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A Phenome-Wide Association Study (PheWAS) of Late Onset Alzheimer Disease Genetic Risk in Children of European Ancestry at Middle Childhood: Results from the ABCD Study

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Abstract

Genetic risk for Late Onset Alzheimer Disease (AD) has been associated with lower cognition and smaller hippocampal volume in healthy young adults. However, whether these and other associations are present during childhood remains unclear. Using data from 5556 genomically-confirmed European ancestry youth who completed the baseline session of the ongoing the Adolescent Brain Cognitive Development[SM] Study (ABCD Study®), our phenome-wide association study estimating associations between four indices of genetic risk for late-onset AD

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Alexander S. Hatoum and Ryan Bogdan contributed equally to the project.

Author contributions AJG, SEP, NRK, IN, LB, ISH cleaned the phenotypic data. AJG, SEP, ECJ, SC, ASH cleaned the genomic data and calculated/coded genetic risk (i.e., PRS, *APOE4*). AJG, SEP, ASH conducted analyses. AJG and RB conceptualized the study and AJG, RB, ASH, ECJ, NRK, and SEP drafted the initial manuscript. All coauthors provided input on study conceptualization and edited the manuscript with important intellectual content.

Conflict of interest Aaron J. Gorelik, Sarah E. Paul, Nicole R. Karcher, Emma C. Johnson, Isha Nagella, Lauren Blaydon, Hailey Modi, Isabella S. Hansen, Sarah M.C. Colbert, David A.A. Baranger, Sara A. Norton, Isaiah Spears, Brian Gordon, Wei Zhang, Patrick L. Hill, Thomas F. Oltmanns, Janine D. Bjisterbosch, Arpana Agrawal, Alexander S. Hatoum, and Ryan Bogdan declare that they have no conflict of interest.

Ethical approval Working with ABCD NDA data was approved by the Washington University in St. Louis Institutional Review Board: IRB ID#201708123.

Human and Animal Rights and Informed consent All data was obtained through the Adolescent Brain and Cognitive Development study. Informed consent was handled by each site. The ABCD data is publicly available (secondary data analysis). Informed consent was obtained from each site before data collection from the Childs parent or guardian. Data was deanonymized before download via the public NDA App. ABCD has extensive protocols for participant consent, safety, and anonymity, see https://doi.org/10.1016/j.dcn.2017.06.005.

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(i.e., AD polygenic risk scores (PRS), *APOE* rs429358 genotype, AD PRS with the *APOE* region removed ($AD_{PRS\text{-}APOE}$), and an interaction between $AD_{PRS\text{-}APOE}$ and *APOE* genotype) and 1687 psychosocial, behavioral, and neural phenotypes revealed no significant associations after correction for multiple testing (all ps > 0.0002; all $p_{fdr} > 0.07$). These data suggest that AD genetic risk may not phenotypically manifest during middle-childhood or that effects are smaller than this sample is powered to detect.

Keywords

Alzheimer disease; Polygenic risk scores; Phenome-wide association study; Middle childhood; Imaging; APOE

Introduction

Alzheimer Disease (AD) is a growing international public health problem. Alongside increases in global life expectancy (Wang et al. 2020), there have been increases in the AD and other dementia cases (117% increase from 1990 to 2016; (Nichols et al. 2019). This trend is expected to continue with projections of a 60% increase from 2019 to 2050 (from 57.4 to 152.8 million cases) due to three risk factors (i.e., high body-mass-index, fasting glucose, and smoking; GBD 2019 Dementia Forecasting Collaborators 2022). This anticipated increase in AD will generate further socioeconomic burden and negatively impact individuals, families, and health care (Grabher 2018; GBD 2019 Dementia Forecasting Collaborators 2022). As late-onset AD (LOAD) is largely heritable (58–79%) and characterized by an extensive polygenic architecture and a highly penetrant single common locus (i.e., *APOE*-ε4 Odds Ratio: 3.2; Sims et al. 2020; Mol et al. 2022), understanding the correlates of AD genetic risk across the lifespan may help identify and characterize early phenotypic signs, to ultimately improve our understanding of AD and limit its impact.

AD genetic risk is associated with variability in behavioral and neural phenotypes in healthy young adults

The typical late-life onset of (Late Onset) AD has led to efforts to identify precursors of the disorder that may enable early identification. Measures of cognition, brain structure, biomarkers (e.g., amyloid β), and genetic risk have been most frequently proposed and used to prognosticate later dementia and AD risk (Livingston et al. 2020). Mild cognitive impairment (MCI), which is characterized by memory complaints and/or impairment in the context of relatively preserved cognition, often precedes AD dementia (Albert et al. 2011). Similarly, hippocampal volume has been linked to reduced memory performance across ages, MCI, and progression to AD dementia (Filippini et al. 2009). Genetic risk (e.g., Apolipoprotein E genotype; polygenic risk scores) and measures of AD-related biomarkers (e.g. Amyloid β 42/40 ratio) have also been shown to predict the development of AD dementia (Bekris et al. 2010; Reitz et al. 2020; Bellenguez et al. 2022).

The investigation of AD genetic risk (i.e., *APOE* genotype, polygenic risk) among healthy individuals prior to the typical onset of AD dementia has revealed that variability in these cognitive and neural risk factors are observable in healthy young adults as early as in their thirties (Hendriks et al. 2021). For example, genetic risk for AD (i.e., *APOE* genotype, polygenic risk) has been associated with smaller hippocampal volume and lower cognition across many studies of young (mean age = 26.8), middle (ages 45–55), and older aged adults (mean age = 72) (Fleisher et al. 2005; O'Dwyer et al. 2012; Evans et al. 2020; Walhovd et al. 2020; Murray et al. 2021). These data suggest that subtle differences in cognition and brain structure are present even before onset of clinical impairment. What remains unclear is whether these differences emerge during childhood and if AD genetic risk is associated with factors beyond cognition and hippocampal volume including other behavioral, neural, experiential, and social factors (Dean et al. 2014; Korologou-Linden et al. 2022).

The current study

Here, we conducted a phenome-wide association study (PheWAS) of genetic risk for late-onset Alzheimer Disease among children of European ancestry who completed the baseline session of the Adolescent Brain and Cognitive Development[SM] (ABCD) Study. We hypothesized that genetic risk for AD (e.g., *APOE* rs429358 risk allele and AD polygenic risk) would be associated with smaller hippocampal volume and lower cognitive performance during middle childhood, and that novel associations with behavioral and brain phenotypes and experiential and social factors would be identified.

Methods

Participants

Data were drawn from data release 3.0 and 4.0 of the ongoing longitudinal Adolescent Brain and Cognitive Development[SM] (ABCD) Study (Volkow et al. 2018). The ABCD Study® is following 11,879 children (ages 8.9–11) recruited at baseline from 22 research sites across the United States to study the development of complex behavior and biology during middle childhood to late adolescence/young adulthood in the context of experience and genetic background. We drew data only from the baseline session. Participants of non-European genomic ancestry were excluded (see "Genetic Data" section below) from analyses due to the lack of a well powered ancestry-specific discovery GWAS of Alzheimer Disease in other ancestries, the relatively uninformative and low predictive utility of PRS when applied across ancestries (Martin et al. 2019), and evidence of divergence in genetic risk for AD across ancestries (Kunkle et al. 2021). After further excluding individuals with missing covariate data, our final analytic sample consisted of 5,556 children of genomically-confirmed European ancestry with baseline study data. Analytic Ns ranged from 120 to 5556 (mean N = 5012; median N = 5509) due to missing phenotypic data.

Phenotypes

All ABCD Study baseline behavioral, self-report, and neuroimaging phenotype data (data release 3.0 and 4.0) as well as genomic data (data release 3.0) were downloaded from the National Institute of Mental Health Data Archive (NDA; https://nda.nih.gov/). Phenotypes

were reviewed for inclusion according to: (1) relevance (e.g., administrative items [e.g., measurement device], redundancy [e.g., excluding t-scored data and using raw data]; Supplement), and (2) missingness and frequency variability (i.e., continuous phenotypes were required to have ≥ 100 participants with non-missing values; categorical variables required ≥ 100 endorsements/category). When applicable (e.g., substance use questions that were not asked following a response that the child had not heard of the substance), missing data were recoded to 0. Otherwise, all missing values were coded as missing (e.g., distress related to the presence of psychotic-like experiences was coded as missing in participants who reported no psychotic-like experiences). All data were triple checked by multiple investigators for relevance, variability, and accurate recoding.

Data were separated into those corresponding to behavioral and psychosocial phenotypes (N = 1269; Supplementary Tables 1 and 3) and brain imaging phenotypes (N = 418; Supplementary Table 2) for analyses (see “Statistical Analyses”). Behavioral and psychosocial data were categorized into the following 8 domains: (1) cognition (N = 14), (2) screen time (N = 18), (3) demographics (N = 27), (4) substance (N = 48), (5) culture/environment (N = 113), (6) physical health (N = 170), (7) family mental health (N = 239), and (8) child mental health (N = 640) (Supplementary Table 3). Neuroimaging indices of brain structure and resting state functional connectivity (RSFC) included the following domains (processing details provided in the Supplement): (1) gray matter volumes (global N = 9; subcortical N = 35, cortical N = 68; Supplementary Tables 5–6), (2) cortical thickness (global N = 3; regional N = 68; Supplementary Table 5–6), (3) cortical surface area (global N = 3; regional N = 68; Supplementary Table 5–6), (4) DTI fractional anisotropy (global N = 1; N = 37; Supplementary Table 5–6), (5) DTI mean diffusivity (global N = 1; N = 37; Atlas Tract; Supplementary Table 5–6), (6) RSFC (within network, N = 13; between network, N = 78; Supplementary Table 7). Brain phenotypes were derived using Freesurfer segmentation (subcortical volumes; Dale et al. 1999), the Desikan-Killianry atlas (cortical thickness and surface area; (Desikan et al. 2006), Atlas Tract (FA, MD; Basser et al. 1994), and Gordon networks RSFC; Gordon et al. 2016). No task-related functional magnetic resonance imaging (fMRI) data were examined due to test–retest reliability concerns surrounding this method (Elliott et al. 2020).

AD genetic risk

Genetic data and quality control—Saliva samples were genotyped on the Smokescreen array (Baurley et al. 2016) by the Rutgers University Cell and DNA Repository (now incorporated with other companies as Sampled; https://sampled.com/). Genotyped calls were aligned to GRC37 (hg19). Rapid Imputation and COmputational PIpeLIne for Genome-Wide Association Studies (RICOPILI) (Lam et al. 2020) was used to perform quality control (QC) on the 11,099 individuals with available ABCD Study phase 3.0 genotypic data, using RICOPILI’s default parameters. The 10,585 individuals who passed QC checks were matched to broad self-reported racial groups using the ABCD Study parent survey. Of the 6787 parents/caregivers indicating that their child’s race was only “white,” 5561 of those individuals did not endorse any Hispanic ethnicity/origin. After performing a second round of genetic data QC on these sub-samples, 5556 non-Hispanic White individuals were retained in the analyses. Principal component analysis (PCA) in RICOPILI was used

to confirm the genetic ancestry of these individuals by mapping onto the 1000 Genomes reference panel, resulting in a PCA-selected European-ancestry subset. The TOPMed imputation reference panel was used for imputation (Taliun et al. 2021). Imputation dosages were converted to best-guess hard-called genotypes, and only SNPs with Rsq > 0.8 and MAF > 0.01 were kept for PRS analyses.

Generating polygenic risk scores and *APOE* genotype—Genetic risk for AD was represented using 4 indices: (1) polygenic risk across the genome (AD_{PRS}), (2) *APOE* rs429358 genotype (*APOE*), (3) polygenic risk for AD excluding the *APOE* region ($AD_{PRS\text{-}APOE}$), and (4) a moderation analysis in which polygenic risk for AD excluding the *APOE* region was moderated by *APOE* rs429358 genotype ($AD_{PRS\text{-}APOE}$ × *APOE* genotype).

PRS-CS (Ge et al. 2019) was used to generate AD polygenic risk scores using effect size estimates from the largest GWAS of AD (N = 1,126,563; Wightman et al. 2021). Given the European ancestry background of the AD GWAS and the ABCD analytic sample, the corresponding European ancestry LD reference panel from the 1000 Genomes Project Phase 3 samples (available for download from https://github.com/getian107/PRScs) was used. The 'auto' function of PRS-CS was applied, allowing the software to learn the global shrinkage parameter from the data with 10,000 iterations and 5,000 burn-in. After deriving SNP weights using PRS-CS, PLINK 1.9's—score command was used to produce PRS in the ABCD sample. For the creation of the PRS for AD excluding the *APOE* region ($AD_{PRS\text{-}APOE}$); chr19:45,116,911–46,318,605). This definition was selected based on previous papers' definitions of the *APOE* genomic region (e.g., Kunkle et al. 2019) and based on a regional association plot of GWAS signals around the *APOE* gene. *APOE* genotype was derived from the ABCD sample by using Plink 1.9's—recode flag to generate a count of the number of 'C' "risk" alleles for the rs429358 SNP, which has been used to index *APOE* genetic risk (Cruchaga et al. 2012). Risk (i.e., "C") allele counts for *APOE* rs429358 are given in Table 1.

Statistical analyses—Numeric data were scaled to a mean of 0 and standard deviation of 1 prior to analysis. PheWAS associations between *genetic risk for AD* (i.e., $AD_{PRS,}$ *APOE*, $AD_{PRS\text{-}APOE,}$ $AD_{PRS\text{-}APOEx}$ *APOE*) and phenotypes were estimated using independent mixed effects models in the lme4 R software package (Bates et al. 2015); the lmer() function was used for continuous outcomes (Bates et al. 2015), and the glmer() function was used for dichotomous outcomes (Austin 2010). All non-imaging models were nested by site and family ID while imaging models were nested by scanner and family ID to account for the non-independence of these data. Fixed effect covariates for all analyses included: the first 10 ancestry principal components, age, and sex (sex was removed for models where the outcome was a sex-specific phenotype, e.g. "Have you noticed a deepening of your voice?" (pds_m4_y) from the ABCD Youth Pubertal Development Scale and Menstrual Cycle Survey History). For brain structure regional estimates, a global index was also included as a covariate (Supplementary Table 6; i.e., total cortical thickness for regional cortical thickness analyses; total cortical and subcortical volume for cortical and subcortical gray matter volume, respectively; total surface area for regional surface area analyses; and average

fractional anisotropy or mean diffusivity across all fibers for all DTI analyses). To ensure seed stability within generalized linear mixed-effects models (GLMER), all models were run seven times using the base R set.seed() function for the following randomly generated seeds: 10, 18, 29, 42, 73, 96, and 168. The marginal R^2 of fixed effects was calculated using the MuMIn package (Bartoń 2009). R^2 was calculated by using the difference of the marginal R^2 of the genetic indice and the marginal R^2 without the genetic indice. Given that there is no true R^2 with logistic models, to calculate the R^2 of the GLMER models Nagelkerke pseudo R^2 was used (Nagelkerke et al. 1991).

To adjust for multiple testing, false discovery rate (FDR) and a Bonferroni-corrected phenome-wide significance threshold were used separately for psychosocial and behavioral phenotypes (0.05/1269 = 0.000039 Bonferroni alpha level) and each respective imaging modality: subcortical volume (0.05/35 = 0.00143 Bonferroni alpha level); cortical volume, cortical thickness, and surface area for each (0.05/68 = 0.00074 Bonferroni alpha level); mean diffusivity and fractional anisotropy for each (0.05/37 = 0.00135 Bonferroni alpha level); and RSFC (0.05/91 = 0.00055 Bonferroni alpha level) within each of our 4 genetic risk indices (i.e., AD_{PRS}, *APOE*, $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE} \times$ *APOE*).

Results

None of the AD genetic risk indices (i.e., $AD_{PRS,}$ *APOE*, $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE} \times$ *APOE*) were significantly associated with any non-imaging or imaging phenotypes after either Bonferroni or FDR multiple testing correction (non-imaging: all |B|s or ORs < 2.42; all p > 0.00118; all p_{fdrs} > 0.23, Fig. 1, Supplementary Table 4; imaging: all |B|s < 0.03; all ps > 0.003; all p_{fdrs} > 0.22, Supplementary Tables 5–7). A monte-carlo based simulation power analysis using SIMR (Green and MacLeod 2016) suggested our most significant effect only had 58% power.

Psychosocial and behavioral phenotypes

No psychosocial or behavioral phenotypes, within any domain (i.e., cognition, screen time, demographics, substance, culture/environment, physical health, family mental health, and child mental health) were significantly associated with any index of AD genetic risk after either Bonferroni or FDR multiple testing correction. Across the four indices of genetic risk for AD: AD_{PRS}, *APOE*, $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE} \times$ *APOE* genotype, six of the eight assessed domains had nominally significant associations (p < 0.01) and are reported in Tables 2, 3, 4. There were no nominally significant associations in either the Demographics or Screen Time domain. In total, across six domains (i.e., Child Mental Health, Family Mental Health, Physical Health/Development, Culture/Environment, Substances, Cognition) and AD_{PRS}, *APOE, and* $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE} \times$ *APOE* genotype, there were 18, 12, 10, and 15 nominally significant associations, respectively (nominal significance considered as p < 0.01 due to the large number of phenotypes investigated). Specifically, the following number of nominally significant associations were observed for each AD genetic risk by domain: *Child Mental Health* (AD_{PRS} = 10, *APOE* = 4, $AD_{PRS\text{-}APOE}$ = 3, $AD_{PRS\text{-}APOE} \times$ *APOE* genotype = 7), *Family Mental Health* (AD_{PRS} = 3, *APOE* = 4, $AD_{PRS\text{-}APOE}$ = 4, $AD_{PRS\text{-}APOE} \times$ *APOE* genotype = 3), *Physical Health/Development* (AD_{PRS} = 3,

APOE = 3, $AD_{PRS\text{-}APOE}$ = 3, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 5), *Culture/Environment* (AD_{PRS} = 0, *APOE* = 1, $AD_{PRS\text{-}APOE}$ = 0, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 0), *Substance* (AD_{PRS} = 1, *APOE* = 0, $AD_{PRS\text{-}APOE}$ = 0, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 0), *Cognition* (AD_{PRS} = 0, *APOE* = 1, $AD_{PRS\text{-}APOE}$ = 0, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 0. Below and reported in Tables 2, 3, 4, we briefly summarize the directionality of associations that were below an uncorrected p value threshold of 0.01 within each of these domains for AD_{PRS}, *APOE*, and $AD_{PRS\text{-}APOE}$. Nominally significant $AD_{PRS\text{-}APOE}$ × *APOE* interactions are not described below as no post-hoc tests were conducted to characterize the directionality of these moderation effects due to the lack of significant interactions when accounting for multiple testing.

Cognition—*APOE* risk alleles were associated with reduced performance on the Rey Auditory Verbal Learning Test, a neuropsychological assessment of auditory-verbal attention, memory, and learning (Total score: B = − 0.04, p = 0.0061, p_{fdr} = 0.70). No other associations p < 0.01 were observed for any AD genetic risk index. No other cognition phenotypes were associated with any AD genetic index at even nominal p < 0.05 levels of significance.

Screen time—No associations ps < 0.01 were observed for any AD genetic risk index.

Demographics—No associations ps < 0.01 were observed for any AD genetic risk index.

Substances—Higher AD_{PRS} was associated with greater substance accessibility (i.e., “If your child wanted to get a drug like cocaine, LSD, or amphetamines, how easy would it be for them to get some?”; B = 0.04, p = 0.008, p_{fdr} = 0.64). No other associations ps < 0.01 were observed for any AD genetic risk index.

Culture/environment—*APOE* risk alleles were associated with talking more often to one’s parent/guardian about daily plans (B = 0.04, p = 0.001, p_{fdr} = 0.43). No other associations ps < 0.01 were observed for any AD genetic risk index.

Physical health (inclusive of development)—Both higher AD_{PRS} and *APOE* risk alleles were associated with a later age (in months) when being able to sit up by oneself as an infant/toddler (both Bs > 0.04, ps < 0.002, ps_{fdr} > 0.23) and being evaluated by a medical professional for a sprain (both Bs > 0.12, ps < 0.002, ps_{fdr} > 0.23). Higher AD_{PRS} was associated with greater pubertal development among males (B = 0.05, p = 0.006, p_{fdr} = 0.57) and *APOE* risk alleles were associated with more hospitalizations (B = 0.10, p = 0.005, p_{fdr} = 0.66). Finally, $AD_{PRS\text{-}APOE}$ was associated with receiving stitches from a medical practitioner and birth complications as well as a (all |B|s > 0.08, all ps < 0.008, all ps_{fdr} > 0.77). No other associations < 0.01 were observed for any AD genetic risk index.

Family mental health—The caregivers (predominantly mothers) of individuals with high AD_{PRS} reported increased bragging, being less mean, and increased intrusive thoughts (all |B|s > 0.02, all ps < 0.01, all ps_{fdr} > 0.23). Among those with more *APOE* risk alleles, caregivers reported more bragging and talking too much as well as being less mean to others and that their behavior is less changeable (all |B|s > 0.02, all ps < 0.01, all ps_{fdr} > 0.43).

Caregivers of those with elevated $AD_{PRS\text{-}APOE}$ reported lower emotional disturbance (e.g., less anhedonia, not crying a lot), dependence on others, and difficulty making decision (all Bs < − 0.03, all ps < 0.01, all ps_{fdr} > 0.82). No other associations < 0.01 were observed for any AD genetic risk index.

Child mental health—Greater AD_{PRS} was associated with reduced anxiety (e.g., difficulty controlling worries) and manic symptoms (e.g., racing thoughts) and impairment (e.g., clinically significant distress due to worry) as well as increased impairment due to compulsions (all |B|s > 0.14, all ps < 0.009, all ps_{fdr} > 0.23). *APOE* risk alleles were associated with greater compulsive symptoms (e.g., past compulsions) and impairment (e.g., past impairment in function due to compulsions) and reduced anxiety symptoms (i.e., difficulty controlling worries) (all |B|s > 0.17, all ps < 0.007, all ps_{fdr} > 0.43). Finally, greater $AD_{PRS\text{-}APOE}$ was associated with less clinging to adults/dependence and receipt of special services at school as well as greater sleep problems and insomnia (all |B|s > 0.04, all ps < 0.009, all ps_{fdr} > 0.77). No other associations p < 0.01 were observed for any AD genetic risk index. All corrected and uncorrected non-imaging phenotype results are in Supplementary Table 4.

Neuroimaging phenotypes

No brain phenotype, either global or regional, was significantly associated with any index of AD genetic risk, when adjusting for multiple testing using FDR or Bonferroni correction (all |B|s < 0.03; all ps > 0.003; all ps_{fdr} > 0.22; Supplementary Tables 5–7). The association between $AD_{PRS\text{-}APOE}$ and increased cerebellum volume and white matter approached significance with FDR correction (volume: right & left: both |B|s > 0.26, both ps < 0.007, both ps_{fdr} = 0.074; white matter volume: |B|= 0.01, p = 0.0058, p_{fdr} = 0.074). The hippocampus, which was been previously associated with AD genetic risk in healthy samples, was not associated with any index of AD genetic risk (all |B|s < 0.02; all ps > 0.14, all ps_{fdr} > 0.68; Supplementary Table 5–7). Across the four indices of genetic risk for AD: AD_{PRS}, *APOE*, $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE}$ × *APOE* genotype, all eight imaging domains had nominally significant associations (P < 0.05) and are reported in Tables 2, 3, 4. In total, across the eight imaging domains (i.e., Whole Brain, Regional Subcortical Volume, Regional Cortical Thickness, Cortical Surface Area, Regional Mean Diffusivity, Regional Fractional Anisotropy, and RSFC) the four indices of genetic risk for AD (AD_{PRS}, *APOE, and* $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE}$ × *APOE* genotype) had 16, 20, 27, and 25 nominally significant associations, respectively. Specifically, the following number of nominally significant associations were observed for each AD genetic risk by imaging modality: *Whole Brain* (AD_{PRS} = 0, *APOE* = 0, $AD_{PRS\text{-}APOE}$ = 3, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 0) *Regional Subcortical Volume* (AD_{PRS} = 3, *APOE* = 4, $AD_{PRS\text{-}APOE}$ = 5, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 1), *Regional Cortical Volume* (AD_{PRS} = 4, *APOE* = 2 $AD_{PRS\text{-}APOE}$ = 4, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 4), *Regional Cortical Thickness* (AD_{PRS} = 3, *APOE* = 4, $AD_{PRS\text{-}APOE}$ = 5, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 4), *Cortical Surface Area* (AD_{PRS} = 3, *APOE* = 3, $AD_{PRS\text{-}APOE}$ = 4, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 7), *Regional Mean Diffusivity* (AD_{PRS} = 1, *APOE* = 3, $AD_{PRS\text{-}APOE}$ = 2, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 2), *Regional Fractional Anisotropy* (AD_{PRS} = 0, *APOE* = 0, $AD_{PRS\text{-}APOE}$ = 1, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 2), and *RSFC* (AD_{PRS} = 2, *APOE* = 4, $AD_{PRS\text{-}APOE}$

= 3, $AD_{PRS\text{-}APOE}$ × *APOE* genotype = 5). Below, and reported in Tables 2, 3, 4, we briefly summarize associations that were nominally significant, i.e., $p < 0.05$ uncorrected for multiple testing for $AD_{PRS,}$ *APOE* risk alleles, $AD_{PRS\text{-}APOE}$. The $AD_{PRS\text{-}APOE}$ × *APOE* interactions are not described here, as post-hoc tests to characterize these interactions were not conducted due to the lack of significance when accounting for multiple testing.

Whole brain

$AD_{PRS\text{-}APOE}$ was associated with greater total, right, and left cortical volumes at nominal levels of significance (all |B|s > 0.023, all ps < 0.04, all $p_{fdr} = 0.22$). No other nominally significant associations were observed for any AD genetic risk index. All whole brain results are in Supplementary Table 6.

Regional

Volume

Subcortical: Overall, AD genetic risk (i.e., $AD_{PRS,}$ *APOE* risk alleles, $AD_{PRS\text{-}APOE}$) was associated with greater left and right Nucleus Accumbens volumes at nominal levels of significance (all |B|s > 0.02; all ps < 0.05, all $ps_{fdr} > 0.10$). AD_{PRS} was also associated with increased right putamen volume, as well as decreased right thalamic volume (all |B|s > 0.01; all ps < 0.05, all $ps_{fdr} > 0.18$). *APOE* genotype was associated with decreased brain stem volume, cerebellar cortical volume, and right thalamic volume (all |B|s > 0.01; all ps < 0.04, all $ps_{fdr} > 0.20$). Finally, $AD_{PRS\text{-}APOE}$ was associated with increased cerebellar cortex and cerebellar white matter volume (all |B|s > 0.02; all ps < 0.02, all $ps_{fdr} > 0.07$).

Cortical: AD_{PRS} was associated with increased volume in the right precentral gyrus, left superior temporal sulcus, and right lingual gyrus, as well as decreased volume in the right medial orbitofrontal cortex (all |B|s > 0.019; all ps < 0.05, all $ps_{fdr} > 0.48$). *APOE* risk alleles were associated with increased volume in the right paracentral lobule and left superior temporal sulcus (all |B|s > 0.029; all ps < 0.02, all $ps_{fdr} = 0.52$). Finally, $AD_{PRS\text{-}APOE}$ was associated with increased volume in the left precuneus, as well as decreased left caudal anterior cingulate, right inferior parietal, and left parahippocampal cortical volumes (all |B|s > 0.02; all ps < 0.03, all $ps_{fdr} = 0.10$). All regional Volume results are in Supplementary Table 5.

Cortical thickness—AD_{PRS} was associated with decreased thickness in the left and right supramarginal regions as well as the right inferior temporal region and increased thickness in the left superior temporal sulcus region (all |B|s > 0.019, all ps < 0.04, all $ps_{fdr} > 0.30$). *APOE* risk alleles were associated with increased thickness in the both hemispheres of the cuneus and the left superior temporal sulcus, as well as decreased inferior temporal thickness (all |B|s > 0.02, all ps < 0.03, all $ps_{fdr} > 0.13$). $AD_{PRS\text{-}APOE4}$ was associated with increased left middle temporal and right isthmus cingulate thickness, as well as decreased left and right parahippocampal and right precuneus thickness (all |B|s > 0.018, all ps < 0.05, all $ps_{fdr} > 0.42$). All regional Cortical Thickness results are in Supplementary Table 5.

Cortical surface area—AD_{PRS} was associated with increased right paracentral and right inferior temporal surface area, as well as decreased left caudal middle frontal surface area

(all |B|s > 0.018, all ps < 0.04, all ps_{fdr} = 0.73). *APOE* risk alleles were associated with increased surface area in the right paracentral and left superior temporal sulcus, as well as decreased left rostral anterior cingulate surface area (all |B|s > 0.02, all ps < 0.04, all ps_{fdr} = 0.81). $AD_{PRS\text{-}APOE}$ was associated with increased left precuneus and right inferior temporal surface area, as well as decreased left caudal anterior cingulate and right inferior parietal surface area (all |B|s > 0.019, all ps < 0.03, all ps_{fdr} > 0.19). All Cortical Surface Area results are in Supplementary Table 5.

Mean diffusivity—AD_{PRS} was associated with increased mean diffusivity (MD) within the right anterior thalamic radiations (B = 0.02, p = 0.006, ps_{fdr} = 0.23). *APOE* risk alleles were associated with increased MD within the right anterior thalamic radiations and the left striatal inferior frontal cortex, as well as decreased MD within the right parahippocampal cingulum (all |B|s > 0.02, all ps < 0.03, all ps_{fdr} = 0.27). $AD_{PRS\text{-}APOE4}$ was associated with increased MD within the left parietal superior longitudinal fasciculus and the right inferior-fronto-occipital fasciculus (B > 0.01, all ps < 0.05, all ps_{fdr} = 0.39). All regional Mean Diffusivity results are in Supplementary Table 5.

Fractional anisotropy—$AD_{PRS\text{-}APOE}$ was associated with decreased FA within the right inferior-fronto-occipital fasciculus (B = − 0.01, p = 0.037, ps_{fdr} = 0.61). No other nominally significant associations were observed for any AD genetic risk index. All regional Fractional Anisotropy results are in Supplementary Table 5.

Resting state functional connectivity—AD_{PRS} was associated with less functional coupling within the cingulo-opercular network and between the salience network and ventral attention network (B < − 0.02, all ps < 0.05, all ps_{fdr} = 0.95). *APOE* risk alleles were associated with increased correlated activity between the retrosplenial temporal network and both the “none” network and the default network and negative correlations between the retrosplenial temporal network and both the visual network and the dorsal attention network (all |B|s > 0.03, all ps < 0.02, all ps_{fdr} = 0.97). $AD_{PRS\text{-}APOE4}$ was associated with increased correlation between the dorsal attention network and sensorimotor hand network, between the fronto-parietal network and salience network, and between the auditory network and cingulo-parietal network (B > 0.02, all ps < 0.04, all ps_{fdr} > 0.33). All RSFC results are in Supplementary Table 7.

Discussion

We conducted a PheWAS of behavioral, psychosocial, and neuroimaging phenotypes in relation to four indices of genetic risk for AD (i.e., AD_{PRS}, *APOE*, $AD_{PRS\text{-}APOE}$, $AD_{PRS\text{-}APOE}$ × *APOE*) within individuals of genomically-defined European ancestry in the ABCD Study (Ns = 120–5556). No phenotypes (N = 1687) were associated with any index of the four AD genetic risk indices after correction for multiple testing using Bonferroni or FDR. All nominally significant observed effects were small (Ranges: |B|s = 0.087–0.71; Ors 0.660–1.3). These null associations contrast positive associations observed between polygenic risk scores observed in the ABCD Study sample. Notably, as other psychiatric PRS (e.g., schizophrenia, cannabis use disorder, depression, etc.) have been associated with behavioral, environmental, and neuroimaging phenotypes within the ABCD Study sample

(Johnson et al. 2020; Paul et al. 2021; Ohi et al. 2021; Karcher et al. 2022; Joo et al. 2022), our null findings cannot be attributed to broader poor polygenic prediction within this sample. Indeed, our observed null results raise the possibility that genetic risk for AD may not be phenotypically expressed during middle childhood or that any associations would be characterized by small effect sizes that our study (N = 5556) was underpowered to detect. In light of prior evidence linking AD genetic risk in healthy adults to cognition and brain structure (Bellenguez et al. 2022), it remains possible that individual differences in these phenotypes linked to genetic risk for AD do not emerge until adolescence and/or young adulthood when neurodevelopment transitions from growth to pruning (Tiemeier et al. 2010; Ladouceur et al. 2019; Sakai 2020).

Null and nominally significant associations

A few null associations and patterns of nominally significant association warrant discussion. First, contrary to hypotheses and prior studies in healthy adults (Fleisher et al. 2005; O'Dwyer et al. 2012; Evans et al. 2020; Walhovd et al. 2020; Murray et al. 2021), AD genetic risk was not associated with cognition or hippocampal volume in middle childhood. While APOE risk alleles were nominally associated with reduced auditory-verbal attention/memory/learning (Rey Auditory Verbal Learning Test Total Scores), this association did not approach significance when adjusting for multiple testing using our least stringent adjustment (FDR), and no other cognition phenotypes were associated with any index of genetic risk at nominal levels of significance. It is unlikely that this reflects a false negative association resulting from PheWAS multiple testing burden, as this association remains non-significant when only implementing multiple testing correction for cognition and hippocampal volumes across indices of AD genetic risk (N = 64 total tests; $p_{fdr} > 0.38$). When interpreted alongside evidence from adult studies linking AD genetic risk to reduced cognition and hippocampal volume (Ns = 44–2690; (Fleisher et al. 2005; O'Dwyer et al. 2012; Evans et al. 2020; Walhovd et al. 2020; Murray et al. 2021), our null findings raise the possibility that lower cognition and smaller hippocampal volumes observed in healthy adults at elevated genetic risk for AD may arise after middle childhood.

Second, increased cerebellum volume and white matter among individuals with higher AD $AD_{PRS\text{-}\textit{APOE}}$ scores approached significance with FDR adjustment for multiple testing correction within this modality. Notably, this observed effect was small (|B|= 0.0286 [95% CI 0.0097–0.0478]) and does approach significance if adjusting for all phenotypes examined simultaneously in the subcortical volume modality $P_{fdr} = 0.069$) and does not approach significance when applying FDR to all imaging phenotypes ($P_{fdr} = 0.283$). Reports of both larger (Lin et al. 2020) and smaller cerebellum (particularly gray matter; Gellersen et al. 2021) volume have been reported in AD dementia and related phenotypes (e.g., MCI; Jacobs et al. 2018). The effect size we observed (|B|= 0.0286, $R^2 = 0.0009$) was drastically smaller than these phenotypic associations observed in adult cases (|B|= 0.05; Lin et al. 2020, Cohen's D < 0.1; Gellersen et al. 2021). Other nominally significant brain structure findings (e.g., greater cortical volumes associated with $AD_{PRS\text{-}\textit{APOE}}$ and increased Nucleus Accumbens volumes associated with all AD genetic risk indices) run counter to some observations in AD (Nie et al. 2017) as well as adults at genetic risk (Muir et al. 2021). Overall, there was a general pattern of nominally significant associations between

AD risk and larger brain volumes. It is important to consider this pattern of findings in the context of the age of the sample (i.e., middle childhood). During typical development, there is extensive neural growth during middle childhood, after which a period of extensive pruning begins in adolescence, which slows in adulthood and then accelerates again in later life (Tiemeier et al. 2010; Ladouceur et al. 2019; Sakai 2020). While it is plausible that AD genetic risk may manifest as potentiated trajectories across development (i.e., including growth during childhood and pruning that begins in adolescence), the present pattern of nominally significant associations would need to be observed in independent samples before credence could be given to this possibility.

Third, nominally significant associations between AD genetic risk and development were observed. In particular both AD_{PRS} and *APOE* genotype were nominally associated with delayed infant development (i.e., a later age when an infant is first able to sit up by themself) and greater pubertal development among males. This directional association may be partially explained by the prevailing theory that later infant motor development may be related to worse cognitive and motor functioning that has been previously associated with cognitive ability (Murray et al. 2007). Earlier pubertal timing is also associated with worse cognitive functioning (Ghassabian et al. 2016). Thus, this may potentially reflect broad developmental signs associated with poor cognitive outcomes that are shared with AD genetic risk.

Fourth, several nominally significant associations were observed between different indices of AD genetic risk and increased injuries by middle childhood (e.g., more hospitalizations; evaluation by medication professionals for a sprain, receiving stitches from a medical practitioner, and birth complications). There is a wide variety of evidence suggesting that mild traumatic brain injury is associated with the future development of AD (Graham et al. 2022). It is possible that AD genetic risk may emerge through gene-environment correlation (e.g., increasing the likelihood of injury; Graham et al. 2022) and/or that AD genetic risk may moderate recovery following injury (e.g., inflammation) that increases AD risks (Alexander et al. 2007). However, there also was evidence of opposing associations (i.e., reduced broken bones) that should generate caution in overly interpreting this pattern of association with injury without additional evidence.

Fifth, there was nominally significant evidence that AD genetic risk was associated with reduced psychopathology symptoms (e.g., anxiety, anhedonia, anxiety) in children and their caregivers (predominantly mothers) and less receipt of special services at school, but increased compulsive behavior in children. As anxiety, psychopathology, and related behavior have been associated with increased risk for AD and related risk factors (e.g., mild cognitive impairment; Stafford et al. 2022), these findings counter what has been observed in adults, with the exception of compulsions which have been linked to AD risk (Dondu et al. 2015).

Overall, while there was little consistency in nominally significant associations across the three genetic indices of AD risk (AD_{PRS}, *APOE*, $AD_{PRS\text{-}APOE}$), the following phenotypes emerged in both the AD_{PRS} and *APOE* analyses: Child Mental Health (ksads_10_324_p, “Symptom—Difficulty controlling worries Present” and ksads_11_346_p, “Symptom—Impairment in functioning due to compulsions Past”), Family Mental Health (asr_q07_p

"I brag"), and Physical Health/Development: (medhx_6b, "Has he/she ever been to a doctor, a nurse, nurse practitioner, the emergency room or a clinic because of sprains"). This pattern may partially arise through the large risk conferred by *APOE* genotypes that heavily weights PRS; this interpretation is further supported by the lack of overlap between AD_{PRS} and *APOE* with $AD_{PRS\text{-}APOE}$. Interestingly, only the AD_{PRS} had nominally significant association in the Substance domain (su_risk_p_5, "If your child wanted to get a drug like cocaine, LSD, or amphetamines, how easy would it be for them to get some?"), and only the *APOE* genotype had nominally significant results in Cognition (RAVLT, "Rey Auditory Verbal Learning Test total score."

Limitations

The large sample size and deeply phenotyped sample permitted the PheWAS approach; however, the revealed null associations should also be interpreted in the context of study limitations. First, this is a cross-sectional study in a European ancestry subsample of individuals volunteering for research. This limits study generalizability and prohibits the evaluation of change, which may be especially important for neurodegenerative disorders. Second, the current PheWAS only estimated the associations between indices of genetic risk for late-onset AD, which has a heritability rate of 70–80% (Bekris et al. 2010). Importantly, non-mendelian early onset AD (< 65 years old) has a heritability rate of 92–100%, but there currently is not sufficient GWAS data from either national or international representative samples due to its low incidence and prevalence rate, (Reitz et al. 2020). Third, it is possible that our PheWAS did not include important indicators of AD risk that may be present during childhood. PheWAS variables were constrained by those measured in the ABCD study and do not include indices that may be more proximal to AD (e.g., to the best of the author's knowledge, the ABCD study does not collect family history of AD, dementia, or assess parental cognition) and others that have been previously linked to AD risk (e.g., inflammation; Zhang et al. 2022).

Fourth, the discovery GWAS of AD (Wightman et al. 2021) used to generate the AD PRS applied case–control association mapping by proxy, a method which results in potentially less specific accuracy of identifying AD, compared to the case–control approach where a clinical or pathological diagnosis of AD is used (Liu et al. 2017). A recent report highlights low SNP heritability (0.03), which may limit associations with the polygenic scores (Escott-Price and Hardy 2022). However, the case–control approach can be difficult to conduct, as collecting a large enough sample size can be both time consuming and expensive (Liu et al. 2017). Thus, the tradeoff for using the case–control association mapping by proxy method which generates "noisier" data is potentially mitigated by this increased sample size, which in turn reduces false positive associations as well as improves discovery rate (Hong and Park 2012) of significant loci of AD risk. It will be important to continue to examine this association as GWASs with more cases become available (Bellenguez et al. 2022) and evaluate the impact of proxy case inclusion on observed estimates.

Conclusions

Associations between genetic risk for AD and the psychosocial and neural phenotypes in childhood that we examined are small in magnitude. We did not find evidence for significant associations between AD Genetic risk with cognitive, behavioral, psychosocial, or imaging phenotypes in the European ancestry sample of ABCD during middle childhood. These data suggest that the manifestation of genetic risk for AD may not emerge, at least measurably, until adolescence and/or young adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

All ABCD data used in this study are available through the National Institute of Mental Health Data Archive (NDA), which may be accessed here: https://nda.nih.gov/.Code availability https://github.com/WashU-BG/ABCD_AD_PHEWAS.

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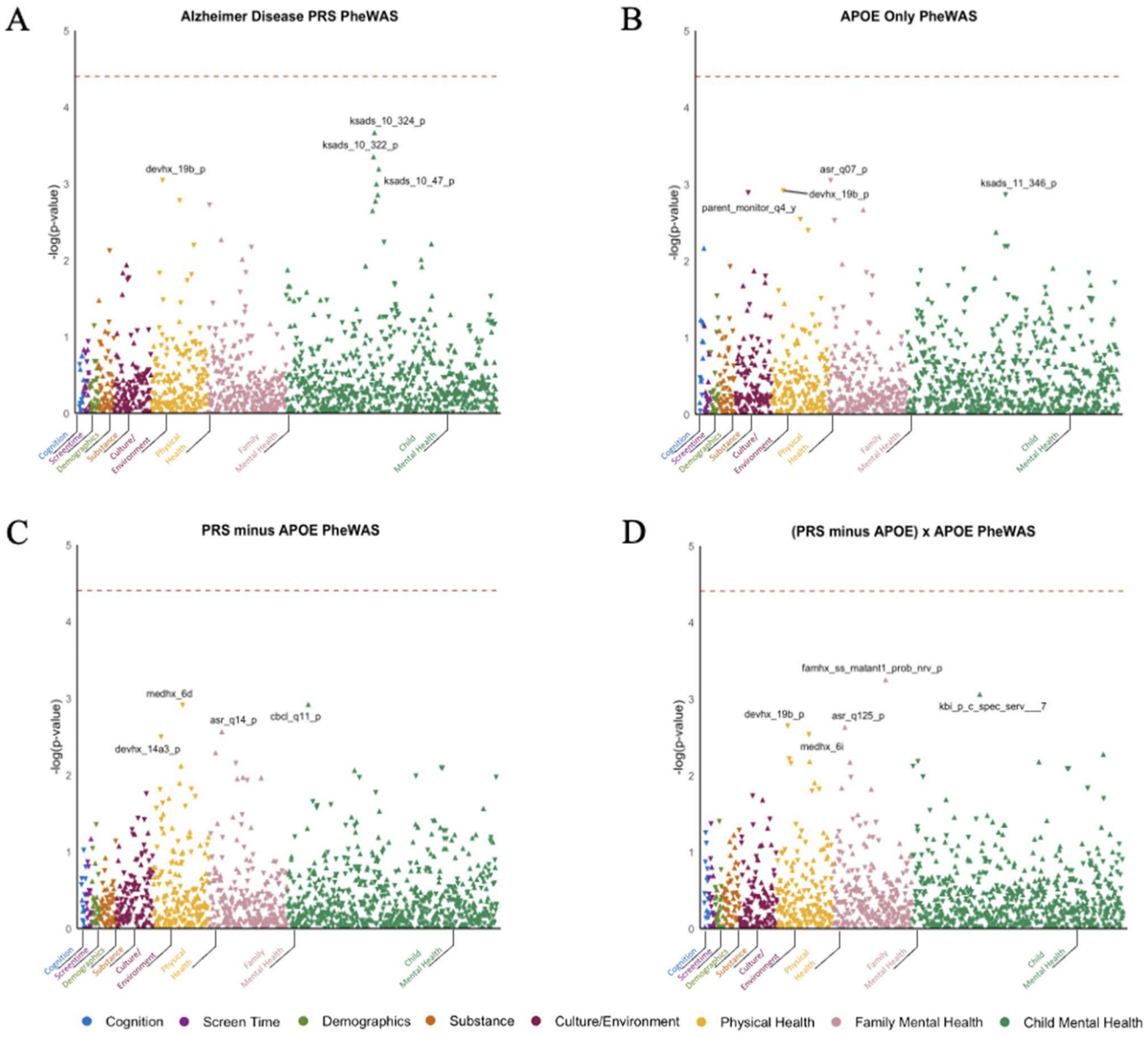

Fig. 1.

PheWAS Results for Non-imaging Phenotypes. Association between four genetic risk indices and cognitive, behavioral, and psychosocial phenotypes: **A** polygenic risk score (PRS) derived from the largest AD GWAS, **B** *APOE rs429358* risk alleles, **C** a PRS that excludes the APOE4 region, and **D** the moderation of the PRS that excludes the APOE4 region by APOE4. Key for figure: 1a: ksads_10_324_p = "Symptom—Difficulty controlling worries Present," ksads_10_322_p = "Symptom—Worry associated with defined symptom(s) Present," devhx_19b_p = "At approximately what age (number of months) was he/she FIRST able to sit without assistance?," and ksads_10_47_p = "Symptom—Worrying has lasted at least 6 months Present." Key for Fig. 1B: asr_q07_p = "I brag", devhx_19b_p = "At approximately what age (number of months) was he/she FIRST able to sit without assistance?," parent_monitor_q4_y = "How often do you talk to your parent or guardian about your plans for the coming day, such as your plans about what will happen at school

or what you are going to do with friends?," and ksads_11_346_p = "Symptom—Impairment in functioning due to compulsions Past." Key for Fig. 1C: medhx_6d = "Has he/she ever been to a doctor, a nurse, nurse practitioner, the emergency room or a clinic because Stitches," cbcl_q11_p = "Clings to adults or too dependent," asr_q14_p = "I cry a lot," and devhx_14a3_p = "Did he/she have any of the following complications at birth? Blue at birth? Key for Fig. 1D: famhx_ss_matant1_prob_nrv_p = "maternal aunt 1 nerves/nervous breakdown problem," kbi_p_c_spec_serv___7 = "Does your child receive special services at school?," devhx_19b_p = "At approximately what age (number of months) was he/she FIRST able to sit without assistance?," asr_q125_p = "In the past 6 months, on how many days were you drunk?," and medhx_6i = "Has he/she ever been to a doctor, a nurse, nurse practitioner, the emergency room or a clinic because of a head injury."

Table 1

Summary demographic information (N = 5556)

Variable	Mean (SD)/n (%)
Sex (male)	2612 (47.0%)
Age (years)	9.93 (0.63)
Household income	
< $35,000	375 (7.1%)
$35,000-$49,000	283 (5.1%)
$50,000-$74,999	717 (13.5%)
$75,000-$99,999	896 (16.9%)
$100,00-$199,999	2178 (41.1%)
$200,000	849 (16.0%)
Count of APOE rs429358 risk (C) Alleles	
0	4007 (72.1%)
1	1414 (25.4%)
2	135 (2.4%)
Highest caregiver education	
Less than high school	25 (0.45%)
High school degree or equivalent	188 (3.4%)
Some college, associate degree	1046 (18.8%)
College degree	1753 (31.6%)
Master’s degree	1723 (31.0%)
Doctorate/professional degree	829 (14.8%)

Table 2

PRS nominal significant P value results

Domain	Phenotype	Beta/OR [95% CI]	R^2	pval	FDR pval
A. Non-imagingp < 0.01					
Substances	Substance access- su_risk_p_5 (n = 5133)	0.04 [0.0106, 0.062]	0.0019	0.0075	0.639
Physical health	Sitting up age- devhx_19b_p (n=4937)	0.047 [0.022, 0.0851]	0.0022	0.0009	0.236
	Sprain assessment—medhx_6b* (n = 5555)	1.148 [1.061, 1.2290]	0.003	0.0016	0.236
	Male pubertal development—pds_y_ss_male_ cat_2 (n = 2647)	0.053 [0.018, 0.093]	0.0031	0.0062	0.568
Family mental health	Caregiver bragging—asr_q07_p (n = 5556)	0.04 [0.0180, 0.0680]	0.0013	0.0012	0.236
	Caregiver less mean—asr_q16_p (n = 5556)	− 0.036 [− 0.059, − 0.01]	0.0023	0.002	0.258
	Caregiver intrusive thoughts—asr_scr_ intrusive_r (n = 5556)	0.029 [0.0078, 0.0555]	0.0025	0.0097	0.71
Child mental health	Worry associated with defined anxiety symptoms- ksads_10_322_P* (n = 5509)	0.685 [0.5347, 0.8228]	0.013	0.0004	0.236
	Reduced racing thoughts, past- ksads_2_200_t* (n = 5531)	0.844 [0.7611, 0.9589]	0.0038	0.0097	0.718
	Current worry distress—ksads_10_328_P* (n = 5509)	0.743 [1.6405, 0.8685]	0.009	0.0009	0.236
	Current Difficulty controlling worries— ksads_10_324_P* (n = 5509)	0.660 [0.5337, 0.8098]	0.015	0.0002	0.236
	Current Worrying ≥ 6 months— ksads_10_47_P* (n = 5509)	0.729 [0.5993, 0.852]	0.010	0.0006	0.236
	Symptom—Excessive worries more days than not Present- ksads_10_45_P* (n = 5509)	0.755 [0.6219, 0.8772]	0.008	0.0013	0.236
	Symptom—Impairment in functioning due to worries Present- ksads_10_326_P* (n = 5509)	0.728 [0.5827, 0.8790]	0.0099	0.0016	0.236
	Symptom—Excessive worries across domains Present- ksads_10_320_P* (n = 5509)	0.752 [0.6281, 1.1252]	0.0084	0.0022	0.258
	Symptom—Impairment in functioning from compulsions Past- ksads_11_346_P* (n = 5509)	1.28 [1.070, 1.4771]	0.0077	0.0058	0.568
	Symptom—Elevated Mood, Past-ksads_2_8_t* (n = 5531)	0.863 [0.7874, 1.0513]	0.0034	0.006	0.568
Imaging modality	Phenotype	Beta/OR [95%CI]	R^2	pval	FDR pval
B. Imaging p < 0.05					
Subcortical volume (n = 5516)	Left-accumbens-area- smri_vol_scs_aal	0.0284 [0.0099, 0.04977]	0.0008	0.0053	0.172
	Right-thalamus-proper—smri_vol_scs_tprh	− 0.016 [− 0.0301, − 0.0025]	0.0002	0.0205	0.328
	Right-putamen—smri_vol_scs_putamenrh	0.0173 [0.0003, 0.0342]	0.0002	0.0453	0.483
Cortical volume (n = 5516)	Rh-paracentral—smri_vol_cdk_paracnrh	0.0312 [0.0134, 0.0599]	0.0001	0.0071	0.483
	Lh-Banks of Superior Temporal Sulcus—smri_ vol_cdk_banksstslh	0.0260 [0.0067, 0.0549]	0.0008	0.0325	0.768
	Lh precuneus—smri_vol_cdk_pclh	− 0.0195 [0.0059, 0.0440]	0.0006	0.0345	0.768
	Rh-lingual—smri_vol_cdk_tmpolelh	− 0.02488 [− 0.0001, − 0.0492]	0.0003	0.0452	0.768

Domain	Phenotype	Beta/OR [95% CI]	R^2	pval	FDR pval
Cortical thickness (n = 5516)	Lh-Banks of Superior Temporal Sulcus—smri_ thick_cdk_banksstslh	0.031 [0.0081,0.0526]	0.0008	0.0091	0.309
	Lh-supramarginal—smri_thick_cdk_smlh	− 0.0237 [− 0.0418, − 0.0085]	0.0008	0.0067	0.309
	Rh-supramarginal—smri_thick_cdk_smrh	− 0.019 [− 0.0361, − 0.0012]	0.0006	0.030	0.520
Surface area (n = 5516)	Lh-caudal middle frontal—smri_area_cdk_ cdmdfrlh	− 0.023 [− 0.0435, − 0.0032]	0.0004	0.023	0.738
	Rh-paracentral—smri_area_cdk_paracnrh	0.0245 [0.0013, 0.0460]	0.0004	0.031	0.738
	Rh-inferiortemporal—smri_area_cdk_iftmrh	0.0184 [0.0017, 0.0354]	0.0003	0.0325	0.738
Mean diffusivity (n = 5270)	Right anterior thalamic radiations—dmri_ dtimd_fiberat_atrrh	0.0232 [0.0059, 0.0363]	0.0008	0.006	0.232
RSFC (n = 5306)	Cingulo-opercular network and cingulo-opercu- lar network—rsfmri_c_ngd_cgc_ngd_cgc	− 0.0297 [− 0.0557, − 0.0054]	0.0009	0.0217	0.953
	Salience network and ventral attention net- work—rsfmri_c_ngd_sa_ngd_vta	− 0.0263 [− 0.0505, − 0.0011]	0.0006	0.046	0.953

Table 3

APOE4 nominal significant P value results

Domain	**Phenotype**	**Beta/OR [95%CI]**	**R^2**	**pval**	**FDR pval**
A. Non-imagingp < 0.01					
Cognition	Rey Auditory Verbal Learning Test total score- RAVLT (n = 5441)	− 0.04 [− 0.064, − 0.012]	0.0009	0.006	0.699
Culture/environment	Sharing plans with guardian/parent- parent_ monitor_q4_y (n = 5552)	0.043 [0.0168, 0.069]	0.0019	0.0012	0.432
Physical health	Sitting up age—devhx_19b_p (n = 4937)	0.046 [0.02005, 0.076]	0.0021	0.0012	0.432
	Sprain assessment prof—medhx_6b* (n = 5555)	1.136 [0.960, 0.8171]	0.0033	0.0028	0.613
	How many other times hospitalized- medhx_6t_times (n = 792)	0.101 [0.034, 0.1667]	0.0087	0.0046	0.662
Family mental health	Caregiver bragging—asr_q07_p (n = 5556)	0.044 [0.018, 0.069]	0.0013	0.0004	0.432
	Caregivers less mean- asr_q16_p (n = 5556)	− 0.034 [− 0.059, − 0.01]	0.0015	0.0036	0.662
	Caregivers behavior is less changeable- asr_ q81_p (n = 5556)	− 0.037 [− 0.06, − 0.013]	0.0007	0.0021	0.558
	Caregivers talking to much- asr_q93_p (n = 5556)	0.029 [− 0.063, − 0.013]	0.0016	0.0095	0.889
Child mental health	Symptom—Difficulty controlling worries Present- ksads_10_324_P* (n = 5509)	0.696 [0.5504, 1.1630]	0.0102	0.0041	0.662
	Current compulsion purpose anxiety— ksads_11_344_P* (n = 5509)	1.18 [1.002, 1.3324]	0.004	0.0066	0.699
	Symptom—Impair. in functioning due to compulsions Past- ksads_11_346_P* (n = 5509)	1.3 [1.1174, 1.5044]	0.01	0.0013	0.432
	Symptom—Compulsions Past -ksads_11_51_p* (n = 5509)	1.18 [0.002, 1.3324]	0.0045	0.0066	0.699
Imaging modality	Phenotype	Beta/OR [95%CI]	R^2	pval	FDR pval
B. Imaging p < 0.05					
Subcortical volume (n = 5516)	Brain-stem—smri_vol_scs_bstem	− 0.022 [− 0.0399, − 0.0058]	0.0004	0.0109	0.196
	Right-thalamus-proper—smri_vol_scs_tprh	− 0.0246 [− 0.0293, − 0.0018]	0.0002	0.0123	0.196
	Left-cerebellum-cortex—smri_vol_scs_crbcor-texlh	− 0.02468 [− 0.0444, − 0.0057]	0.0005	0.0123	0.196
	Right-cerebellum-cortex—smri_vol_scs_crb- cortexrh	− 0.0209 [− 0.0403, − 0.0200]	0.0003	0.0318	0.252
	Left-accumbens-area—smri_vol_scs_aal	0.002 [0.0016, 0.0415]	0.0005	0.0499	0.266
Cortical volume (n = 5516)	Rh-paracentral- smri_vol_cdk_paracnrh	0.0304 [0.0124, 0.0589]	0.0011	0.0086	0.527
	Lh-Banks of Superior Temporal Sulcus—smri_ vol_cdk_banksstslh	0.029 [0.0093, 0.0576]	0.0010	0.0155	0.527
Cortical thickness (n = 5516)	Rh-inferiortemporal -smri_thick_cdk_iftmrh	− 0.028 [− 0.0471, − 0.0100]	0.0008	0.0028	0.135
	Rh-cuneus—smri_thick_cdk_cuneusrh	− 0.0237 [0.0102, 0.0540]	0.0009	0.0067	0.309
	Lh-cuneus- smri_thick_cdk_cuneuslh	0.0314 [0.0081, 0.0538]	0.0009	0.0076	0.172
	lh-Banks of Superior Temporal Sulcus—smri_ thick_cdk_banksstslh	0.0256 [0.0048, 0.0494]	0.0006	0.026	0.446

Domain	Phenotype	Beta/OR [95%CI]	R^2	pval	FDR pval
Surface area (n = 5516)	Lh-rostralanteriorcingulate—smri_area_cdk_ rracatelh	− 0.022 [− 0.0428, − 0.0038]	0.0004	0.023	0.818
	Rh-paracentral—smri_area_cdk_paracnrh	0.0257 [0.0032, 0.0479]	0.0005	0.024	0.818
	Lh-Banks of Superior Temporal Sulcus—smri_ area_cdk_banksstslh	0.024 [0.0012, 0.0473]	0.0005	0.0361	0.819
Mean diffusivity (n = 5270)	Right anterior thalamic radiations—dmri_ dtimd_fiberat_atrrh	0.0228 [0.0033, 0.0339]	0.0008	0.0074	0.274
	Right parahippocampal cingulum—dmri_ dtimd_fiberat_cghrh	− 0.024 [− 0.0406, − 0.0023]	0.0002	0.0191	0.276
	Left striatal inferior frontal cortex -dmri_dtimd_ fiberat_sifclh	0.0224 [0.0001, 0.0357]	0.0004	0.0224	0.276
RSFC (n = 5306)	Default network and retrosplenial temporal network—rsfmri_c_ngd_dt_ngd_rspltp	0.0391 [0.0099, 0.0647]	0.0013	0.005	0.971
	Retrosplenial temporal network and visual network—rsfmri_c_ngd_rspltp_ngd_vs	− 0.0363 [− 0.0634, − 0.0096]	0.0012	0.005	0.971
	dorsal attention network and retrosplenial temporal network—rsfmri_c_ngd_dla_ngd_rspltp	− 0.035 [− 0.0637, − 0.0189]	0.0013	0.0095	0.971
	“none” network and retrosplenial temporal network—rsfmri_c_ngd_n_ngd_rspltp	0.0349 [0.0058, 0.0598]	0.0010	0.0116	0.971

Table 4

PRS-APOE4 nominal significant P value results

Domain	Phenotype	Beta/OR [95%CI]	R^2	pval	FDR pval
A. Non-imagingp < 0.01					
Physical health	Infant born blue at birth- devhx_14a3_p* (n=5459)	1.2 [1.0128, 1.0688]	0.0016	0.0031	0.822
	Went to medical prof. for stitches- medhx_6d* (n = 5555)	1.1120 [1.0161, 1.0736]	0.0029	0.0012	0.778
	Number times broken bones- medhx_6a_notes (n = 942)	− 0.087 [− 0.153, − 0.023]	0.007	0.0075	0.822
Family mental health	Caregivers less dependent on others- asr_q11_p (n = 5556)	− 0.031 [− 0.056, − 0.007]	0.0012	0.0081	0.822
	Caregivers enjoy very little- asr_q60_p (n = 5556)	− 0.032 [− 0.0575, − 0.0078]	0.0011	0.0073	0.822
	Caregivers cry less- asr_q14_p (n = 5556)	0.71 [− 0.0544, − 0.0069]	0.0017	0.0091	0.822
	Caregivers trouble making decisions- asr_ q78_p (n = 5556)	− 0.029 [− 0.054, − 0.006]	0.0003	0.0095	0.822
Child mental health	Symptom—Insomnia, Present- ksads_22_141_t* (n = 5531)	1.159 [1.0088, 1.0695]	0.0034	0.0081	0.822
	Diagnosis—SLEEP PROBLEMS, Present- ksads_22_969_t* (n = 5531)	1.159 [1.0088, 1.0692]	0.0034	0.0081	0.822
	School special services—kbi_p_c_spec_ serv_7* (n = 5556)	0.839 [0.7573, 1.0460]	0.0044	0.0084	0.822
Imaging modality	Phenotype	Beta/OR [95% CI]	R^2	pval	FDR pval
B. Imaging p < 0.05					
Subcortical volume (n = 5516)	Right-cerebellum-cortex-smri_vol_scs_crbcor- texrh	0.0286 [0.0097,0.0478]	0.0009	0.0033	0.069
	Left-cerebellum-cortex—smri_vol_scs_crb- cortexlh	− 0.0267 [0.007, 0.0461]	0.0008	0.0065	0.069
	Left-cerebellum-white-matter—smri_vol_scs_ crbwmatterlh	0.0301 [0.0070, 0.0494]	0.0007	0.0057	0.069
	Right-accumbens area—smri_vol_scs_aar	0.0264 [0.006, 0.0481]	0.0006	0.0128	0.103
	Right-cerebellum-white-matter—smri_vol_ scs_crbwmatterrh	0.025 [0.0029, 0.0443]	0.0005	0.0162	0.104
Cortical volume (n = 5516)	Lh-caudalanteriorcingulate—smri_vol_cdk_ cdacatelh	− 0.0386 [− 0.0561, − 0.0077]	0.0009	0.0015	0.108
	Lh-precuneus—smri_vol_cdk_pclh	0.0251 [0.0125, 0.0506]	0.0001	0.0062	0.212
	Rh-inferiorparietal—smri_vol_cdk_ifplrh	− 0.0246 [− 0.0445, − 0.004]	0.0004	0.0163	0.370
	Lh-parahippocampal—smri_vol_cdk_parah- pallh	− 0.0291 [− 0.0515, − 0.0005]	0.0005	0.0253	0.4303
Cortical thickness (n = 5516)	Lh-parahippocampal—smri_thick_cdk_parah- pallh	− 0.031 [− 0.0560, − 0.0058]	0.0001	0.0130	0.4252
	Lh-middletemporal—smri_thick_cdk_mdtmlh	0.0227 [0.0020, 0.0385]	0.0002	0.0166	0.425
	Rh-isthmuscingulate—smri_thick_cdk_ihcaterh	0.0310 [0.0045, 0.0562]	0.0008	0.0187	0.108
	Rh-parahippocampal—smri_thick_cdk_parah- palrh	− 0.0259 [− 0.0498, − 0.0022]	0.0008	0.0335	0.570
	Rh-precuneus—smri_thick_cdk_pcrh	− 0.0183 [− 0.037, − 0.003]	0.0003	0.042	0.576

Domain	Phenotype	Beta/OR [95%CI]	R^2	pval	FDR pval
Surface area (n = 5516)	Lh-caudalanteriorcingulate—smri_area_cdk_ cdacatelh	− 0.035 [− 0.055, − 0.0096]	0.0009	0.0028	0.192
	Rh-inferiorparietal—smri_area_cdk_ifplrh	− 0.0267 [− 0.0468, − 0.0081]	0.0005	0.0068	0.231
	Lh-precuneus—smri_area_cdk_pclh	0.0209 [0.0033, 0.0385]	0.0004	0.0197	0.422
	Rh-inferiortemporal—smri_area_cdk_iftmrh	0.0193 [0.0024, 0.0361]	0.0004	0.0248	0.422
Mean diffusivity (n = 5270)	Left superior longitudinal fasiculus—dmri_ dtimd_fiberat_tslflh	− .0162 [− 0.0296, − 0.0028]	0.0003	0.0176	0.4882
	Left temporal superior longitudinal fasiculus— dmri_dtimd_fiberat_slflh	− 0.015 [− 0.0282, − 0.0018]	0.0002	0.0264	0.4882
Fractional anisotropy (n = 5270)	Right inferior-fronto-occipital fasiculus -dmri_ dtifa_fiberat_iforh	− 0.0172 [− 0.0338, − 0.0021]	0.0003	0.037	0.613
Whole Brain (n = 5516)	Total whole brain cortical volume—smri_vol_ cdk_total	0.02402 [0.0019, 0.0462]	0.0006	0.0335	0.221
	Total right hemisphere cortical volume—smri_ vol_cdk_totalrh	0.0246 [0.0014, 0.0539]	0.0008	0.0295	0.221
	Total left hemisphere cortical volume—smri_ vol_cdk_totallh	0.0233 [0.0021, 0.0464]	0.0006	0.039	0.221
RSFC (n = 5306)	Fronto-parietal network and salience network— rsfmri_c_ngd_fo_ngd_sa	0.0295 [0.0024, 0.0547]	0.0008	0.0270	0.979
	Auditory network and cingulo-parietal net- work—rsfmri_c_ngd_ad_ngd_ca	0.0278 [0.0017, 0.0538]	0.0008	0.0362	0.979
	Dorsal attention network and sensorimotor hand network—rsfmri_c_ngd_dla_ngd_smh	0.0382 [0.0120, 0.0629]	0.0015	0.0033	0.302