 0.02 −0.03 0.08 0.445 0.572
NIH Reading Recog. 8,106 −0.00 −0.06 0.06 0.992 0.992
Vocabulary comp. 8,140 0.01 −0.04 0.06 0.724 0.815
Processing speed
NIH Pattern Comparison 6,296 −0.06 −0.15 0.03 0.163 0.293
Attention & Executive
NIH Flanker 6,324 −0.03 −0.09 0.03 0.278 0.417
Memory
NIH Picture Sequence 8,082 −0.09 −0.15 −0.03 0.005 0.045
RAVLT Immediate 8,075 −0.04 −0.09 0.01 0.143 0.293
RAVLT Delayed 8,012 −0.04 −0.10 0.01 0.107 0.293
Memory comp. 8,389 −0.05 −0.10 −0.00 0.034 0.153
−.3
−.2
−.1
0
.1
.2
.3

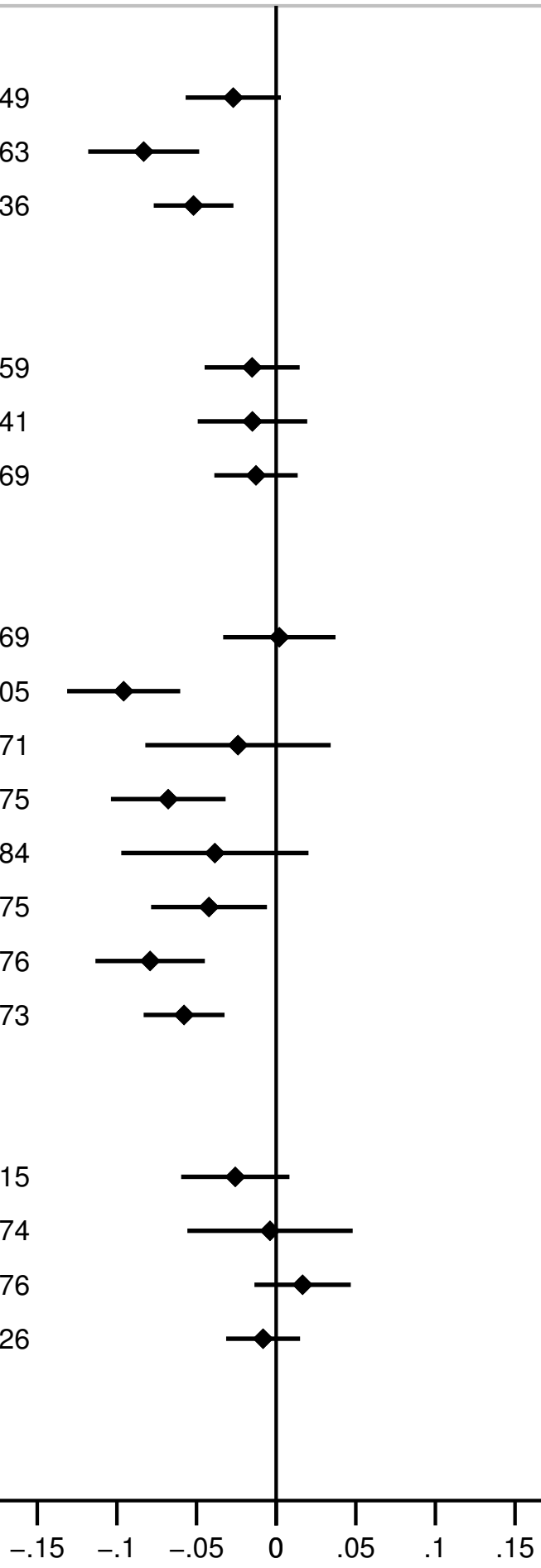

Lower performance | Higher performance
Cognitive Score
n
Estimate
95% CI Lower
95% CI Upper
p
p(FDR)
Vocabulary
NIH Picture Vocab. 4,450 −0.05 −0.08 −0.01 0.010 0.045
NIH Reading Recog. 4,437 −0.02 −0.06 0.02 0.266 0.342
Vocabulary comp. 4,451 −0.03 −0.06 −0.00 0.042 0.126
Processing speed
NIH Pattern Comparison 3,601 −0.04 −0.09 0.01 0.120 0.184
Attention & Executive
NIH Flanker 3,617 −0.03 −0.06 0.01 0.123 0.184
Memory
NIH Picture Sequence 4,424 −0.07 −0.11 −0.03 0.000 0.000
RAVLT Immediate 4,423 −0.01 −0.04 0.03 0.657 0.657
RAVLT Delayed 4,395 −0.01 −0.05 0.03 0.576 0.648
Memory comp. 4,594 −0.03 −0.06 0.00 0.087 0.184
−.3
−.2
−.1
0
.1
.2
.3


Lower performance | Higher performance
Cognitive Score
n
Estimate
95% CI Lower
95% CI Upper
p
p(FDR)
Attention & Executive
Digit span 879 0.03 −0.16 0.22 0.778 0.778
Memory
Word recall immed. 852 −0.13 −0.30 0.05 0.165 0.220
Word recall delayed 855 −0.16 −0.31 −0.01 0.043 0.120
Memory composite 861 −0.15 −0.30 0.00 0.060 0.120
−.6 −.4 −.2 0 .2 .4 .6


Lower performance | Higher performance
Cognitive Score
n
Estimate
95% CI Lower
95% CI Upper
p
p(FDR)
Attention & Executive
Digit span 348 0.15 0.01 0.29 0.032 0.128
Memory
Word recall immed. 339 0.01 −0.13 0.15 0.889 0.889
Word recall delayed 338 −0.05 −0.21 0.12 0.582 0.889
Memory composite 341 −0.02 −0.15 0.12 0.800 0.889
−.6 −.4 −.2 0 .2 .4 .6

Lower performance | Higher performance

Cognitive Score	n	Estimate	95% CI Lower	95% CI Upper	p	p(FDR)
Processing speed						
Reaction time	41,149	−0.03	−0.06	0.00	0.077	0.173
Symbol−digit	29,863	−0.08	−0.12	−0.05	0.000	0.000
Proc. speed comp.	41,236	−0.05	−0.08	−0.03	0.000	0.000
Reasoning						
Verbal−numerical	40,659	−0.02	−0.04	0.01	0.322	0.476
Matrix patterns	29,841	−0.01	−0.05	0.02	0.396	0.504
Reasoning comp.	40,869	−0.01	−0.04	0.01	0.344	0.476
Attention & Executive						
Digit span	30,569	0.00	−0.03	0.04	0.911	0.911
Trails A time	29,805	−0.10	−0.13	−0.06	0.000	0.000
Trails A errors	29,871	−0.02	−0.08	0.03	0.420	0.504
Trails B time	29,075	−0.07	−0.10	−0.03	0.000	0.000
Trails B errors	29,684	−0.04	−0.10	0.02	0.200	0.360
Trails B−A time	29,075	−0.04	−0.08	−0.01	0.023	0.059
Tower test	29,576	−0.08	−0.11	−0.04	0.000	0.000
Attn/Exec comp.	30,873	−0.06	−0.08	−0.03	0.000	0.000
Memory						
Visual memory−6pairs	40,715	−0.03	−0.06	0.01	0.139	0.278
Visual memory−8pairs	16,174	−0.00	−0.06	0.05	0.885	0.911
Verbal paired assoc.	30,176	0.02	−0.01	0.05	0.282	0.461
Memory comp.	41,026	−0.01	−0.03	0.02	0.489	0.550



Lower performance | Higher performance

Cognitive Score	n	Estimate	95% CI Lower	95% CI Upper	p	p(FDR)
Processing speed						
Reaction time	38,656	0.00	−0.01	0.01	0.814	0.814
Symbol−digit	27,928	−0.03	−0.04	−0.02	0.000	0.000
Proc. speed comp.	38,743	−0.01	−0.02	−0.00	0.004	0.006
Reasoning						
Verbal−numerical	38,198	−0.03	−0.04	−0.02	0.000	0.000
Matrix patterns	27,917	−0.03	−0.04	−0.02	0.000	0.000
Reasoning comp.	38,401	−0.03	−0.04	−0.02	0.000	0.000
Attention & Executive						
Digit span	28,572	−0.02	−0.03	−0.01	0.002	0.003
Trails A time	27,873	−0.03	−0.04	−0.01	0.000	0.000
Trails A errors	27,932	0.00	−0.02	0.02	0.787	0.814
Trails B time	27,149	−0.05	−0.06	−0.03	0.000	0.000
Trails B errors	27,758	−0.03	−0.05	−0.02	0.000	0.000
Trails B−A time	27,149	−0.04	−0.05	−0.03	0.000	0.000
Tower test	27,682	−0.01	−0.03	−0.00	0.010	0.013
Attn/Exec comp.	28,865	−0.03	−0.03	−0.02	0.000	0.000
Memory						
Visual memory−6pairs	38,259	−0.03	−0.04	−0.02	0.000	0.000
Visual memory−8pairs	15,243	−0.02	−0.03	−0.00	0.034	0.038
Verbal paired assoc.	28,216	−0.01	−0.02	−0.00	0.013	0.016
Memory comp.	38,554	−0.02	−0.03	−0.01	0.000	0.000