Supplementary Material for Cullen et al. 'Cognitive Function in People with Familial Risk of Depression: Evidence from Four Cohorts Across the Lifespan'

eMethods

Cohort Information

Three Generations

A cohort comprising adult outpatients receiving treatment for moderate-severe depression and a comparison group of adults with no psychiatric illness history was established in 1982 in the New Haven area, Connecticut, US. First-generation probands from 91 families, and second- and third-generation offspring and their spouses, have been followed up over multiple assessment waves, with Wave 6 (the follow-up wave for the present study) taking place around 2015.[1] The analysis sample for the present study was the third-generation participants, so that family history data were available across two prior generations. The mean age of all third-generation participants was 18 years (SD 7) at Wave 6.[1] Study approvals were granted by the New York State Psychiatric Institute Institutional Review Board (IRB; protocol 6145). Adult participants provided written informed consent; child participants provided verbal assent and their parent provided written informed consent.

ABCD

The ABCD Study® includes 21 research sites across the US.[2] Probability sampling of schools was conducted within the catchment areas of the study sites, and more than 11,800 children aged 9-11 years were assessed at baseline between 2016 and 2018. Post-stratification propensity weights have been provided to calibrate ABCD weighted distributions to nationally representative controls from the American Community Survey. The present study used baseline and Year 2 follow-up data from Release 4.0. Participants were aged 10-13 years at follow-up. The ABCD study was approved centrally by the University of California San Diego IRB (reference 160091) and study sites obtained approval from their local IRBs. Children gave written assent and parents/caregivers gave written consent.

Add Health

A sample of 80 high schools and 52 middle schools from across the US was selected with unequal probability of selection.[3] Adolescents in grades 7 to 12 (age range 12-18; n=20,745) were assessed at baseline in 1994-95. Incorporating systematic sampling methods and implicit stratification into the Add Health study design ensured this sample is representative of US schools with respect to region of country, urbanicity, school size, school type, and ethnicity. The most recent assessment wave (Wave V) was conducted in 2016-18 when participants were aged 32-42 years. Participants provided written informed consent in accordance with the University of North Carolina School of Public Health IRB requirements. Ethical approval for the use of the data for the present study was granted by the University of Glasgow College of Medical, Veterinary and Life Sciences Ethics Committee (reference 20018013).

UK Biobank

UK Biobank recruited more than 502,000 adults from the general population across 22 centres in Great Britain between 2006 and 2010.[4] The target age range at baseline was 40 to 69 years and no other exclusion criteria were applied. Postal invitation lists were generated from National Health Service (NHS) registers, with a response rate of approximately 6%.[5] Follow-up data for the present study were taken from the first imaging visit ('Instance 2'; 2014-2022) when participants were aged 44-83 years. UK Biobank received approval as a research tissue bank from the UK National Health Service Research Ethics Committee (references 16/NW/0274, 11/NW/0382, and 21/NW/0157). Participants provided written informed consent.

Family History of Depression

In all cohorts, family history of other psychiatric conditions apart from depression was not taken into account and so both exposed and unexposed participants may have had such family history.

Three Generations

Participants in all generations in the cohort were assessed at each wave by trained interviewers, blind to the clinical status of the other generations, using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)[6] or the K-SADS for children.[7,8] Major depressive disorder (MDD) diagnoses were made by experienced clinicians using a best-estimate procedure, with an additional requirement of impaired functioning (mean Global Assessment Scale score ≤70), in order to maintain comparability between MDD definitions in the first generation and their offspring.[1] The family history exposure measures in the present study were based on the diagnoses of the parents and grandparents of the third-generation participants, up to and including Wave 5.

ABCD

At baseline, the parent of the ABCD participant was asked "Has ANY blood relative of your child ever suffered from 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?", and then indicated which relative(s) were affected.

Add Health

At Wave V, a subsample of Add Health participants who took part in an in-person interview ('Sample 2b')[9] was asked "Has your [biological mother/father/any of your biological grandparents] ever had depression?". Wave V also included an add-on study in which parents of Add Health participants were asked about family history of depression; preliminary analyses indicated that there was insufficient overlap between these data and the cognitive outcome data and so this was not considered further.

UK Biobank

In the computerized assessment at each in-person visit, participants were asked "Has/did your [mother/father] ever suffer from severe depression?". If the participant activated the Help button they were shown the message: "Answer this question for blood relations only". The information was collected from participants who indicated they were not adopted as a child and knew whether their natural mother [father] was still alive or had died. For the present study, data were taken from the baseline visit.

Polygenic Risk Scores in ABCD and UK Biobank

ABCD

DNA was extracted from saliva and genotyped by ABCD centrally on the NIDA SmokeScreen Array (Affymetrix, Santa Clara, CA, USA). Full details are described online at https://doi.org/10.15154/1503209. The LDpred[10] method of polygenic risk scoring requires linkage disequilibrium (LD) to be established in a discovery set of n=1000; as this was not feasible in the relatively small ABCD cohort, the discovery step was instead conducted in UK Biobank (see below) and applied to the ABCD data to generate the risk scores for ABCD participants using an infinitesimal model. We have previously shown the validity of this approach.[11] SNPs were filtered by minor allele frequency (MAF) >0.01, Hardy-Weinberg equilibrium $P>1x10^{-6}$, and imputation quality score >0.3.

UK Biobank

DNA was extracted from saliva and genotyped by UK Biobank centrally using the UK BiLEVE Axiom or the UK Biobank Axiom array (Affymetrix, Santa Clara, CA, USA). Full details of quality control and imputation have been published elsewhere.[12] SNPs were filtered by MAF >0.01, Hardy-Weinberg equilibrium $P>1x10^{-6}$, and imputation quality score >0.8. LDpred established the LD structure of the genome using a reference panel of 1000 unrelated White British UK Biobank participants (the discovery set). Scores were then created for the remaining UK Biobank participants using an infinitesimal model.

Cognitive Outcome Measures

Three Generations

These were taken from Wave 6 follow-up and were only available for participants who attended an in person visit. Tests were administered by trained assessors. Memory was assessed using the Wechsler Memory Scale (WMS-III)[13] or the Children's Memory Scale (CMS)[14] depending on participant age, yielding index scores for Auditory/Verbal Immediate, Auditory/Verbal Delayed, Visual Immediate, Visual Delayed, and Working Memory (represented by the CMS Numbers subtest score in children). Attention, speed and executive function were assessed using the Kinsbourne Dual Task decrement score,[15] Conners Continuous Performance Test (CPT-II)[16] Hit Reaction Time and Commission Errors, and Stroop Color-Word Interference.[17] Verbal and Performance intelligence quotient (IQ) were measured with the Wechsler Abbreviated Scale of Intelligence (WASI).[18] Scores were age-corrected using published norms where possible and converted into z-scores for analysis. Higher z-scores represent better performance.

ABCD

These were taken from the Year 2 follow-up. Five test scores were available from the National Institutes of Health NIH Toolbox®,[19] which is a well-validated computerized battery: Picture Vocabulary, Flanker Inhibitory Control & Attention, Pattern Comparison Processing Speed, Picture Sequence Memory, and Oral Reading Recognition. These scores were age-corrected centrally by ABCD and for the purpose of present study were converted into z-scores (higher = better). Raw scores were also available for a computerized version of the Rey Auditory Verbal Learning Test (RAVLT) Immediate Recall and Delayed Recall.[20] These were converted into z-scores based on the analysis sample distribution (higher = better). The Year 2 wave overlapped with COVID-19 restrictions and so the mode of test administration was a mix of in person and remote; this was accounted for in the analyses by covarying for administration mode.

Add Health
These were taken from Wave V and were only available systematically for participants who completed in person assessments as part of 'Sample 2b'. Trained assessors administered brief bespoke tests of word recall (immediate and delayed recall of a 15-word list presented once) and backward digit span.[21] Raw scores provided by Add Health were converted into z-scores based on the analysis sample distribution (higher = better).

UK Biobank
These were taken from the imaging follow-up visit. The battery comprised self-administered computerized touchscreen tests of processing speed (Reaction Time and Symbol-Digit Substitution), Reasoning (Verbal-Numerical Reasoning [referred to as 'Fluid Intelligence' by UK Biobank] and Matrix Pattern Completion), attention and executive function (Digit Span ['Numeric Memory'], Trails A and B, Tower Test), and memory (Visual Pairs Matching, Verbal Paired Associates, Prospective Memory). The content, administration and psychometric properties of these tests have been reported previously.[22,23] Raw scores provided by UK Biobank were standardized within five-year age strata into z-scores (higher = better). It was not possible to standardize the prospective memory data in this way because responses were dichotomized (correct response at the first attempt or not), and so the raw data were used in the analyses involving this test.

We also analyzed a composite score for each cognitive domain in each cohort (calculated as the mean of the separate z-scores in that domain, provided there were at least two separate tests available in that domain).

Covariate Measures

Three Generations
Data were available on age in years, sex (female or male), and self-identified ethnic group (coded as non-Hispanic White or not). All participants were US-native English speakers. Educational qualifications were recorded on the SADS (administered to adults only) and dichotomized according to whether participants held at least a bachelor's degree or not; this was taken from Wave 6 to maximize the adult-age sample size. Socioeconomic status (SES) was indexed by the head-of-household Hollingshead occupational prestige code taken from the Wave 6 SADS or informant-reported K-SADS; responses were ordinal categories from 1 (Higher executive proprietor of large concern, major professional) to 8/9 (Never worked in paid employment/Homemaker who never worked). Participants' lifetime history of depression (best-estimate diagnosis of MDD) was derived from the SADS or informant-reported K-SADS up to and including Wave 6. Participants' lifetime history of neurological disorders was derived from medical checklist data up to and including Wave 6, covering multiple sclerosis, epilepsy, encephalitis, head injury, meningitis, and stroke.

ABCD
Data were available on age in months (converted to years for analysis), sex (female or male), self-identified ethnic group (coded as Asian, Black, Hispanic, Other, White), and country of birth (re-coded as born in US or not). SES at baseline was represented by total family income in the past year, as this has been reported to best correlate with cognitive function in this cohort;[24] responses were ordinal categories from 1 (Less than $5,000) to 10 ($200,000 and greater). Participants' lifetime history of depression was derived from the parent-reported K-SADS lifetime MDD items at Year 2 follow-up. Derived diagnoses were not provided by ABCD in data release 4.0 owing to a data coding error, and so an approximation of the DSM-5 MDD diagnostic criteria was derived for the present study based on data regarding depressive symptoms and functional impairment (five or more symptoms AND the symptoms include at least one of the three core symptoms [depressed/irritable mood or anhedonia] AND impairment). Participants' lifetime history of neurological disorders was derived from data up to and including Year 2 follow-up on the Ohio State University Traumatic Brain Injury questionnaire[25] and a medical history questionnaire which asked about brain/head injury, cerebral palsy, epilepsy, and multiple sclerosis.

Add Health
Data were available on age in years, sex (female or male), and self-identified ethnic group (coded as American Indian or Alaska Native, Asian, Black/African-American, Hispanic, Multiple [selected more than one category], Pacific Islander, Some other race or origin, White). A separate variable was created from the genetic and self-reported data by Add Health centrally to represent genetic ancestry (coded as African, East Asian, European, Hispanic). A binary variable indicated whether participants were born in the US or not. Educational qualifications were dichotomized according to whether participants held at least a college degree or not. SES was represented in two ways: household income was recorded as ordinal categories from 1 (less than $5,000) to 13 ($200,000 and greater), and self-perceived socioeconomic rank was recorded on an ordinal scale from 1 to 10 in response to the question "Think of this ladder as representing where people stand in the United States. At the top of the ladder (step 10) are the people who have the most money and education, and the most respected jobs. At the bottom of the ladder (step 1) are the people who have the least money and education, and the least respected jobs or no job. Where would you place yourself on this ladder? Pick the number for the step that

shows where you think you stand at this time in your life, relative to other people in the United States". Participants' lifetime history of depression was a yes/no response to the question "Has a doctor, nurse, or other health care provider ever told you that you have or had depression?". Participants' lifetime history of neurological disorders was only available with regard to stroke and related conditions, indicated by yes/no responses to the following questions: "Has a doctor, nurse, or other health care provider ever told you that you have or had a stroke, mini-stroke, or have you had surgery for clogged neck arteries (including endarterectomy, bypass, angioplasty or stent)?"; "For each of the following items, indicate whether or not you have ever had the injury or condition … A stroke".

UK Biobank

Data were available on age in years, sex (female or male), and self-identified ethnic group (coded as Asian/Asian British, Black/Black British, Chinese, Mixed or Other group, White). Participants who had self-reported a White British background were further grouped by UK Biobank centrally according to similarity of genetic ancestry based on principal components, to form a 'White British' subgroup for genetic analyses. Participants self-reported their birth country, and these were grouped according to whether or not English was an official/first language (UK, Isle of Man, Channel Islands, Gibraltar, Ireland, Australia, New Zealand, USA, Canada, Anguilla, Antigua & Barbuda, Aruba, Bahamas, Barbados, Bermuda), as per previous cognitive analyses in UK Biobank.[26] Self-reported data regarding participants' highest educational qualification were dichotomized as university/college degree or not. Neighborhood deprivation level (as an indicator of SES) was recorded by UK Biobank prior to baseline using the Townsend Index,[27] and this was converted into quintiles in the whole cohort (quintile 1 = least deprived). Participants' lifetime history of depression up to and including the date of the cognitive outcome assessment was based on the 'First Occurrence' fields created by UK Biobank to record ICD-10-equivalent diagnoses derived from linked health records and self-report, with history of depression represented by ICD-10 codes F32 or F33. Participants' lifetime history of neurological conditions up to and including the date of the cognitive outcome assessment was based on the same First Occurrences fields, and included any of the following: F00-F03 dementia; F70-F79 mental retardation; G00-G09 infection; G10 Huntington's disease; G20 Parkinson's disease; G30-G37 Alzheimer's disease, degenerative disorders, demyelinating disorders; G40-G41 epilepsy; G45-G46 cerebrovascular disease; G80 cerebral palsy; G91 hydrocephalus; G92 toxic encephalopathy; I60-I64 cerebrovascular disease.

Statistical Analyses

Different techniques were required to account for survey design, sampling weights and family clustering in each cohort. Three Generations does not have a complex survey structure so there are no weights; cluster standard errors took account of family ID. In ABCD, the survey weight was entered using the propensity weight option in the regression command, and cluster standard errors took account of family ID. The Add Health analyses followed the recommendations in the Add Health user guide,[28] using Stata's `svy` suite of commands to take account of sampling units and weights (Wave 5 Sample 2b cross-sectional weight); this weighting already takes account of family clusters in the sampling scheme. UK Biobank does not have sampling weights and there are no family ID variables, so this dataset was analyzed using unweighted regression with robust standard errors.

In all cohorts, the primary family history analysis used the binary exposure measure based on parents only. The binary and dose measures that also incorporated grandparents' history were used in secondary analyses. Models were run unadjusted, and adjusted for age, sex, ethnicity, country of birth, and duration between assessment waves. We also ran models with additional adjustment for education and SES; these were not in the core adjustment set because they may act as mediators rather than confounders in explaining part of the association between family history and outcome, and so caution is needed in interpreting their potential influence on the results. All primary models included participants regardless of personal history of depression or neurological conditions, and secondary analyses were run to compare results after excluding participants with such history. Sensitivity analyses were conducted to examine the influence of relatedness: in ABCD and Add Health, this was done by keeping one randomly-selected member within each family ID; in UK Biobank this was done by keeping one randomly-selected member within each cluster of third degree or closer relatives based on the genetic kinship coefficient; in Three Generations the sample size of unrelated participants (within family ID) was insufficient to run the models. Sensitivity analyses were also run to take account of missingness in the exposures and covariates using full information maximum likelihood (FIML) estimation, implemented in Stata's structural equation model functions.

The primary polygenic risk score (PRS) analyses were restricted to participants with White or European ethnicity/ancestry (see Covariate Measures above for definitions), because of potential biases with applying PRS derived from single-ancestry GWAS in multi-ancestry samples. The base models were adjusted for the first 10 genetic principal components (for population stratification) and genotyping batch where available. The main adjusted models additionally included age, sex, and country of birth. These adjustments are typical in PRS analyses, to increase statistical power and precision.[29] Further adjusted models checked for the influence of education and SES, as described above. Models were

run including related participants (with cluster-adjusted standard errors), and restricted only to unrelated participants as described above. Secondary analyses in ABCD and Add Health included all participants (multi-ancestry sample), with ethnic group included as a covariate; it was not possible to do this in UK Biobank as the genotyping imputation that was done in this cohort is not appropriate for multi-ancestry analysis. Further secondary and sensitivity analyses were conducted to exclude participants with depression or neurological conditions, and to account for missingness using FIML.

eResults

Descriptive Statistics for Each Cohort

The analysis sample in Three Generations was limited to third-generation members who attended Wave 6 in person for cognitive assessment (n=87); they were similar to the whole third-generation group (n=251[1]) with regard to age, but a greater proportion were male (52% vs 48%) and had attended post-high school education (40% vs 33%).

eTable 1. Three Generations Descriptive Statistics

	All Participants (n=87)	Has Family History of Depression[a] (n=21)	No Family History of Depression[a] (n=54)
Demographics & Health			
Age at Wave 5			
No. missing[b]	27	9	17
Mean (SD), y	14.22 (4.98)	15.20 (4.72)	14.11 (5.42)
Age at Wave 6			
No. missing	0	0	0
Mean (SD), y	19.71 (6.55)	20.78 (5.89)	18.89 (7.09)
Duration from Wave 5 to Wave 6			
No. missing	27	9	17
Mean (SD), y	7.84 (1.69)	7.98 (1.63)	7.69 (1.69)
Sex, No. (%)			
No. missing	0	0	0
Female	42 (48)	9 (43)	26 (48)
Male	45 (52)	12 (57)	28 (52)
Ethnic group, No. (%)			
No. missing	17	5	12
Non-Hispanic White	67 (96)	13 (81)	42 (100)
Other ethnic group	3 (4)	3 (19)	0 (0)
College degree, No. (%)			
No. missing[c]	35	7	25
Yes	11 (21)	1 (7)	10 (34)
Hollingshead, No. (%)			
No. missing	3	1	2
Categories 1-3[d]	45 (54)	4 (20)	36 (69)
Categories 4-6	39 (46)	16 (80)	16 (31)
Categories 7-9	0 (0)	0 (0)	0 (0)
Lifetime depression, No. (%)			
No. missing	0	0	0
Yes	18 (21)	7 (33)	9 (17)
Lifetime neurological condition, No. (%)			
No. missing	0	0	0
Yes	12 (14)	3 (14)	8 (15)
Familial Risk			
Parental history, No. (%)			
No. missing	12	0	0
At least one parent with depression	21 (28)	21 (100)	0 (0)
Multi-generation history, No. (%)			
No. missing	6	0	0
At least one parent or grandparent with depression	53 (65)	21 (100)	26 (48)

	All Participants (n=87)	Has Family History of Depression[a] (n=21)	No Family History of Depression[a] (n=54)
Multi-generation 'dose', No. (%)			
No. missing	12	0	0
Neither generation	28 (37)	0 (0)	28 (52)
Grandparent only	26 (35)	0 (0)	26 (48)
Parent only	8 (11)	8 (38)	0 (0)
Both generations	13 (17)	13 (62)	0 (0)
Cognitive Function[e]			
Auditory/Verbal Immediate			
No. missing	4	0	3
Mean (SD), z-score	0.20 (0.95)	0.12 (1.15)	0.27 (0.89)
Auditory/Verbal Delayed			
No. missing	3	0	3
Mean (SD), z-score	0.42 (0.85)	0.32 (0.98)	0.50 (0.81)
Visual Immediate			
No. missing	2	0	2
Mean (SD), z-score	0.18 (0.75)	0.02 (0.93)	0.19 (0.68)
Visual Delayed			
No. missing	3	0	3
Mean (SD), z-score	0.18 (0.85)	0.08 (0.83)	0.18 (0.88)
Working Memory			
No. missing	4	1	3
Mean (SD), z-score	0.19 (0.93)	0.12 (1.09)	0.17 (0.88)
Dual Task Decrement			
No. missing	5	1	4
Mean (SD), z-score	0.03 (0.96)	-0.19 (1.20)	0.10 (0.85)
CPT-II Hit Reaction Time			
No. missing	9	4	3
Mean (SD), z-score	0.51 (1.05)	0.50 (0.84)	0.48 (1.10)
CPT-II Commission Errors			
No. missing	9	4	3
Mean (SD), z-score	-0.23 (1.13)	-0.39 (0.74)	-0.17 (1.14)
Stroop Color-Word Interference			
No. missing	4	1	2
Mean (SD), z-score	0.04 (0.96)	0.16 (1.01)	0.02 (1.01)
Verbal IQ			
No. missing	0	0	0
Mean (SD), z-score	0.30 (0.97)	0.15 (1.11)	0.43 (0.98)
Performance IQ			
No. missing	0	0	0
Mean (SD), z-score	0.50 (0.83)	0.49 (0.69)	0.54 (0.92)
Reasoning domain composite			
No. missing	0	0	0
Mean (SD), z-score	0.40 (0.78)	0.32 (0.83)	0.49 (0.82)
Attention & Executive domain composite			
No. missing	0	0	0
Mean (SD), z-score	0.00 (0.56)	-0.09 (0.52)	0.02 (0.57)
Memory domain composite			
No. missing	2	0	2
Mean (SD), z-score	0.24 (0.66)	0.13 (0.78)	0.27 (0.62)

Abbreviations: CPT, Continuous Performance Test; IQ, intelligence quotient; No., number; SD, standard deviation.
a. Primary exposure based on parental history.
b. 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.
c. Only available for adult participants.
d. Hollingshead categories: 1=Higher exec proprietor of large concern, major professional; 2=Business manager of large concern, proprietor of medium sized business, lesser professional; 3=Admin personnel, owner of small independent business, minor professional, farm owner with large farm; 4=Clerical or sales worker, technician, owner of little business, farmer with medium farm; 5=Skilled manual, farmer with small farm; 6=Machine operator, semi-skilled, tenant farmer; 7=Unskilled, farm hand, welfare recipient, chronic unemployed; 8=Never worked in paid employment; 9=Homemaker who never worked. Categories have been combined in the table owing to low numbers in some categories.
e. On all tests, higher scores represent better performance.

eTable 2. ABCD Descriptive Statistics

	All Participants (n=10,258)	Has Family History of Depression[a] (n=3,059)	No Family History of Depression[a] (n=6,633)
Demographics & Health			
Age at baseline			
No. missing	0	0	0
Mean (SD), y	9.92 (0.63)	9.90 (0.63)	9.92 (0.62)
Age at Year 2 follow-up			
No. missing	0	0	0
Mean (SD), y	12.00 (0.66)	11.98 (0.66)	12.00 (0.66)
Duration from baseline to Year 2 follow-up			
No. missing	0	0	0
Mean (SD), y	2.08 (0.22)	2.08 (0.22)	2.08 (0.22)
Sex, No. (%)			
No. missing	0	0	0
Female	4,899 (47.76)	1,468 (47.99)	3,157 (47.60)
Male	5,359 (52.24)	1,591 (52.01)	3,476 (52.40)
Ethnic group, No. (%)			
No. missing	0	0	0
Asian	214 (2.09)	16 (0.52)	157 (2.37)
Black	1,386 (13.51)	359 (11.74)	931 (14.04)
Hispanic	2,056 (20.04)	507 (16.57)	1,452 (21.89)
Other ethnic group	1,073 (10.46)	374 (12.23)	622 (9.38)
White	5,529 (53.90)	1,803 (58.94)	3,471 (52.33)
Born in US, No. (%)			
No. missing	12	6	5
Yes	9,950 (97.11)	3,018 (98.85)	6,435 (97.09)
Family income, No. (%)			
No. missing	814	204	551
Less than $5,000	303 (3.21)	108 (3.78)	184 (3.03)
$5,000-$11,999	328 (3.47)	105 (3.68)	206 (3.39)
$12,000-$15,999	212 (2.24)	71 (2.49)	129 (2.12)
$16,000-$24,999	428 (4.53)	143 (5.01)	260 (4.27)
$25,000-$34,999	565 (5.98)	213 (7.46)	322 (5.29)
$35,000-$49,999	803 (8.50)	280 (9.81)	479 (7.88)
$50,000-$74,999	1,306 (13.83)	466 (16.32)	777 (12.78)
$75,000-$99,999	1,422 (15.06)	421 (14.75)	929 (15.27)
$100,000-$199,999	2,981 (31.57)	828 (29.00)	1,975 (32.47)
$200,000 and greater	1,096 (11.61)	220 (7.71)	821 (13.50)
Lifetime depression, No. (%)			
No. missing	184	58	114
Yes	662 (6.57)	349 (11.63)	265 (4.07)
Lifetime neurological condition, No. (%)			
No. missing	0	0	0
Yes	1,558 (15.19)	544 (17.78)	929 (14.01)
Familial Risk			
Parental history, No. (%)			
No. missing	566	0	0
At least one parent with depression	3,059 (31.56)	3,059 (100.00)	0 (0)
Multi-generation history, No. (%)			
No. missing	570	0	68
At least one parent or	4,447 (45.90)	3,059 (100.00)	1,324 (20.17)

	All Participants (n=10,258)	Has Family History of Depression[a] (n=3,059)	No Family History of Depression[a] (n=6,633)
grandparent with depression			
Multi-generation 'dose', No. (%)			
No. missing	901	267	68
Neither generation	5,241 (56.01)	0 (0)	5,241 (79.83)
Grandparent only	1,324 (14.15)	0 (0)	1,324 (20.17)
Parent only	1,026 (10.97)	1,026 (36.75)	0 (0)
Both generations	1,766 (18.87)	1,766 (63.25)	0 (0)
Polygenic risk score[b]			
No. missing	225	79	132
Mean (SD), z-score	0.00 (1.00)	0.12 (0.99)	-0.07 (1.00)
Cognitive Function[c]			
Picture Vocabulary			
No. missing	406	129	254
Mean (SD), z-score	0.18 (1.07)	0.24 (1.06)	0.16 (1.07)
Flanker			
No. missing	2,323	657	1,530
Mean (SD), z-score	-0.23 (0.95)	-0.25 (0.96)	-0.23 (0.94)
Pattern Comparison			
No. missing	2,361	664	1,559
Mean (SD), z-score	0.51 (1.38)	0.48 (1.41)	0.53 (1.37)
Picture Sequence			
No. missing	375	111	247
Mean (SD), z-score	0.35 (1.12)	0.32 (1.11)	0.38 (1.14)
Reading Recognition			
No. missing	445	138	282
Mean (SD), z-score	0.11 (1.13)	0.12 (1.11)	0.11 (1.13)
Immediate Recall			
No. missing	386	142	225
Mean (SD), z-score	-0.18 (0.93)	-0.19 (0.93)	-0.16 (0.93)
Delayed Recall			
No. missing	454	163	271
Mean (SD), z-score	-0.16 (0.94)	-0.18 (0.94)	-0.15 (0.95)
Vocabulary domain composite			
No. missing	404	129	252
Mean (SD), z-score	0.15 (0.97)	0.18 (0.95)	0.14 (0.97)
Memory domain composite			
No. missing	16	5	11
Mean (SD), z-score	0.00 (0.84)	-0.02 (0.84)	0.02 (0.84)

Abbreviations: No., number; SD, standard deviation.
a. Primary exposure based on parental history.
b. In White subgroup.
c. On all tests, higher scores represent better performance.

297 **eTable 3. Add Health Descriptive Statistics[a]**
298

	All Participants (n=1,064)	Has Family History of Depression[b] (n=344)	No Family History of Depression[b] (n=535)
Demographics & Health			
Age			
No. missing	0	0	0
Mean (SD), y	37.75 (1.88)	37.59 (1.77)	37.75 (1.88)
Sex, No. (%)			
No. missing	0	0	0
Female	584 (49)	217 (60)	274 (42)
Male	480 (51)	127 (40)	261 (58)
Ethnic group, No. (%)[c]			
No. missing	1	0	0
Black/African-American	202 (16.0)	47 (10.0)	106 (18.0)
Hispanic	135 (8.5)	36 (8.1)	78 (10.0)
Multiple [selected more than one category]	76 (4.9)	42 (8.5)	27 (3.4)
Other race or origin[d]	81 (4.7)	10 (2.3)	57 (5.1)
White	569 (66.0)	209 (71.0)	267 (64.0)
Born in US, No. (%)			
No. missing	0	0	0
Yes	967 (94)	329 (96)	467 (91)
College degree, No. (%)			
No. missing	0	0	0
Yes	415 (36)	131 (35)	225 (40)
Household income, No. (%)[c]			
No. missing	21	4	9
Less than $24,999	111 (10.0)	38 (9.6)	44 (8.0)
$25,000-$49,999	179 (18.8)	56 (19.4)	94 (17.8)
$50,000-$74,999	173 (17.0)	58 (14.0)	84 (17.0)
$75,000-$99,999	187 (17.0)	59 (16.0)	98 (18.0)
$100,000-$149,999	207 (20.0)	63 (22.0)	104 (19.0)
$150,000-$199,999	101 (10.0)	39 (11.0)	56 (12.0)
$200,000 or more	85 (7.9)	27 (7.8)	46 (8.7)
Self-perceived socioeconomic rank, No. (%)[c,e]			
No. missing	4	1	1
1-2	47 (5.8)	14 (4.6)	20 (5.7)
3	89 (8.4)	34 (11.0)	38 (6.6)
4	144 (14.0)	49 (17.0)	63 (12.0)
5	268 (26.0)	96 (26.0)	129 (25.0)
6	223 (20.0)	66 (18.0)	113 (20.0)
7	189 (16.0)	53 (14.0)	113 (21.0)
8	64 (6.7)	20 (7.3)	37 (7.3)
9-10	36 (2.9)	11 (2.4)	21 (2.8)
Lifetime depression, No. (%)			
No. missing	2	0	2
Yes	347 (24)	145 (43)	62 (12)
Lifetime neurological condition, No. (%)			
No. missing	0	0	0
Yes	17 (1.5)	11 (2.4)	[f]
Familial Risk			
Parental history, No. (%)			

	All Participants (n=1,064)	Has Family History of Depression[b] (n=344)	No Family History of Depression[b] (n=535)
No. missing	185	0	0
At least one parent with depression	344 (41)	344 (100)	0 (0)
Multi-generation history, No. (%)			
No. missing	293	0	122
At least one parent or grandparent with depression	392 (54)	344 (100)	34 (8)
Multi-generation 'dose', No. (%)			
No. missing	427	120	122
Neither generation	379 (56)	0 (0)	379 (92)
Grandparent only	34 (5)	0 (0)	34 (8)
Parent only	122 (23)	122 (58)	0 (0)
Both generations	102 (16)	102 (42)	0 (0)
Polygenic risk score[g]			
No. missing	0	0	0
Mean (SD), z-score	-0.09 (0.86)	0.01 (0.89)	-0.20 (0.83)
Cognitive Function[h]			
Word recall immediate			
No. missing	36	11	16
Mean (SD), z-score	-0.27 (1.00)	-0.29 (0.92)	-0.26 (1.03)
Word recall delayed			
No. missing	33	8	16
Mean (SD), z-score	-0.23 (1.00)	-0.22 (0.97)	-0.20 (1.00)
Digit span			
No. missing	0	0	0
Mean (SD), z-score	-0.28 (0.97)	-0.24 (0.91)	-0.30 (1.01)
Memory domain composite			
No. missing	25	7	11
Mean (SD), z-score	-0.26 (0.92)	-0.26 (0.86)	-0.23 (0.94)

Abbreviations: No., number; SD, standard deviation.
a. Summary statistics (%, mean, SD) are weighted using `svy` commands in Stata. Sample sizes are reported as observed (unweighted).
b. Primary exposure based on parental history.
c. Some categories have been combined owing to low numbers.
d. Includes Asian; Pacific Islander; American Indian or Alaska Native; Some other race or origin.
e. 10=People who have the most money and education and the most respected jobs; 1=People who have the least money and education and the least respected jobs or no job.
f. Result omitted owing to Add Health disclosure rules for cross-tabulations.
g. In European subgroup.
h. On all tests, higher scores represent better performance.

eTable 4. UK Biobank Descriptive Statistics

	All Participants (n=45,899)	Has Family History of Depression[a] (n=4,401)	No Family History of Depression[a] (n=37,083)
Demographics & Health			
Age at baseline			
No. missing	0	0	0
Mean (SD), y	55.02 (7.55)	54.27 (7.34)	55.04 (7.53)
Age at follow-up			
No. missing	0	0	0
Mean (SD), y	63.99 (7.71)	63.24 (7.44)	64.01 (7.70)
Duration from baseline to follow-up			
No. missing	0	0	0
Mean (SD), y	8.97 (1.78)	8.96 (1.79)	8.97 (1.78)
Sex, No. (%)			
No. missing	0	0	0
Female	23,605 (51.43)	2,511 (57.06)	19,070 (51.43)
Male	22,294 (48.57)	1,890 (42.94)	18,013 (48.57)
Ethnic group, No. (%)			
No. missing	121	7	79
Asian/Asian British	473 (1.03)	31 (0.71)	393 (1.06)
Black/Black British	289 (0.63)	16 (0.36)	207 (0.56)
Chinese	128 (0.28)	4 (0.09)	99 (0.27)
Mixed or Other group	431 (0.94)	45 (1.02)	289 (0.78)
White	44,457 (97.11)	4,298 (97.82)	36,016 (97.33)
Born in English-speaking country, No. (%)			
No. missing	11	1	4
Yes	43,715 (95.26)	4,201 (95.48)	35,366 (95.38)
College degree, No. (%)			
No. missing	747	87	538
Yes	21,154 (46.85)	2,152 (49.88)	17,450 (47.75)
Townsend deprivation index quintiles[b]			
No. missing	45	4	33
1	10,973 (23.93)	930 (21.15)	9,115 (24.60)
2	10,488 (22.87)	1,011 (22.99)	8,622 (23.27)
3	9,525 (20.77)	881 (20.04)	7,729 (20.86)
4	8,525 (18.59)	870 (19.79)	6,738 (18.19)
5	6,343 (13.83)	705 (16.03)	4,846 (13.08)
Lifetime depression, No. (%)			
No. missing	0	0	0
Yes	5,507 (12.00)	1,042 (23.68)	3,873 (10.44)
Lifetime neurological condition, No. (%)			
No. missing	0	0	0
Yes	2,212 (4.82)	232 (5.27)	1,712 (4.62)
Familial Risk			
Parental history, No. (%)			
No. missing	4,415	0	0
Yes	4,401 (10.61)	4,401 (100)	0 (0)
Polygenic risk score[c]			
No. missing	18	0	15
Mean (SD), z-score	0.00 (1.00)	0.11 (1.00)	-0.02 (1.00)
Cognitive Function[d,e]			
Prospective memory, No.			

	All Participants (n=45,899)	Has Family History of Depression[a] (n=4,401)	No Family History of Depression[a] (n=37,083)
(%)			
No. missing	0	0	0
Correct on 1st attempt	38,093 (82.99)	3,703 (84.14)	30,884 (83.28)
Verbal-numerical reasoning			
No. missing	863	74	662
Mean (SD), z-score	-0.24 (0.97)	-0.24 (0.95)	-0.22 (0.97)
Reaction time			
No. missing	287	20	226
Mean (SD), z-score	0.01 (0.96)	-0.01 (0.96)	0.02 (0.96)
Digit span			
No. missing	12,106	1,177	9,678
Mean (SD), z-score	-0.39 (0.96)	-0.39 (0.97)	-0.38 (0.96)
Visual memory (6 pairs)			
No. missing	779	78	602
Mean (SD), z-score	0.24 (1.06)	0.23 (1.08)	0.25 (1.06)
Visual memory (8 pairs)			
No. missing	28,089	2,686	22,587
Mean (SD), z-score	0.17 (1.02)	0.17 (1.04)	0.17 (1.02)
Trails A time			
No. missing	12,932	1,271	10,350
Mean (SD), z-score	0.01 (0.96)	-0.06 (0.96)	0.03 (0.96)
Trails A errors			
No. missing	12,861	1,262	10,293
Mean (SD), z-score	1.29 (1.56)	1.27 (1.57)	1.29 (1.56)
Trails B time			
No. missing	13,787	1,360	10,993
Mean (SD), z-score	0.00 (0.96)	-0.04 (0.96)	0.02 (0.96)
Trails B errors			
No. missing	13,075	1,284	10,459
Mean (SD), z-score	0.98 (1.57)	0.97 (1.59)	1.00 (1.57)
Trails B-A time			
No. missing	13,787	1,360	10,993
Mean (SD), z-score	0.00 (0.96)	-0.02 (0.97)	0.02 (0.96)
Matrix patterns			
No. missing	12,903	1,269	10,317
Mean (SD), z-score	-0.23 (0.94)	-0.23 (0.93)	-0.21 (0.94)
Tower test			
No. missing	13,194	1,292	10,559
Mean (SD), z-score	-0.15 (0.94)	-0.22 (0.93)	-0.13 (0.95)
Symbol-digit			
No. missing	12,879	1,268	10,295
Mean (SD), z-score	-0.11 (0.95)	-0.16 (0.94)	-0.09 (0.94)
Verbal paired associates			
No. missing	12,515	1,231	10,019
Mean (SD), z-score	-0.24 (0.84)	-0.20 (0.84)	-0.23 (0.83)
Processing Speed domain composite			
No. missing	183	17	142
Mean (SD), z-score	-0.03 (0.81)	-0.07 (0.80)	-0.01 (0.81)
Reasoning domain composite			
No. missing	613	57	469
Mean (SD), z-score	-0.23 (0.86)	-0.23 (0.84)	-0.21 (0.86)
Attention & Executive domain composite			

	All Participants (n=45,899)	Has Family History of Depression[a] (n=4,401)	No Family History of Depression[a] (n=37,083)
No. missing	11,748	1,147	9,404
Mean (SD), z-score	0.22 (0.69)	0.18 (0.70)	0.24 (0.68)
Memory domain composite			
No. missing	428	41	328
Mean (SD), z-score	-0.04 (0.73)	-0.03 (0.74)	-0.03 (0.73)

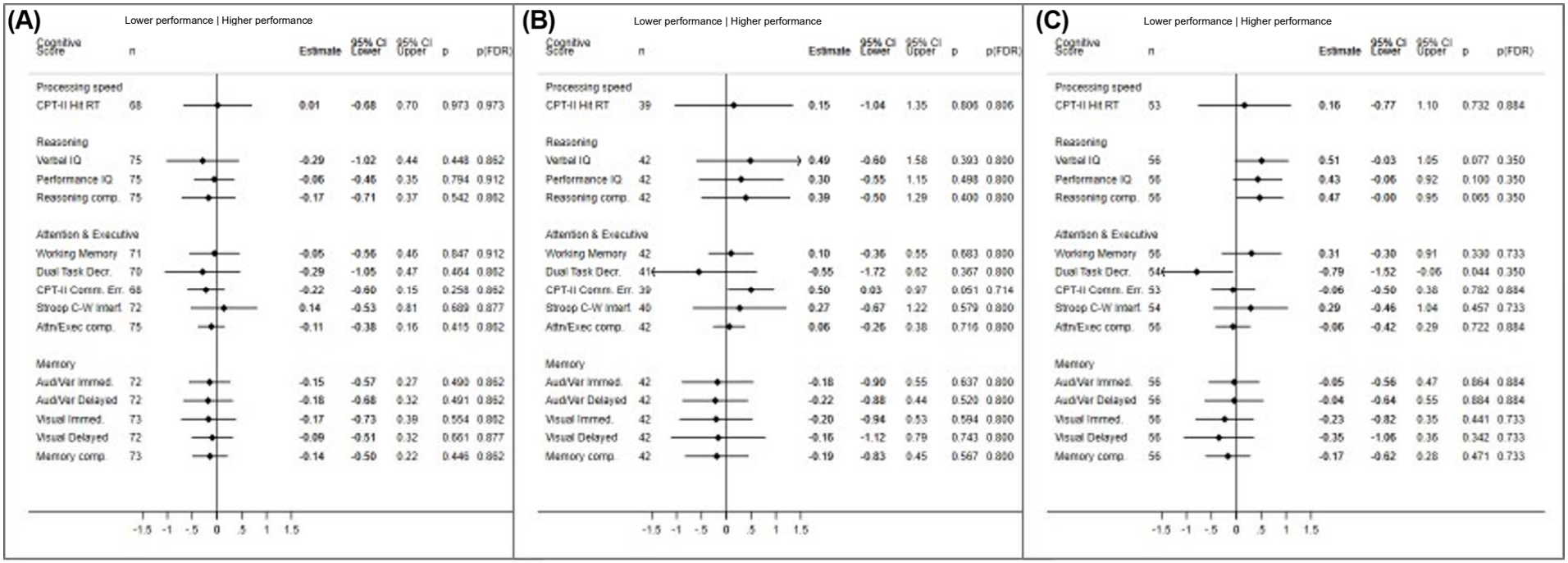
Abbreviations: No., number; SD, standard deviation.
a. Primary exposure based on parental history.
b. 1=Least deprived; 5=Most deprived.
c. In White British subgroup.
d. On all tests, higher scores represent better performance.
e. Some tests were added to the battery part-way through the assessment wave 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.

Associations Between Familial Risk Exposure Measures and Lifetime Depression

The primary family history exposure (at least one parent with depression versus none) was associated with increased odds of depression in the offspring: Three Generations OR 3.10 (95% CI 1.17 to 8.24, *P*=.02); ABCD OR 3.34 (95% CI 2.71 to 4.13, *P*<.001); Add Health OR 5.54 (95% CI 3.43 to 8.93, *P*<.001); UK Biobank OR 2.62 (95% CI 2.56 to 2.69, *P*<.001). Using the 'dose' variable based on parental and grandparental exposure, the association was strongest in the group with both prior generations affected versus none: Three Generations OR 5.81 (95% CI 2.12 to 15.92, *P*=.001); ABCD OR 4.08 (95% CI 3.17 to 5.26, *P*<.001); Add Health OR 14.98 (95% CI 6.58 to 34.09, *P*<.001). The PRS for depression was also associated with increased odds of depression (OR per 1SD increase in PRS): ABCD OR 1.25 (95% CI 1.08 to 1.43, *P*=.002); Add Health OR 1.31 (95% CI 1.18 to 1.46, *P*<.001); UK Biobank OR 1.18 (95% CI 1.17 to 1.19, *P*<.001).

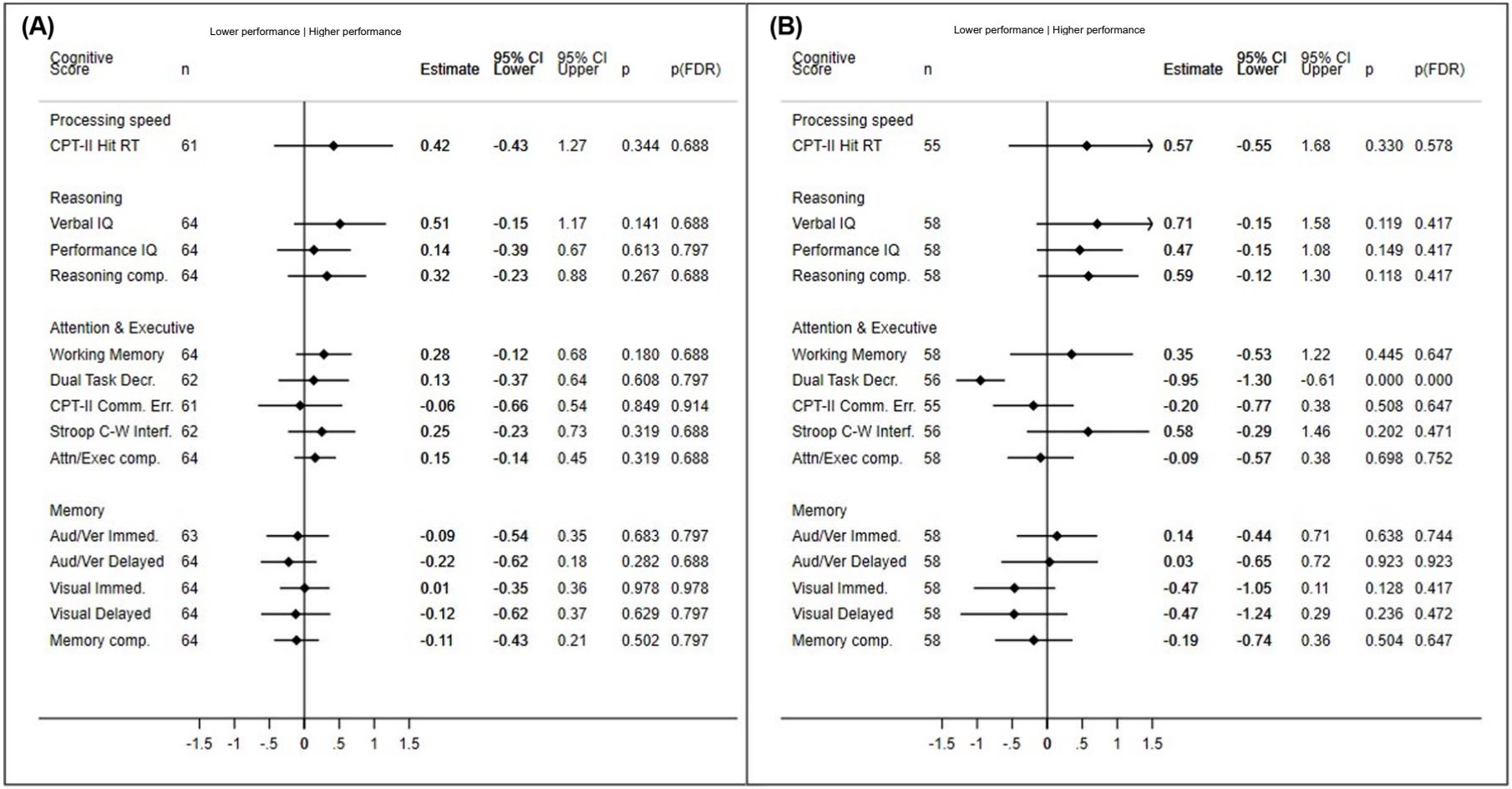
Results of Unadjusted, Secondary, and Sensitivity Analyses in Each Cohort – Family History Analyses

eFigure 1. Three Generations Primary Analyses for Family History, with Different Levels of Covariate Adjustment



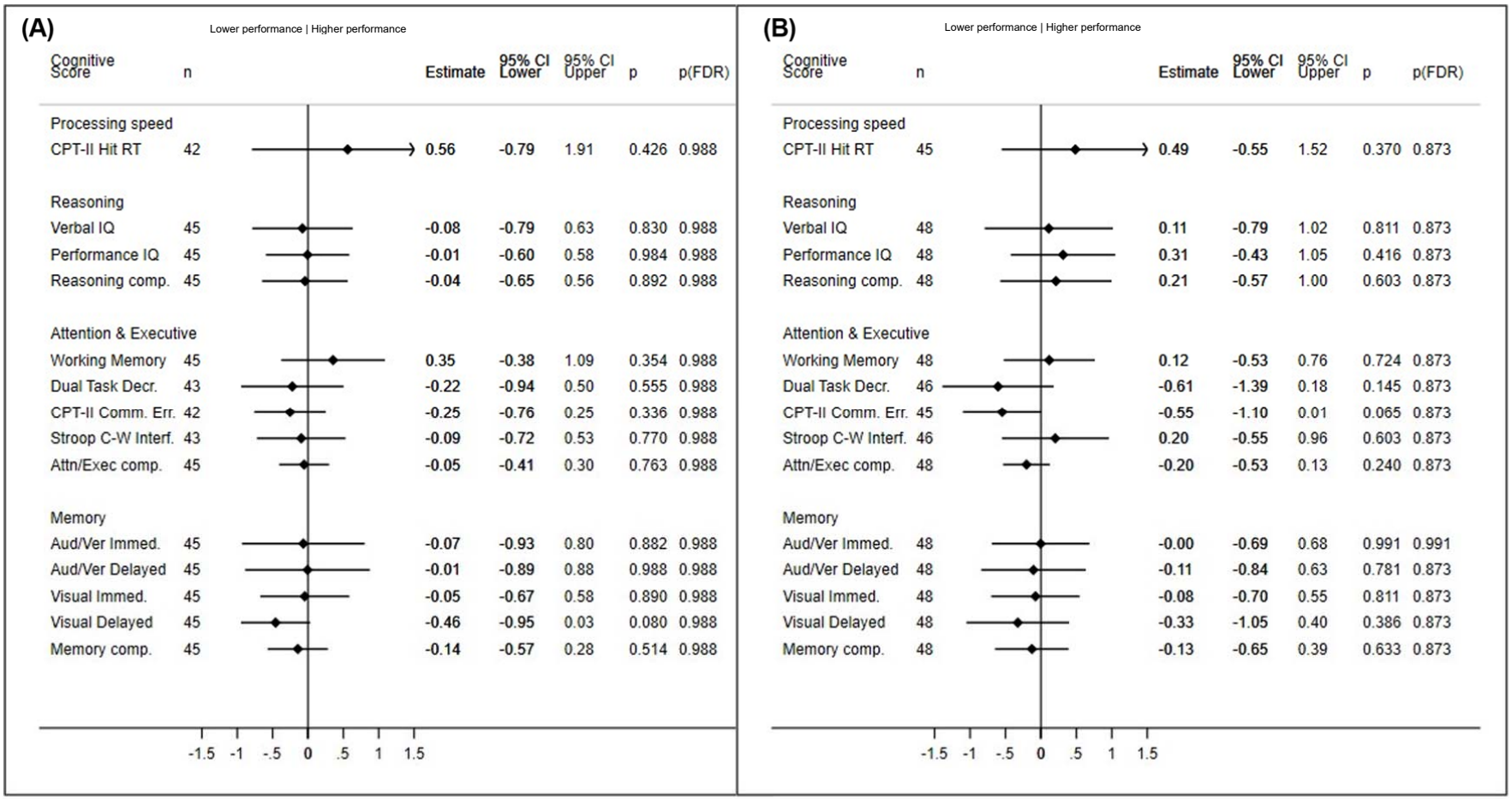
(A) Primary family history exposure (at least one parent with depression versus none), unadjusted. (B) Primary family history exposure, adjusted as per main Figure 2, plus additional adjustment for education (adult participants only). (C) Primary family history exposure, adjusted as per main Figure 2, plus additional adjustment for socioeconomic status.
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: 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.

eFigure 2. Three Generations Secondary Analyses for Family History, Including Grandparental History of Depression



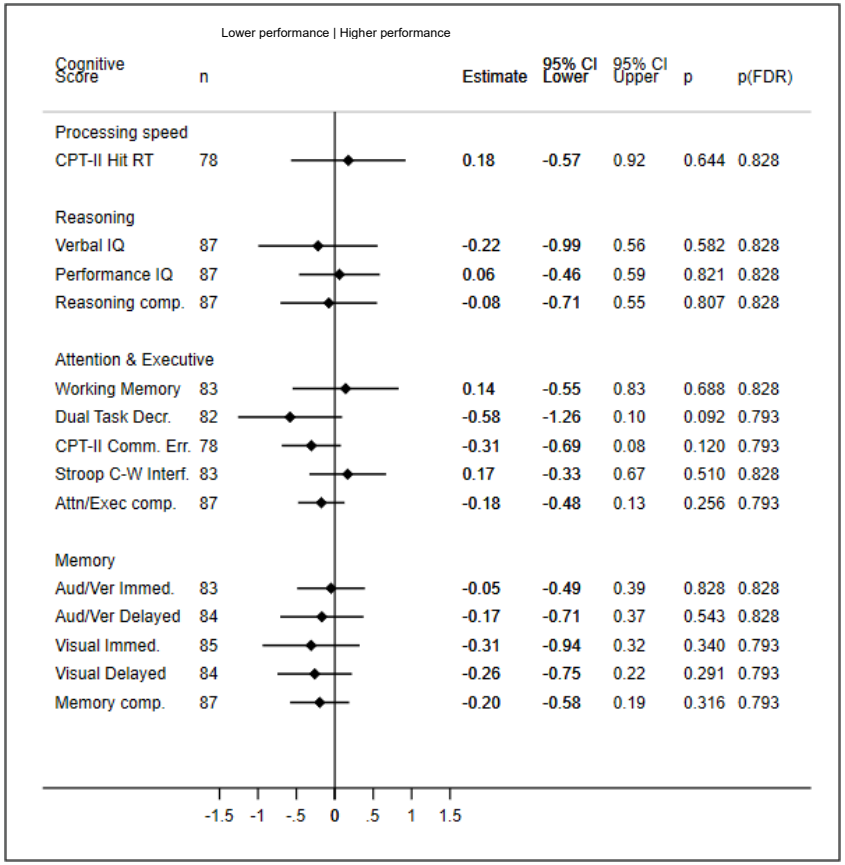
(A) Secondary family history exposure (at least one parent or grandparent with depression versus none), adjusted as per main Figure 2. (B) 'Dose'-based secondary family history exposure (results shown for the subgroup with both prior generations affected versus none), adjusted as per main Figure 2.
Plot 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: 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.

eFigure 3. Three Generations Secondary Analyses for Family History, Excluding Participants with Depression or Neurological Disorders



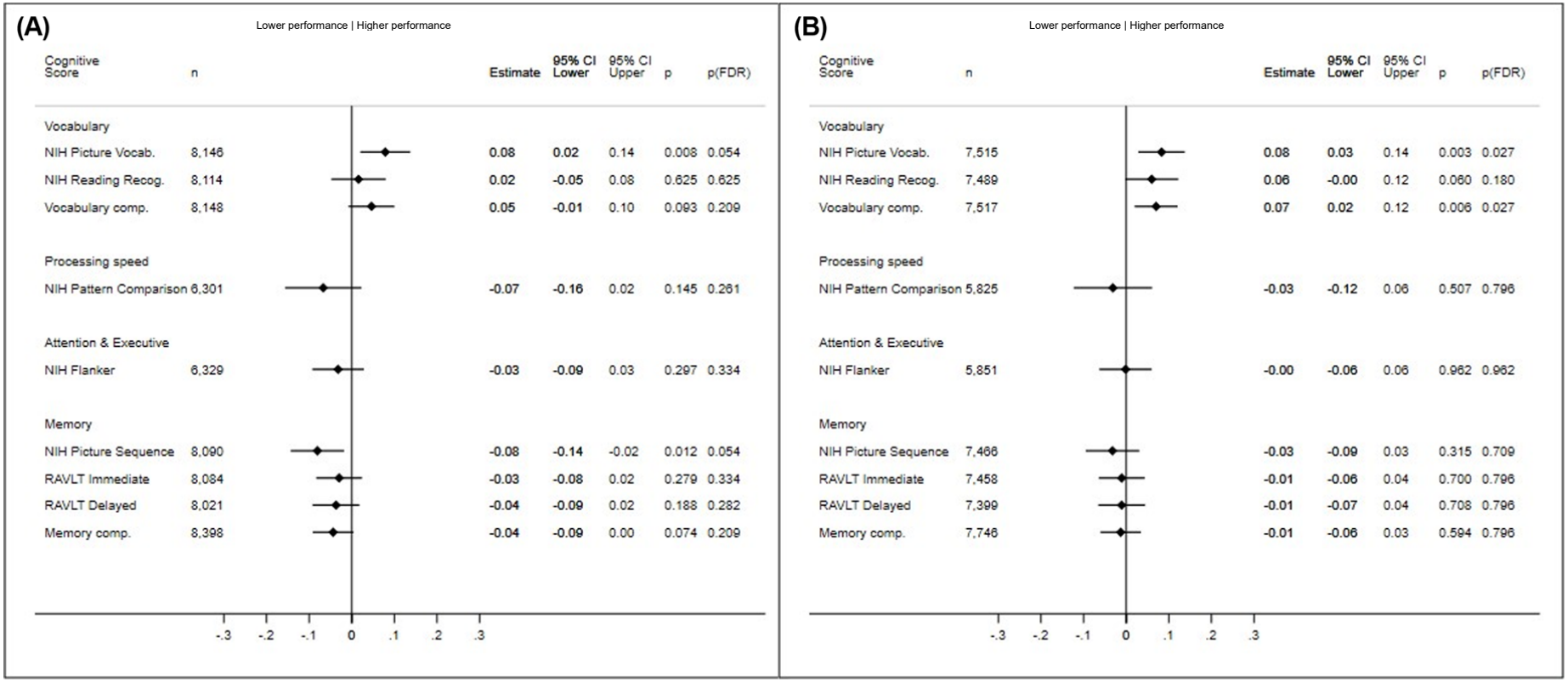
(A) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of depression, adjusted as per main Figure 2. (B) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 2.
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: 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.

eFigure 4. Three Generations Sensitivity Analyses for Family History, Taking Account of Missing Data



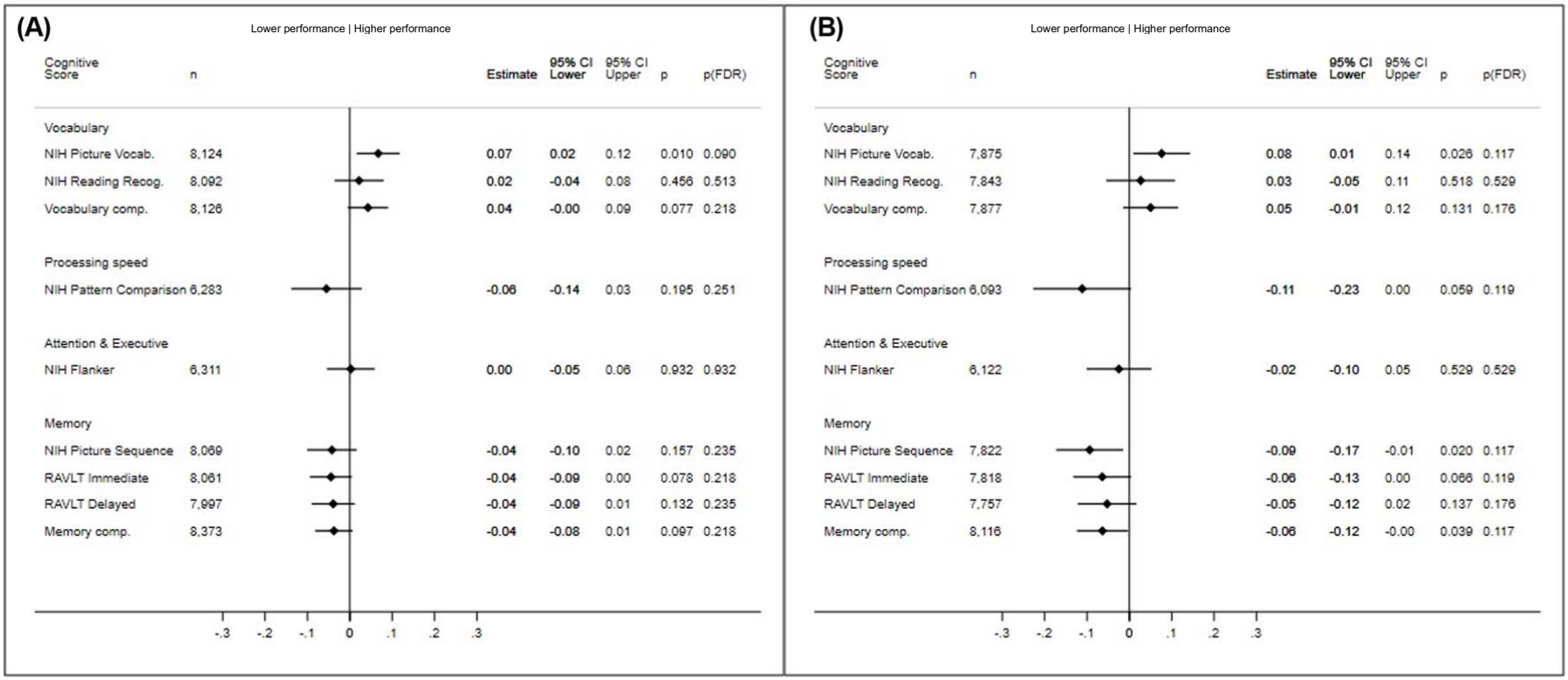
Primary family history exposure (at least one parent with depression versus none), with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 2.
Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean 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; FIML, full information maximum likelihood; Immed., immediate; IQ, intelligence quotient; RT, reaction time.

eFigure 5. ABCD Primary Analyses for Family History, with Different Levels of Covariate Adjustment



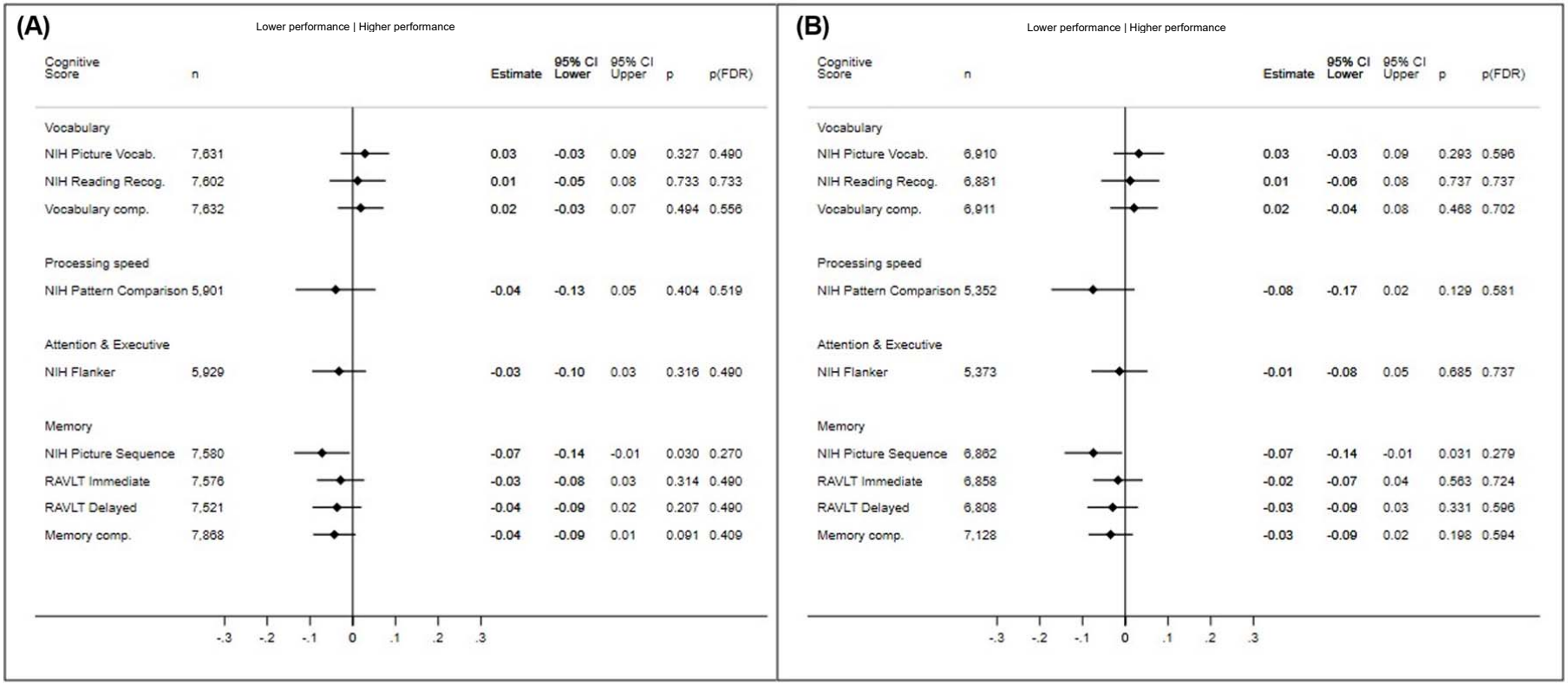
(A) Primary family history exposure (at least one parent with depression versus none), unadjusted. (B) Primary family history exposure, adjusted as per main Figure 1(A), plus additional adjustment for socioeconomic status.
Plot shows point estimates and 95% CI. Estimates are in z-score units and can 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; comp., composite; FDR, false discovery rate; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

eFigure 6. ABCD Secondary Analyses for Family History, Including Grandparental History of Depression



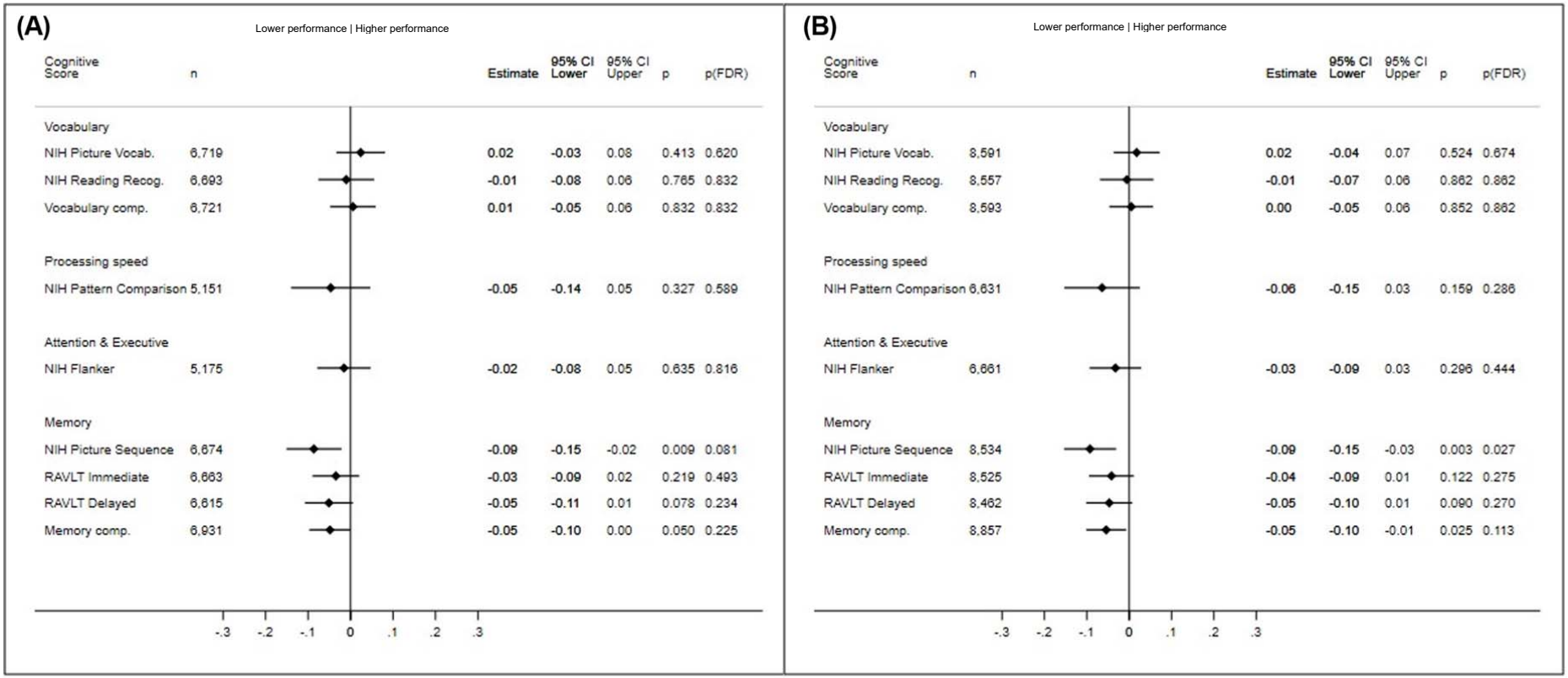
(A) Secondary family history exposure (at least one parent or grandparent with depression versus none), adjusted as per main Figure 1(A). (B) 'Dose'-based secondary family history exposure (results shown for the subgroup with both prior generations affected versus none), adjusted as per main Figure 1(A).
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; comp., composite; FDR, false discovery rate; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

eFigure 7. ABCD Secondary Analyses for Family History, Excluding Participants with Depression or Neurological Disorders



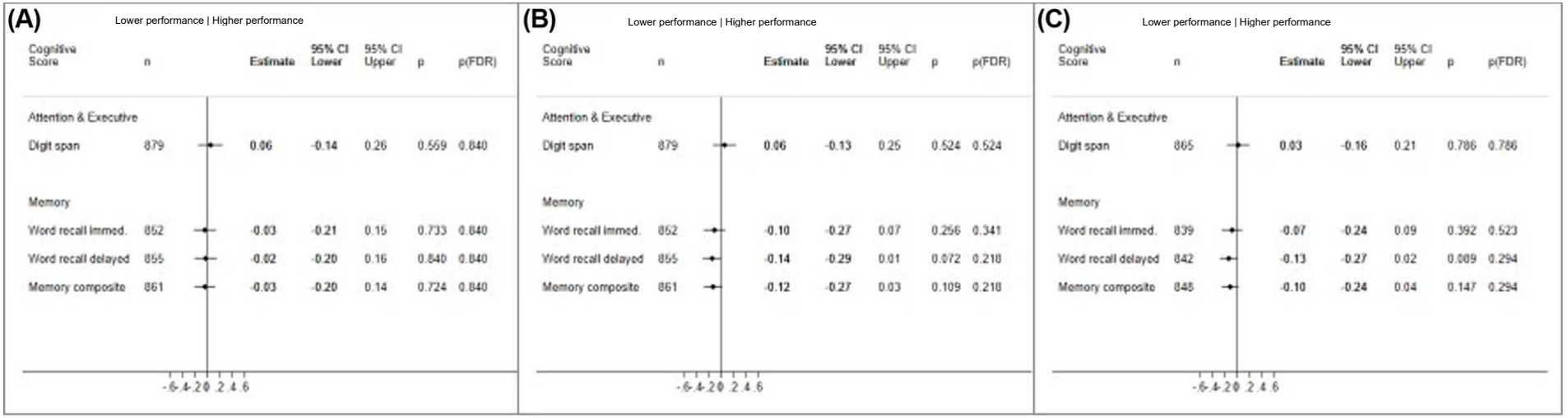
(A) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of depression, adjusted as per main Figure 1(A). (B) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 1(A).
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; comp., composite; FDR, false discovery rate; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

eFigure 8. ABCD Sensitivity Analyses for Family History, Taking Account of Relatedness and Missing Data



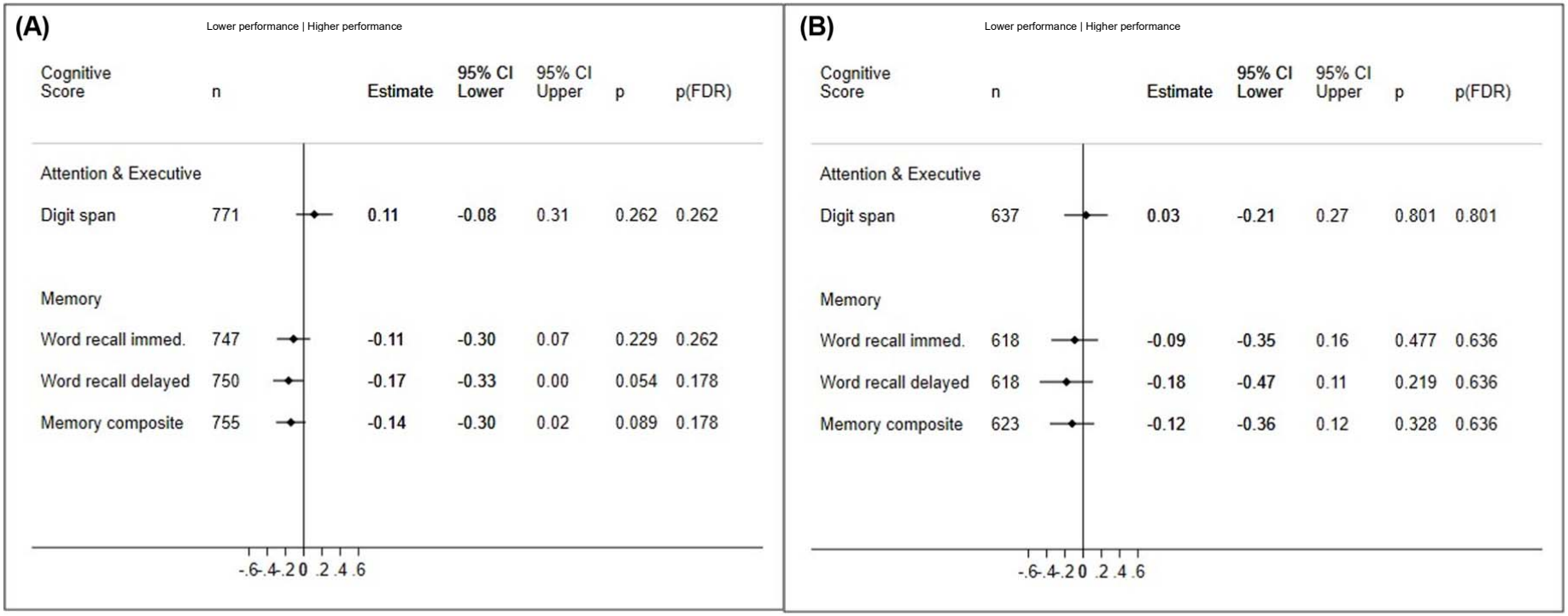
(A) Primary family history exposure (at least one parent with depression versus none), restricted to unrelated participants, adjusted as per main Figure 1(A). (B) Primary family history exposure (at least one parent with depression versus none), with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 1(A).
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; comp., composite; FDR, false discovery rate; FIML, full information maximum likelihood; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

eFigure 9. Add Health Primary Analyses for Family History, with Different Levels of Covariate Adjustment



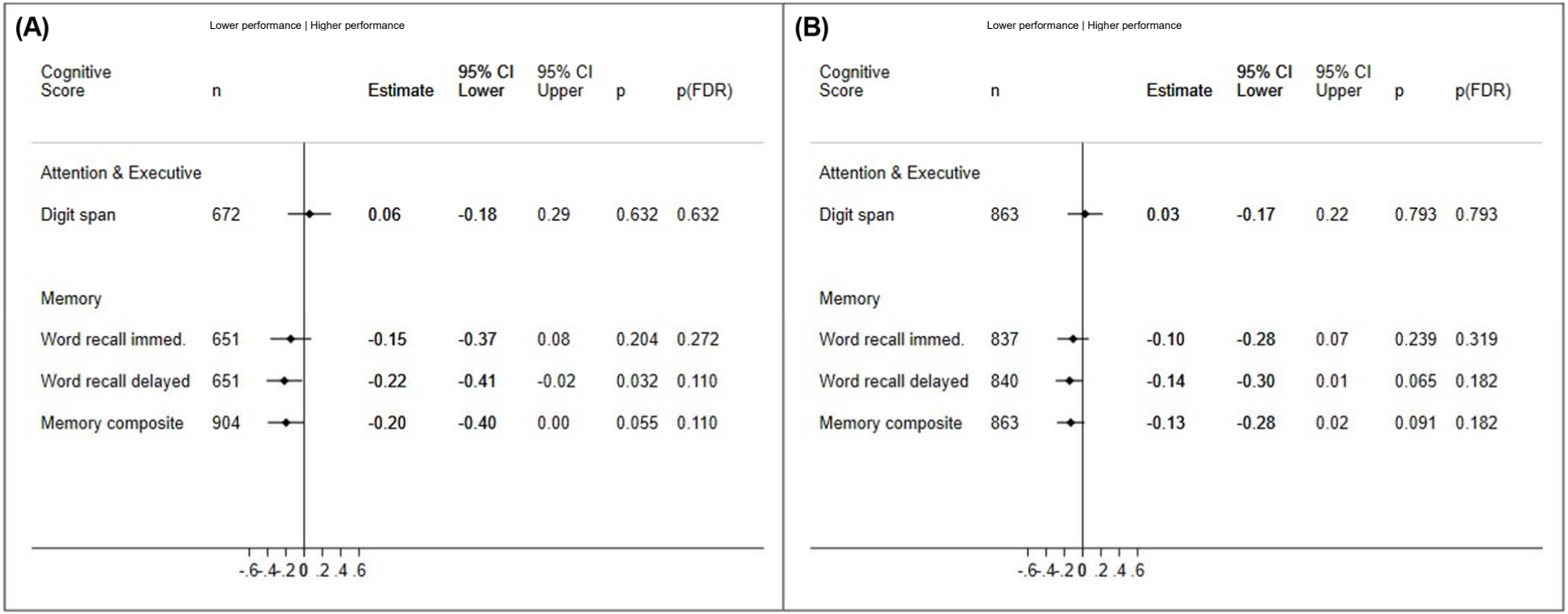
(A) Primary family history exposure (at least one parent with depression versus none), unadjusted. (B) Primary family history exposure, adjusted as per main Figure 3(A), plus additional adjustment for education. (C) Primary family history exposure, adjusted as per main Figure 3(A), plus additional adjustment for socioeconomic status.
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.

eFigure 10. Add Health Secondary Analyses for Family History, Including Grandparental History of Depression



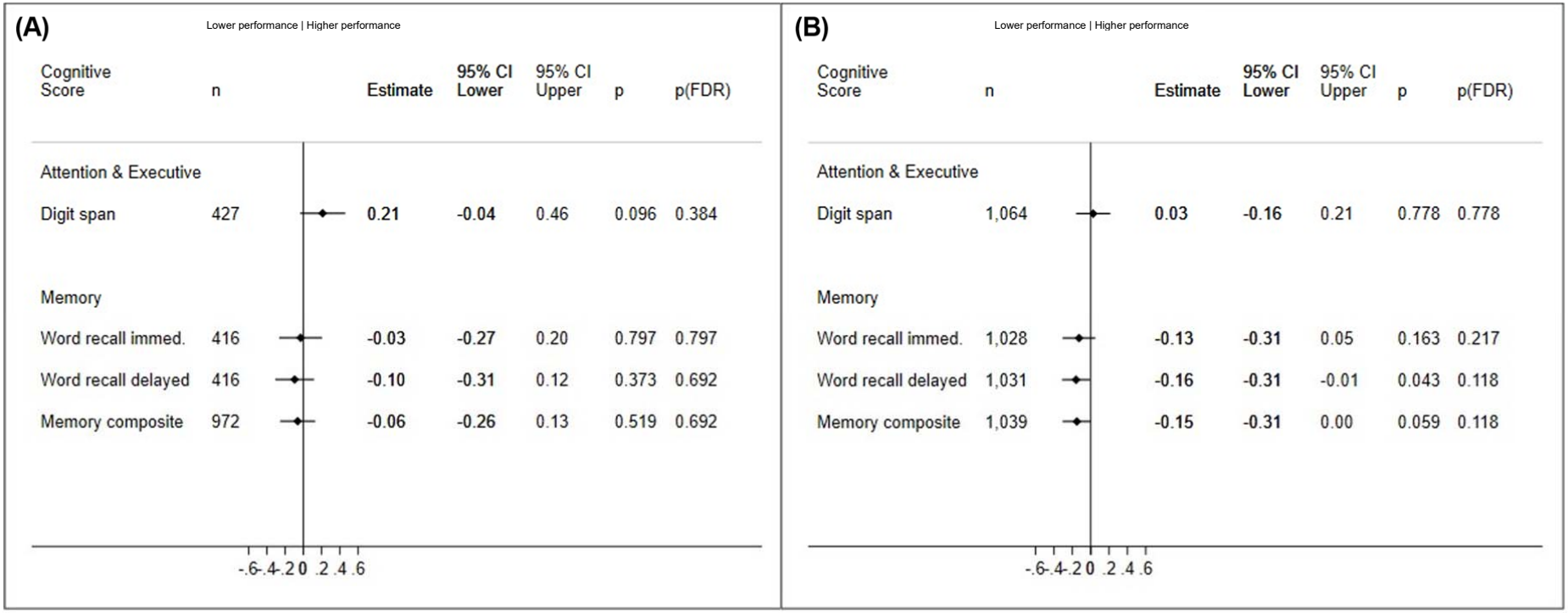
(A) Secondary family history exposure (at least one parent or grandparent with depression versus none), adjusted as per main Figure 3(A). (B) 'Dose'-based secondary family history exposure (results shown for the subgroup with both prior generations affected versus none), adjusted as per main Figure 3(A).
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.

eFigure 11. Add Health Secondary Analyses for Family History, Excluding Participants with Depression or Neurological Disorders



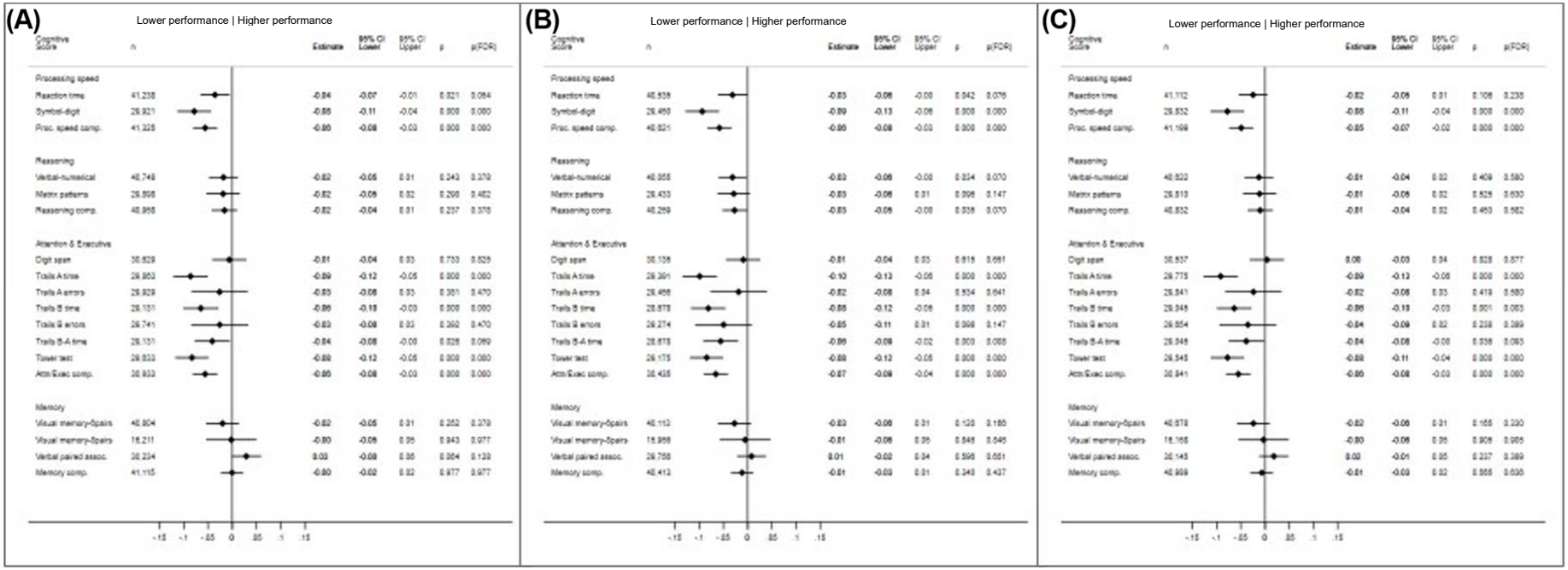
(A) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of depression, adjusted as per main Figure 3(A). (B) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 3(A).
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.

eFigure 12. Add Health Sensitivity Analyses for Family History, Taking Account of Relatedness and Missing Data



(A) Primary family history exposure (at least one parent with depression versus none), restricted to unrelated participants, adjusted as per main Figure 3(A). (B) Primary family history exposure (at least one parent with depression versus none), with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 3(A).
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; FIML, full information maximum likelihood; immed., immediate.

eFigure 13. UK Biobank Primary Analyses for Family History, with Different Levels of Covariate Adjustment

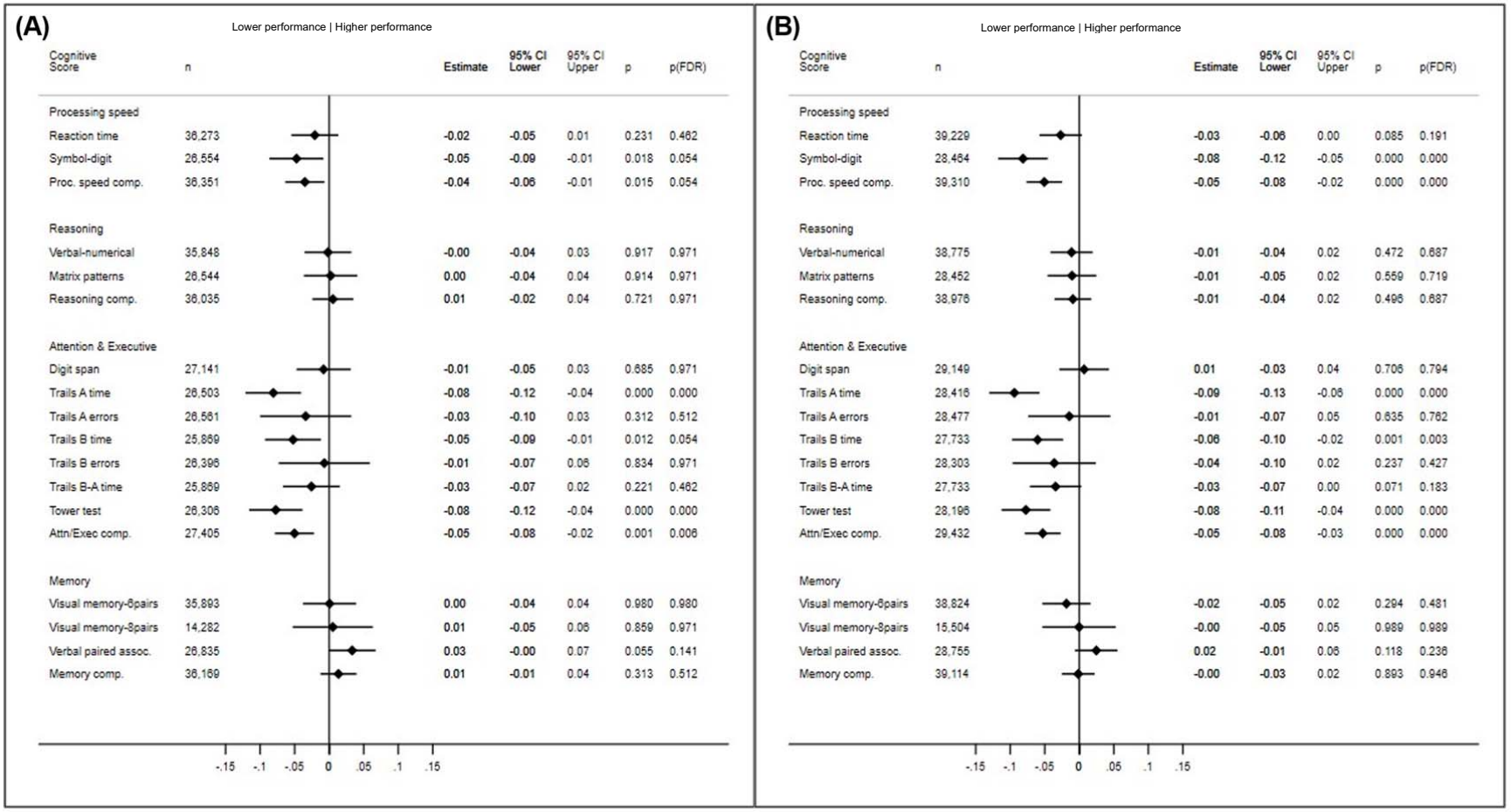


(A) Primary family history exposure (at least one parent with depression versus none), unadjusted. (B) Primary family history exposure, adjusted as per main Figure 4(A), plus additional adjustment for education. (C) Primary family history exposure, adjusted as per main Figure 4(A), plus additional adjustment for socioeconomic status.

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: unadjusted OR 1.06 (95% CI 0.98 to 1.16, *P*=.15, P_{FDR}=.28); adjusted plus education OR 1.00 (95% CI 0.92 to 1.09, *P*=.99, P_{FDR}=.99); adjusted plus socioeconomic status OR 1.02 (95% CI 0.93 to 1.11, *P*=.70, P_{FDR}=.81).

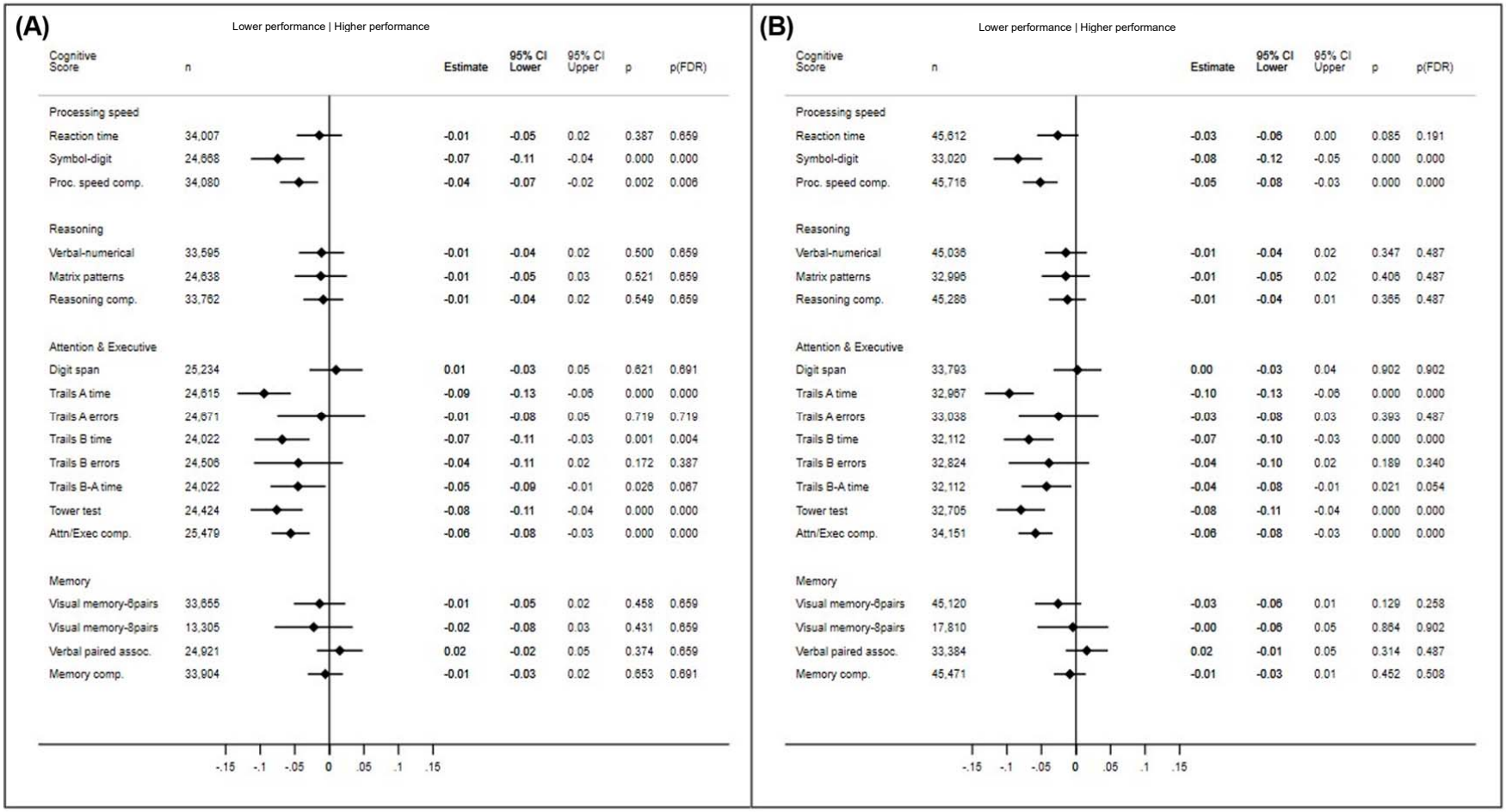
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; OR, odds ratio; Proc., Processing.

eFigure 14. UK Biobank Secondary Analyses for Family History, Excluding Participants with Depression or Neurological Disorders



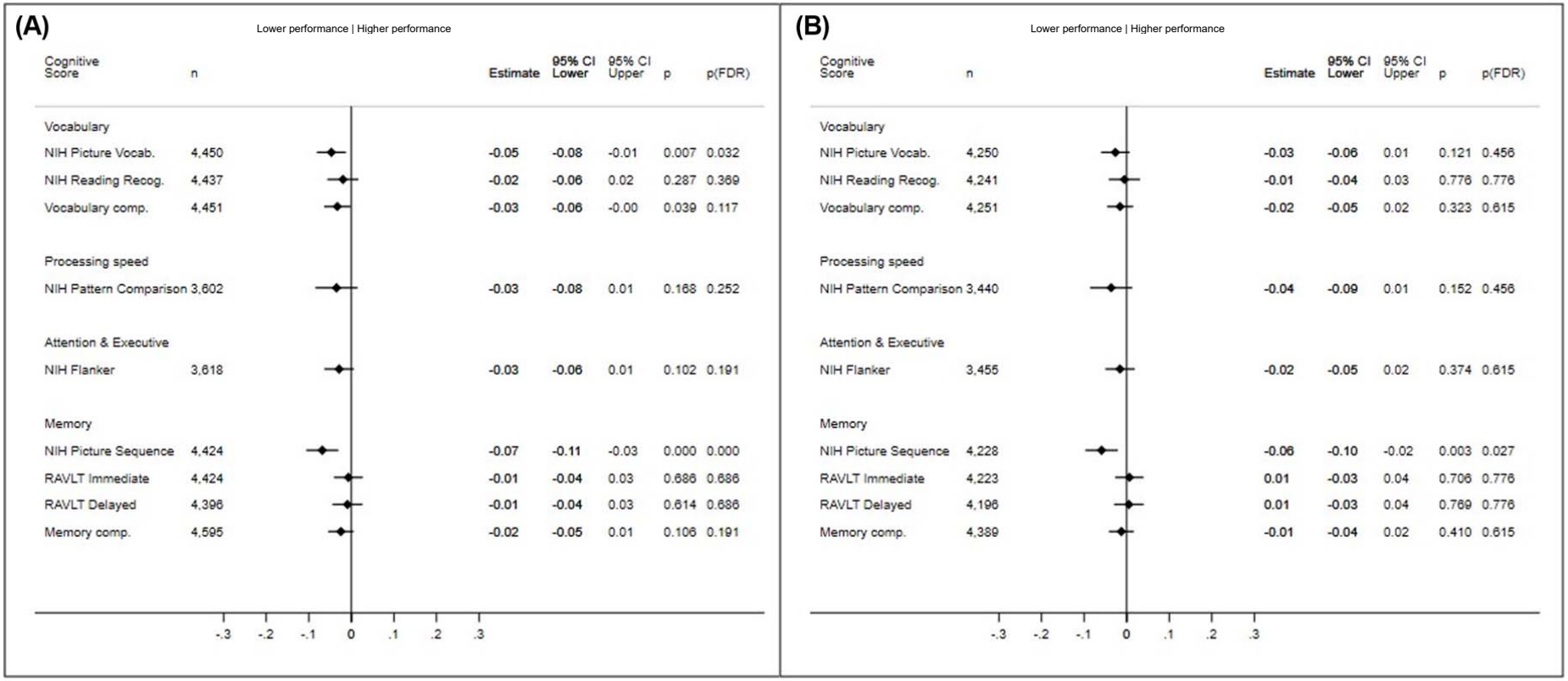
(A) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of depression, adjusted as per main Figure 4(A). (B) Primary family history exposure (at least one parent with depression versus none), excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 4(A).
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: excluding depression OR 1.04 (95% CI 0.94 to 1.15, *P*=.46, P_{FDR}=.76); excluding neurological disorders OR 1.00 (95% CI 0.92 to 1.10, *P*=.92, P_{FDR}=.99).
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; OR, odds ratio; Proc., Processing.

eFigure 15. UK Biobank Sensitivity Analyses for Family History, Taking Account of Relatedness and Missing Data



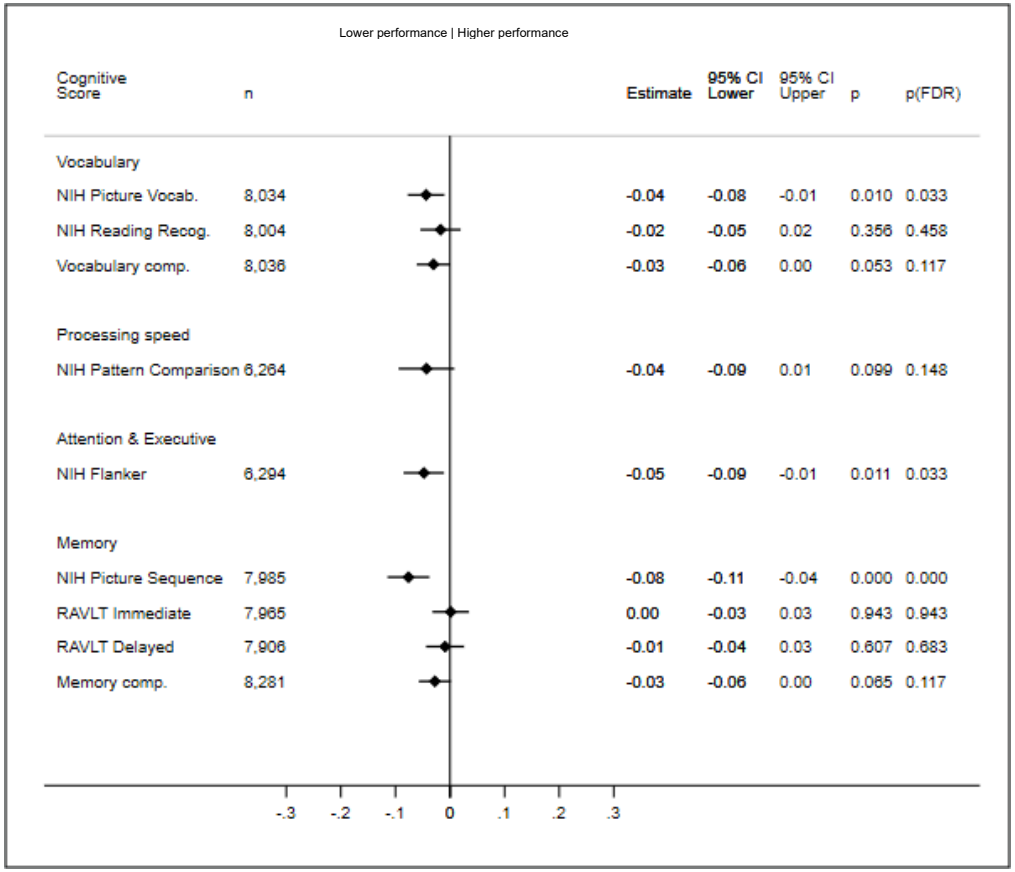
(A) Primary family history exposure (at least one parent with depression versus none), restricted to unrelated participants, adjusted as per main Figure 4(A). (B) Primary family history exposure (at least one parent with depression versus none), with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 4(A).
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: unrelated OR 1.00 (95% CI 0.91 to 1.10, *P*=.96, P_{FDR}=.96); FIML OR could not be estimated as this option is not available in Stata's generalized regression functions.
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; FIML, full information maximum likelihood; OR, odds ratio; Proc., Processing.

eFigure 16. ABCD Primary Analyses for Polygenic Risk, with Different Levels of Covariate Adjustment



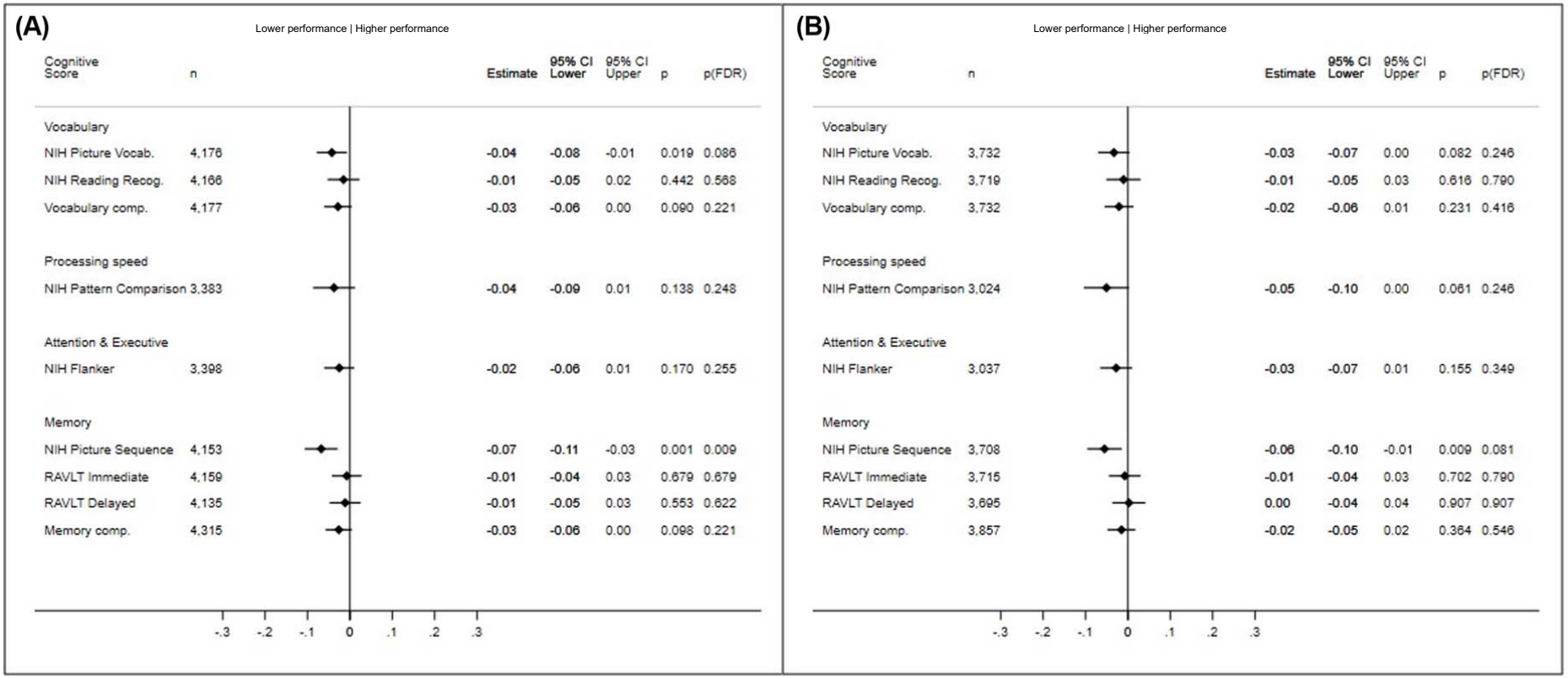
(A) Polygenic risk score for depression, in the White subgroup, adjusted only for first 10 genetic principal components. (B) Polygenic risk score for depression, in the White subgroup, adjusted as per main Figure 1(B), plus additional adjustment for socioeconomic status.
Plot shows point estimates and 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.

eFigure 17. ABCD Secondary Analysis for Polygenic Risk, in Multi-Ancestry Sample



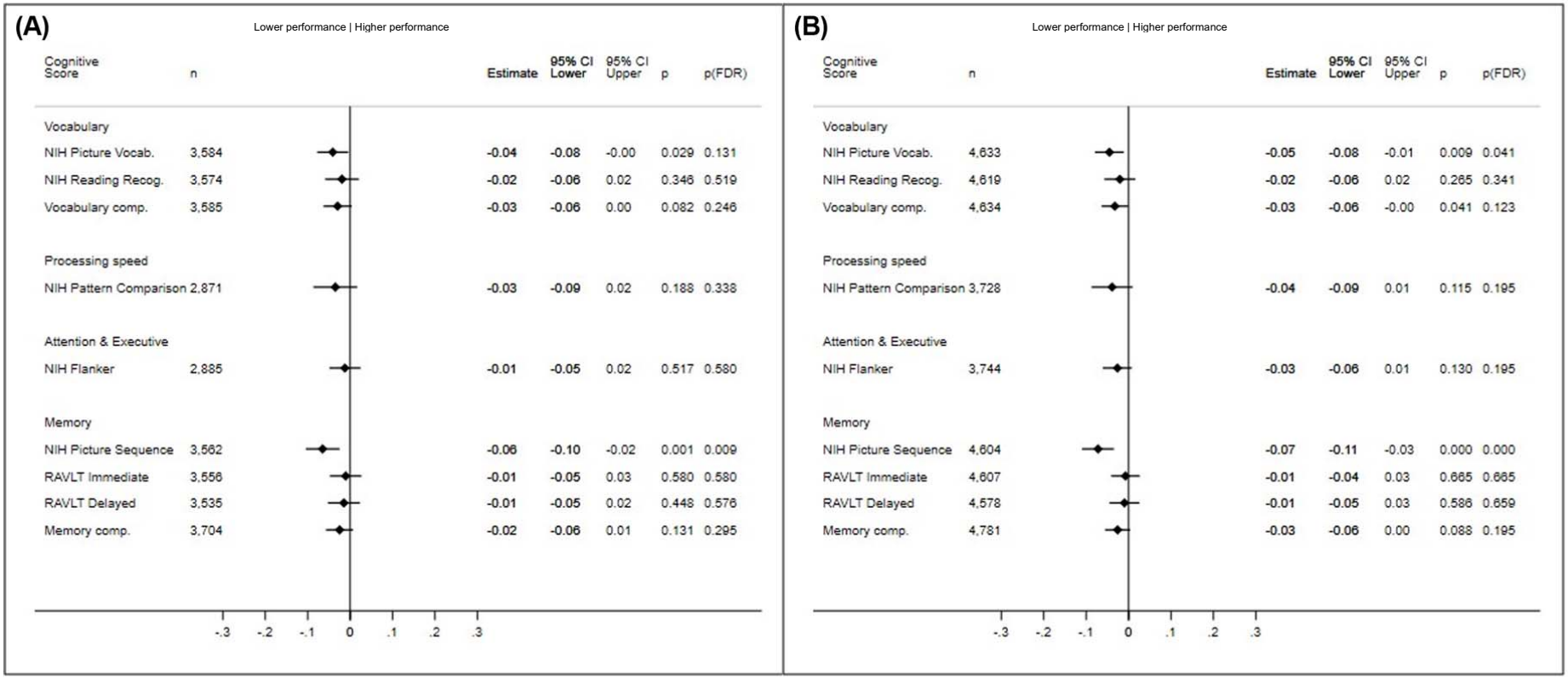
Polygenic risk score for depression, in the whole sample, adjusted as per main Figure 1(B), plus additional adjustment for ethnic group.
Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. 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.

eFigure 18. ABCD Secondary Analyses for Polygenic Risk, Excluding Participants with Depression or Neurological Disorders



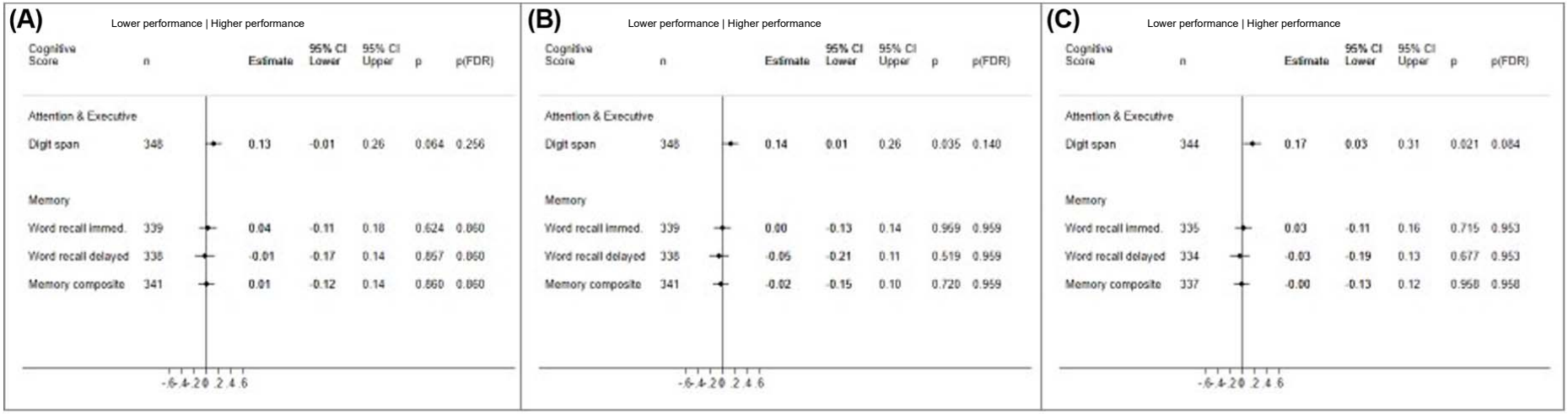
(A) Polygenic risk score for depression, in the White subgroup, excluding participants with a lifetime history of depression, adjusted as per main Figure 1(B). (B) Polygenic risk score for depression, in the White subgroup, excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 1(B).
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.

eFigure 19. ABCD Sensitivity Analyses for Polygenic Risk, Taking Account of Relatedness and Missing Data



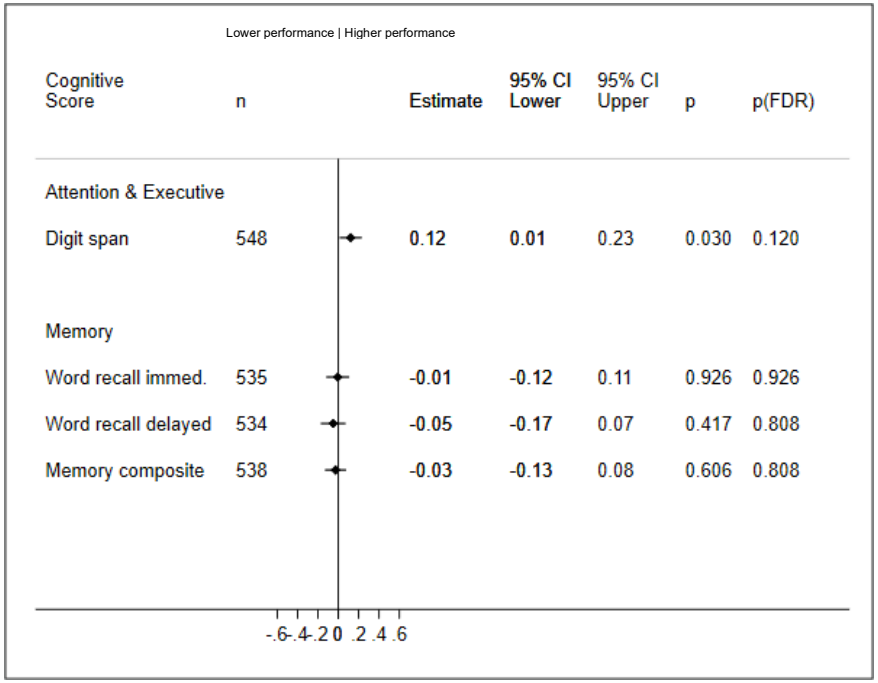
(A) Polygenic risk score for depression, in the White subgroup, restricted to unrelated participants, adjusted as per main Figure 1(B). (B) Polygenic risk score for depression, in the White subgroup, with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 1(B).
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; FIML, full information maximum likelihood; NIH, National Institutes of Health Toolbox; RAVLT, Rey Auditory Verbal Learning Test.

eFigure 20. Add Health Primary Analyses for Polygenic Risk, with Different Levels of Covariate Adjustment



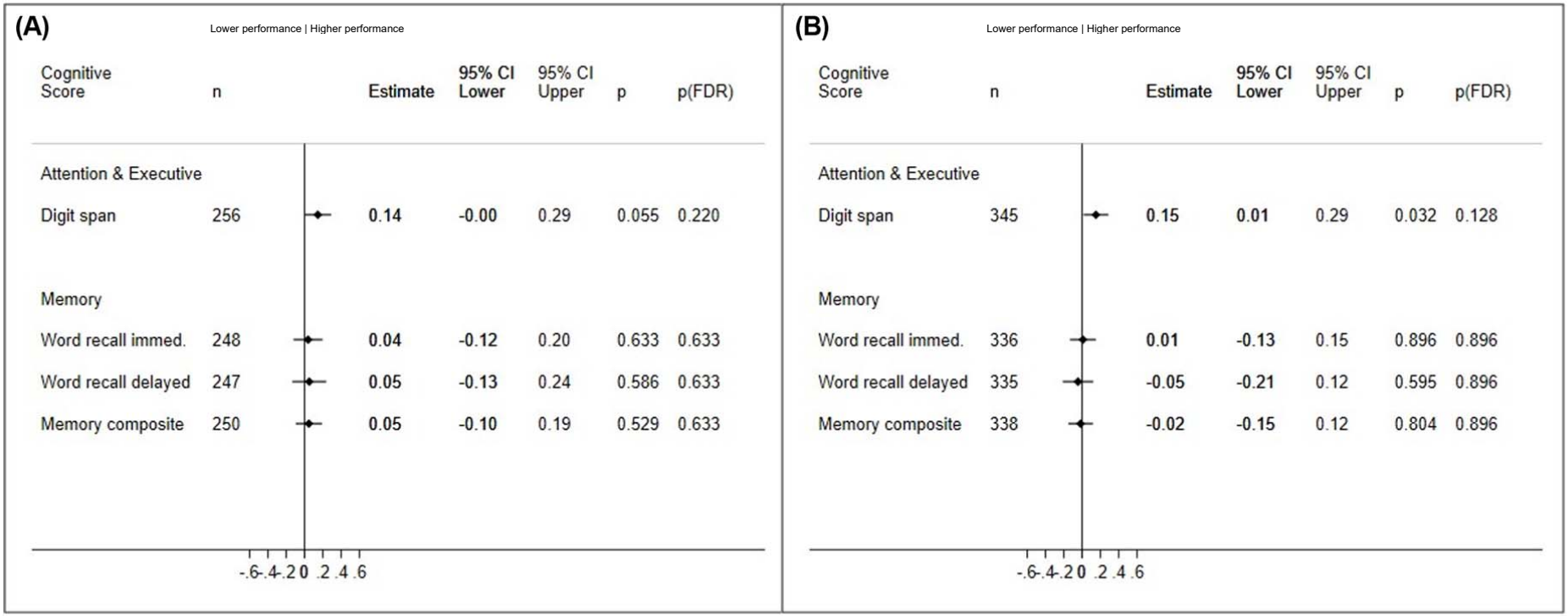
(A) Polygenic risk score for depression, in the European subgroup, adjusted only for first 10 genetic principal components. (B) Polygenic risk score for depression, in the European subgroup, adjusted as per main Figure 3(B), plus additional adjustment for education. (C) Polygenic risk score for depression, in the European subgroup, adjusted as per main Figure 3(B), plus additional adjustment for socioeconomic status. 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; FDR, false discovery rate; immed., immediate.

eFigure 21. Add Health Secondary Analysis for Polygenic Risk, in Multi-Ancestry Sample



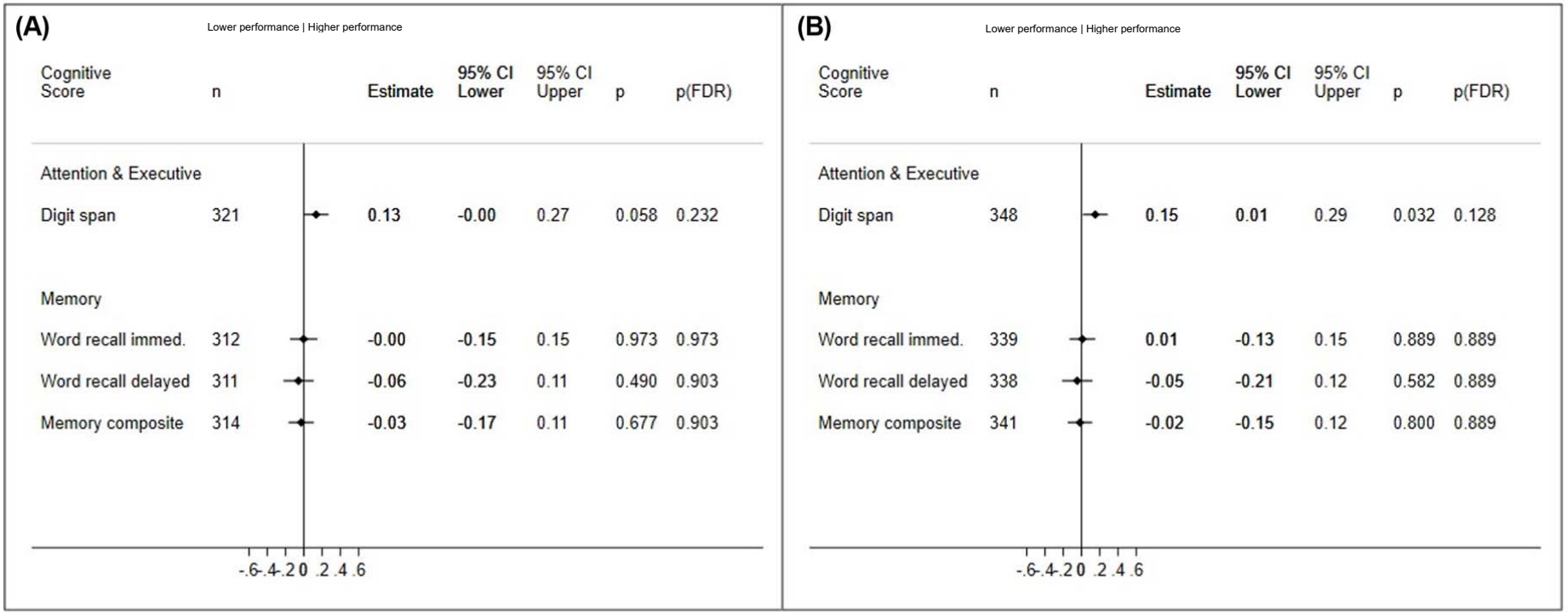
Polygenic risk score for depression, in the whole sample, adjusted as per main Figure 3(B), plus additional adjustment for ethnic group.
Plot shows point estimates and 95% CI. Estimates are in z-score units and can be interpreted as standardized mean differences. Higher scores represent better performance. 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; FDR, false discovery rate; immed., immediate.

eFigure 22. Add Health Secondary Analyses for Polygenic Risk, Excluding Participants with Depression or Neurological Disorders



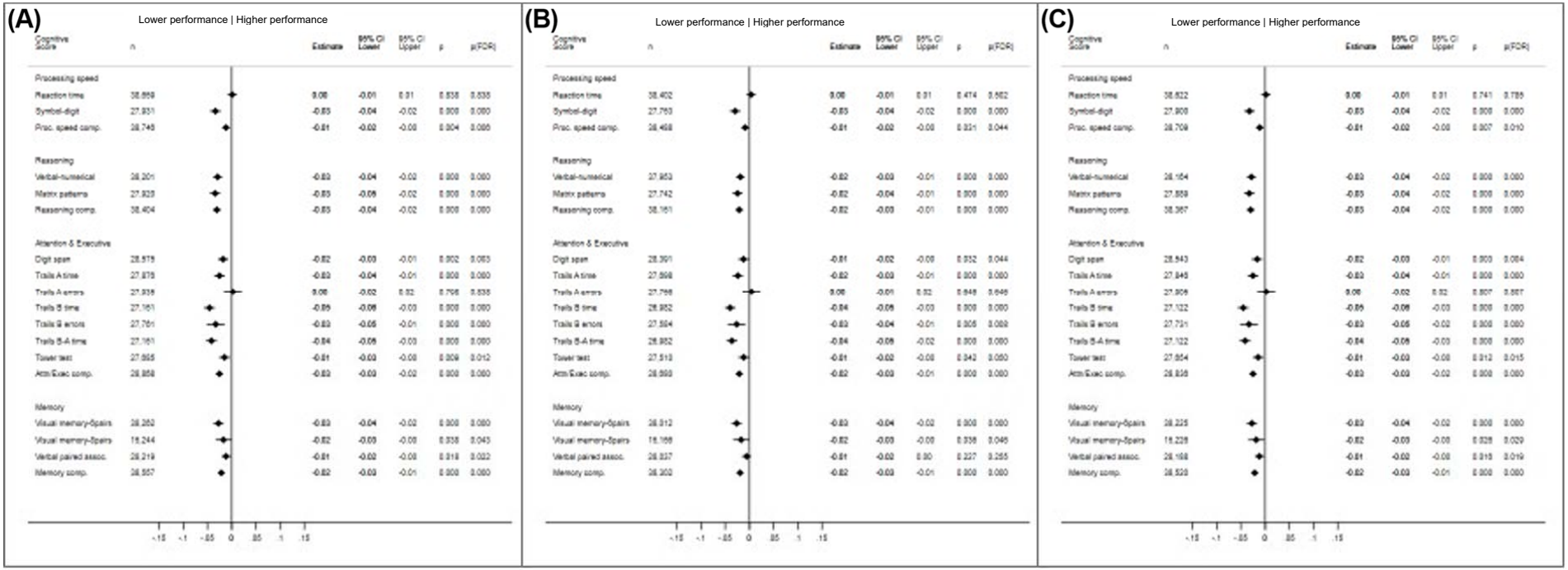
(A) Polygenic risk score for depression, in the European subgroup, excluding participants with a lifetime history of depression, adjusted as per main Figure 3(B). (B) Polygenic risk score for depression, in the European subgroup, excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 3(B).
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; FDR, false discovery rate; immed., immediate.

eFigure 23. Add Health Sensitivity Analyses for Polygenic Risk, Taking Account of Relatedness and Missing Data



(A) Polygenic risk score for depression, in the European subgroup, restricted to unrelated participants, adjusted as per main Figure 3(B). (B) Polygenic risk score for depression, in the European subgroup, with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 3(B).
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; FDR, false discovery rate; FIML, full information maximum likelihood; immed., immediate.

eFigure 24. UK Biobank Primary Analyses for Polygenic Risk, with Different Levels of Covariate Adjustment

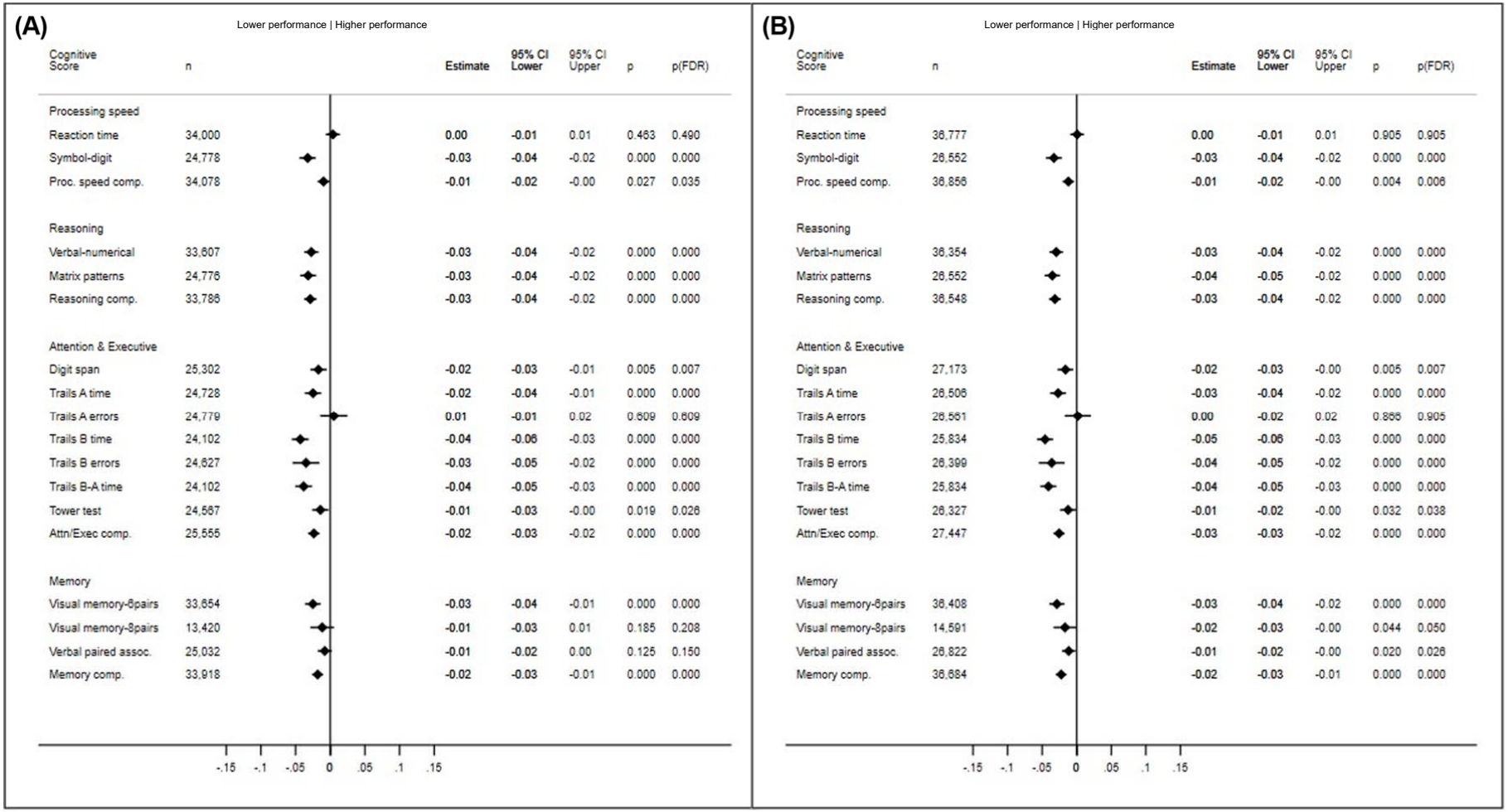


(A) Polygenic risk score for depression, in the White British subgroup, adjusted only for first 10 genetic principal components and batch. (B) Polygenic risk score for depression, in the White British subgroup, adjusted as per main Figure 4(B), plus additional adjustment for education. (C) Polygenic risk score for depression, in the White British subgroup, adjusted as per main Figure 4(B), plus additional adjustment for socioeconomic status.

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: adjusted only for first 10 genetic principal components and batch OR 0.95 (95% CI 0.93 to 0.98, *P*<.001, P_{FDR}<.001); adjusted plus education OR 0.96 (95% CI 0.93 to 0.98, *P*=.001, P_{FDR}=.002); adjusted plus socioeconomic status OR 0.95 (95% CI 0.92 to 0.98, *P*<.001, P_{FDR}<.001).

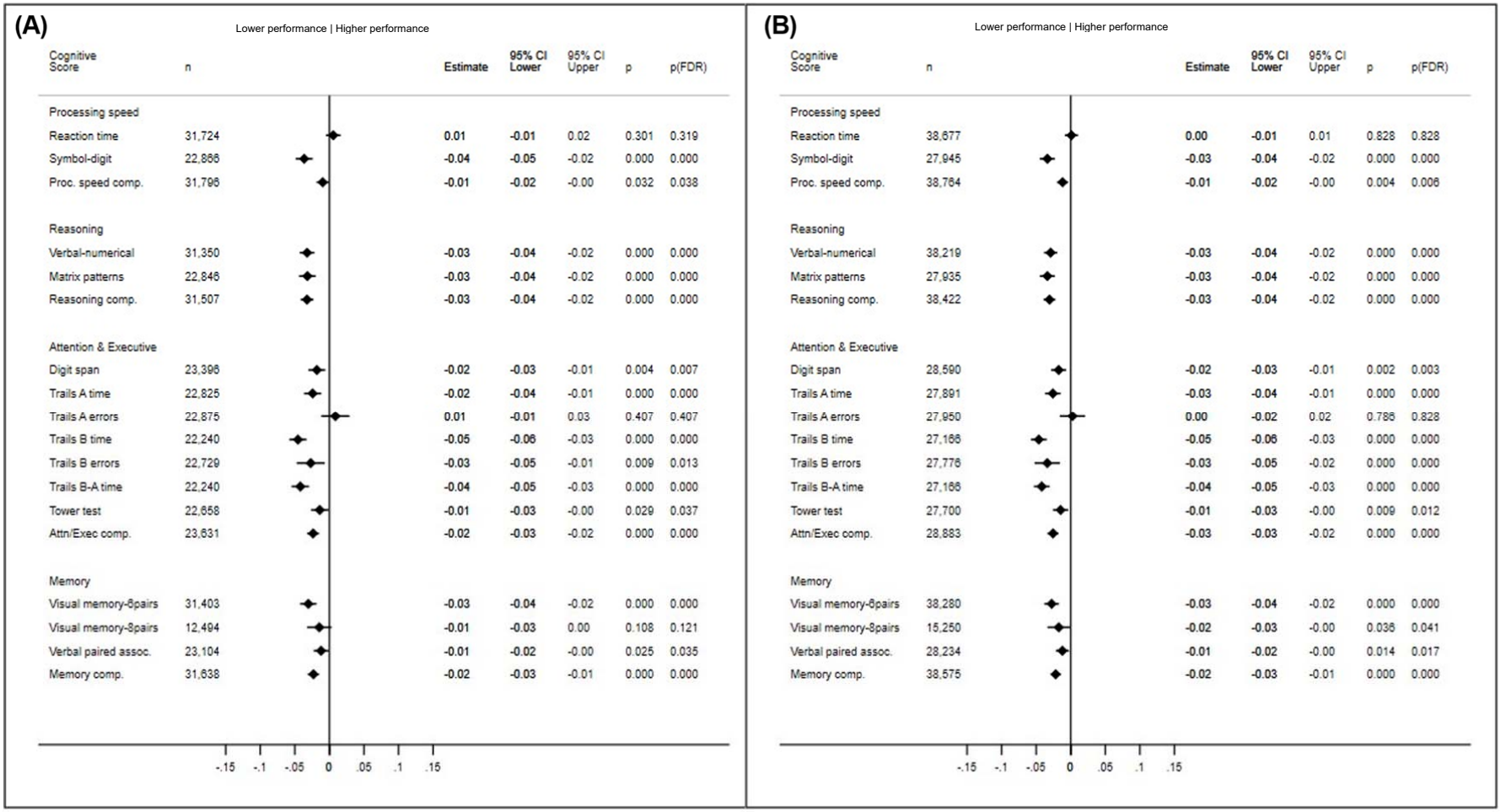
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; OR, odds ratio; Proc., Processing.

eFigure 25. UK Biobank Secondary Analyses for Polygenic Risk, Excluding Participants with Depression or Neurological Disorders



(A) Polygenic risk score for depression, in the White British subgroup, excluding participants with a lifetime history of depression, adjusted as per main Figure 4(B). (B) Polygenic risk score for depression, in the White British subgroup, excluding participants with a lifetime history of neurological disorders, adjusted as per main Figure 4(B).
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: excluding depression OR 0.95 (95% CI 0.93 to 0.98, *P*=.002, P_{FDR}=.003); excluding neurological disorders OR 0.95 (95% CI 0.92 to 0.98, *P*=.001, P_{FDR}=.002).
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; OR, odds ratio; Proc., Processing.

eFigure 26. UK Biobank Sensitivity Analyses for Polygenic Risk, Taking Account of Relatedness and Missing Data



(A) Polygenic risk score for depression, in the White British subgroup, restricted to unrelated participants, adjusted as per main Figure 4(B). (B) Polygenic risk score for depression, in the White British subgroup, with FIML estimation to take account of missing exposure or covariate data, adjusted as per main Figure 4(B).
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: unrelated OR 0.94 (95% CI 0.91 to 0.97, *P*<.001, P_{FDR}<.001); FIML OR could not be estimated as this option is not available in Stata's generalized regression functions.
Abbreviations: Attn/Exec, Attention & Executive; assoc., associates; CI, confidence interval; comp., composite; FDR, false discovery rate; FIML, full information maximum likelihood; OR, odds ratio; Proc., Processing.

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