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APOE effects on cognition from childhood to adolescence

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ABSTRACT

The ε4 allele of *APOE* is a well-established genetic risk factor for cognitive aging and dementia, but its influence on early life cognition is unknown. Consequently, we assessed associations of *APOE* genotypes with cognitive performance during 7, 12, and 16 year-assessments in our ongoing Colorado Adoption/Twin Study of Lifespan behavioral development (CATSLife). In general, APOE ε4 was associated with lower Verbal, Performance, and Full Scale IQ scores during childhood and adolescence (e.g., Full Scale IQ was lower by 1.91 points per ε4 allele, $d = -0.13$), with larger effects in females (e.g., average Full Scale IQ scores were 3.41 points lower in females per each ε4 allele vs. 0.33 points lower in males). Thus, these results suggest that deleterious effects of the APOE ε4 allele are manifested before adulthood, especially in females, and support both early origin theories and differential life-course vulnerabilities for later cognitive impairment.

1. Introduction

Although the origins of late-life cognitive health may begin at conception (Barnett et al., 2013), the extent to which cognitive dysfunction in adulthood is presaged during early life is currently unknown. Individual differences in general cognitive ability occur early in development and are stable longitudinally (Plomin et al., 1988; Walhovd et al., 2016); nevertheless, the effects of early life factors may accumulate over the lifespan and impact subsequent cognitive aging (Liu et al., 2010). To assess the saliency of some early life genetic factors, we evaluated the associations of *APOE* genotypes with cognitive development from childhood to adolescence in the Colorado Adoption/Twin Study of Lifespan Behavioral Development (CATSLife).

The *APOE* gene encodes the brain's primary cholesterol transporter, *apolipoprotein E*, which may play additional roles in synaptic plasticity and cell signaling (Holtzman et al., 2012). There are 3 common *APOE* alleles, ε2, ε3, and ε4 that vary in allele frequency with mean values across populations at about 6.4% (SD = 5.1), 78.3% (SD = 12.1), and 14.5% (SD = 8.5), respectively, (Eisenberg et al., 2010). The *APOE*ε4 variant is implicated in Aβ deposition and tau-pathologies (Shi et al., 2017), respective features in brain plaques and tangles. The *APOE*ε4 allele is an established risk factor for late-onset Alzheimer's disease (AD) (Liu et al., 2013), with a dose-dependent association between the number of ε4 alleles and AD risk and age of onset (Liu et al., 2013). *APOE*ε4 is also implicated in nonpathological cognitive aging, including general cognitive ability, episodic and working memory, verbal, spatial, and perceptual speed abilities (Davies et al., 2014; Reynolds et al., 2006; Schiepers et al., 2012). The least common *APOE*ε2 allele has been associated with reduced risk of AD and is thought to be possibly neuroprotective (Conejero-Goldberg et al., 2014; Liu et al., 2013). Although of keen interest, the role of *APOE* on cognition in childhood and adolescence is inconclusive (Chang et al., 2016; Ihle et al., 2012; Khan et al., 2014; Weissberger et al., 2018). However, it has been suggested that structural brain differences in ε4 carriers' volumes may appear in infancy, including lower hippocampal, frontal and temporal lobe volumes, as well as gray and white matter (Dean et al., 2014; Knickmeyer et al., 2013). A recent large cross-sectional imaging and neuropsychological study of 1187 children and youth, aged 3–20 years, suggested a number of differences in brain volume, fractional anisotropy, or thinning by *APOE* genotypes as well as cognitive ability performance (Chang et al., 2016). For example, smaller hippocampal volumes among ε4/ε4 individuals were associated with poorer performance on attention and working memory tasks (Chang et al., 2016). A recent comparison of mice from lines generated to overexpress 1N4R human tau via a P301S mutation and to either express human ApoE (ε2, ε3, or ε4 knock-ins)

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or not to express ApoE (knockouts) suggested that tau-related atrophy was observed in those expressing ApoE ε4 at 9 months of age, approximately equivalent to human middle adulthood (Shi et al., 2017). Indeed, the P301S/ε4 mice showed greater tau hyperphosphorylation in the hippocampus at 3 months of age, approximately equivalent to human early adulthood, and a bigger loss of neurons in the hippocampal CA1 region at 9 months of age (Shi et al., 2017). Taken together, results of recent studies are consistent with the proposition that early life factors may be associated with later cognitive health, such that the *APOE*ε4 variant is implicated in cognitive health starting in early life.

Whether differential vulnerability is characteristic of all individuals who carry one or two copies of the *APOE*ε4 allele, or whether women are more vulnerable is of interest beyond differential mortality explanations. A recent meta-analysis (Neu et al., 2017) suggests that women with the ε3/ε4 genotype may be at greater risk than men for developing mild cognitive impairment (MCI) between ages 55 and 70 years and at greater risk of Alzheimer's disease between ages 65 and 75 years but are not at differential risk at later ages. Whether sex differences in the association between *APOE*ε4 and cognitive profiles appear earlier in the lifespan is unclear, particularly in childhood and adolescence, although studies of childhood IQ suggest possibly differential associations for females than males on IQ performance (Calderon-Garciduenas et al., 2016; Taylor et al., 2011).

Although the extant literature and early origins theories (Barnett et al., 2013; Liu et al., 2010) of adult-onset disease risk (Barker and Martyn, 1992) suggest that *APOE*—cognition associations might emerge with development, there is little longitudinal data to resolve this question (Ihle et al., 2012). Most childhood studies have been cross-sectional (e.g., Calderon-Garciduenas et al., 2016; Chang et al., 2016; Ihle et al., 2012; Khan et al., 2014) or limited in assessments (i.e., 2 waves [Taylor et al., 2011]). Indeed, to our knowledge, no childhood studies considering *APOE* and general cognitive ability or IQ have evaluated more than a single occasion, despite knowledge that multiple assessment affords greater reliability to evaluate and observe a possible relationship. We examined associations of *APOE* genotypes with cognitive performance, evaluating whether *APOE*ε4 conferred a disadvantage for IQ performance evaluated at 3 assessments between childhood and adolescence. We also explore moderation of APOE ε4 by sex in associations with IQ performance.

2. Materials and methods

2.1. Participants

The CATSLife project includes participants from the Colorado Adoption Project (CAP; [Rhea et al., 2013a]), which was initiated in 1975 and enrolled 245 adoptive and 245 control families, and the Longitudinal Twin Study (LTS; [Rhea et al., 2013b]), which was initiated in 1985 and enrolled 483 twin pairs (265 MZ, 218 DZ). These studies used nearly parallel assessments between infancy and adolescence conducted on a nearly annual basis, and with periodic assessments into adulthood. Age descriptives by sample are reported in Table 1. The current analysis sample of 1321 includes individuals (nested within 773 families) who ranged between the ages of 6.50 years at the year 7 assessment and up to 17.99 years of age at the year 16 assessment. Genotyping was conducted on archival DNA samples and samples obtained from the ongoing CATSLife study (N_{CAP} = 472, 48.7% male; 44.92% adoptive families; N_{LTS} = 849, 48.8% male, 54.42% MZ twins). Self-reported race and ethnicity of the sample are 92.13% white and 7.87% non-white (American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Black/African-American, More than one race, Unknown/Not reported), with 5.90% of the analysis sample identifying as Hispanic. These numbers are representative of the Colorado Front Range ethnic composition at the time participants were recruited into the foundational CAP and LTS studies.

The protocol was approved by the 2 respective institutional review boards of the authors' institutions, the University of Colorado at Boulder, and the University of California at Riverside.

2.2. Measures

The year 7 and 12 cognitive assessments included WISC IQ measures (WISC-R or WISC-III; Wechsler, 1974, 1991) and the age 16 and CATSLife assessments included WAIS IQ measures (WAIS-R or WAIS-III; Wechsler, 1981, 1997) (see Table 2). The WISC-R and WISC-III tests are similar in item content and subtest composition (12/13 subtests overlap) with equivalent covariance structure among the subtests across the 2 versions (Dixon and Anderson, 1995). The WAIS-R and WAIS-III tests are likewise very similar, with respective correlations of Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ scores exceeding 0.80 across versions (Strauss et al., 2006; Tulsky et al., 1997). Last, IQ scores calculated from child versus adult batteries are comparable and strongly correlated, for example, WISC-III versus WAIS-III scores among 16-year old's are correlated 0.78 to 0.88 (Strauss et al., 2006). IQ scores are scaled by age-based norms, and the general expectation would be, therefore, that age effects ought to be minimal; given the shift in the test batteries associated with age and cohort, however, we included study and age covariates in analyses as described further below.

2.2.1. APOE *Genotyping*

Taqman assays of *APOE* SNPS, rs7412 and rs429358, were performed using buccal cell-derived DNA. The success rate was 97%. *APOE* genotypes were formed from the 2 SNPs according to common practice (see Table 3). Where MZ twins were untyped ($N = 4$), they were assigned their cotwin's APOE genotype. Where one of the 2 *APOE* SNP assays failed, we took the MZ cotwins genotype for that SNP ($N = 17$). Hardy Weinberg Equilibrium was achieved for both SNPs in both samples, selecting one sibling in each twin pair or sibship (all $p \geq 0.088$). In addition, the *APOE* genotypes formed from both SNPs achieved Hardy Weinberg Equilibrium in each sample and when combined across the 2 samples (all $p > 0.154$). Supplemental Table S1 presents the distribution of independent *APOE* alleles in a selection of one sibling or twin member from each pair/sibship. Overall, the ε4 allele is more frequent (13.95%) than the ε2 allele (7.89%), as expected (see Supplemental Table S1).

2.3. Analyses

Multi-level regression analyses of WISC and WAIS IQ measures were carried out using SAS Proc Mixed 9.4 (SAS Inc, Cary NC), using full maximum likelihood estimation. In Model I, the main effects model, IQ scores were predicted by the number of *APOE*ε4 alleles (0, 1, or 2), adjusting for the number of *APOE*ε2 alleles (0, 1, or 2) given its possible neuroprotective effect. The reference *APOE* genotype was therefore ε3/ε3. Additional covariates included study, sex, adopted status, and age, with coding as follows. Study was effects-coded as Colorado Adoption Project (CAP; -0.5) and Longitudinal Twin Study (LTS; 0.5). Sex was dummy coded and reflected effects for females (Male = 0, Female = 1). Adopted was dummy coded and reflects adoption status (0 = Not, 1 = Adopted). Age was centered at 16 years and reflected any possible age differences within or across longitudinal assessments but also possible differences due to IQ battery as described previously. Thus, in Model I, the fixed effect intercept reflects the expected mean IQ score for males, who were

Table 1
Analysis sample age descriptives by study

Assessment	CAP $N = 472$	M_{AGE}	SD_{AGE}	Min	Max	LTS $N = 849$	M_{AGE}	SD_{AGE}	Min	Max
Year 7	397	7.42	0.37	6.50	8.42	780	7.43	0.36	6.67	8.50
Year 12	403	12.45	0.41	11.67	14.17	738	12.43	0.37	11.33	14.00
Year 16	451	16.34	0.48	16.00	17.99	724	16.37	0.41	16.00	17.92

Key: CAP, Colorado Adoption Project; LTS, Longitudinal Twin Study.

not adopted, at age 16 years, for those who are *APOE*ε3/ε3, controlling for study. In Model II, interaction terms with sex and *APOE*ε4 alleles were entered to evaluate possible sex moderation of *APOE*ε4 on IQ, adjusting for the interaction of sex and number of ε2 alleles. Hence in Model II, the *APOE*ε4 effect reflects the ε4 effect for males and the *APOE*ε4*Sex interaction reflects the *APOE*ε4 effect for females.

Additional sensitivity tests included fitting the described Models I and II to IQ data at assessment year 7 alone when the WISC-R battery was given to both CAP and LTS participants. Additional sensitivity analyses of the longitudinal IQ results included covariate adjustments by race and ethnicity and a sex by study interaction. Race and ethnicity were coded as white (1 = white, 0 = non-white) and Hispanic (1 = Hispanic, 0 = non-Hispanic). Last, we explored possible nonadditive effects given hints of nonadditivity in the mean IQ patterns; this was done for Model I given that sex by APOE genotype frequencies would be limited for the rarer genotypes. We recoded ε2 and ε4 additive terms where 0 alleles = −1, 1 allele = 0, and 2 alleles = 1 (Model I.a). We coded dominance effects for ε2 alleles (Model I.b) and ε4 alleles (Model I.c) as follows: 0 alleles = 0, 1 allele = 1, and 2 alleles = 0. Models I.b and I.c, respectively, allow for heterozygotes to deviate nonadditively from respective ε2 and ε4 homozygotes and both differentiate ε24 from ε34.

All analyses adjusted for nesting of individuals within family type to account for dependencies in the data that could affect the standard errors of the regression parameters of the fixed effect predictors and covariates. Specifically, random effect variances were estimated for the intercept, decomposed into within-sibling and between-sibling variance, as well as residual variance, each by family/sibling type, that is, siblings were from adoptive (A) or nonadoptive control (C) families, or were dizygotic twins (DZ) or monozygotic twins (MZ). Thus, the analysis accounted for differential dependencies between MZ twins, who share identical genotypes, from DZ twins who share on average 50% of segregating genes in common, as well as for differential dependencies between genetically unrelated siblings and genetically related siblings. The between-sibling intercept variance represents similarity among siblings in IQ performance that is systematic across longitudinal assessments of IQ and varies by sibling type ($\sigma^2_{betweenA}, \sigma^2_{betweenC}, \sigma^2_{betweenDZ}, \sigma^2_{betweenMZ}$) (see Tables S2, S4, S6). The corresponding within-sibling intercept variance represents differences in IQ among siblings that are systematic across longitudinal assessments of IQ and varies by sibling type ($\sigma^2_{withinA}, \sigma^2_{withinC}, \sigma^2_{withinDZ}, \sigma^2_{withinMZ}$). Last, the residual variance represents within-person variability in performance that is occasion specific ($\sigma^2_{residualA}, \sigma^2_{residualC}, \sigma^2_{residualDZ}, \sigma^2_{residualMZ}$). No constraints were placed on the magnitudes of random effects estimated by sibling types. In sensitivity analyses of the IQ data at the year 7 assessment, the decomposition of the random effects of the intercept included between-pair random effects ($\sigma^2_{betweenA}, \sigma^2_{betweenC}, \sigma^2_{betweenDZ}, \sigma^2_{betweenMZ}$) and residual within-pair random effects of IQ (denoted $\sigma^2_{withinA}, \sigma^2_{withinC}, \sigma^2_{withinDZ}, \sigma^2_{withinMZ}$); in these models, age was centered at age 7.

Regression parameter tests of significance were as reported via SAS Proc MIXED 9.4 (SAS Inc, Cary NC), which included asymptotically distributed *t*-statistics formed by taking the parameter estimate over its standard error, with degrees of freedom estimated using the between-within option. For Model I, 1-tailed tests of significance are reported for *APOE*ε4 effects, given our hypothesized direction of effect, whereas Model II reported 2-tailed tests of significance for *APOE*ε4 by sex interactions. We report 95% confidence intervals for all parameters for both Models I and II.

The sample size is appropriate for tests of association. Our expected power for an overall main effect association exceeds 0.94, assuming an effect size contribution of 1% to the outcome, a sibling correlation of 0.40, and an ε4 frequency of 15% (Purcell et al., 2003). Under the same conditions, an expected power of 0.80 is achieved with an effect size contribution of 0.65%. Moreover, the multiple longitudinal assessments of IQ provide increased reliability to evaluate and observe a possible relationship.

3. Results

Unadjusted descriptives of IQ performance at each assessment by *APOE*ε4 status are suggestive of differential performance by *APOE*ε4 (see Table 4), with reduced performance particularly for those carrying one *APOE*ε4 allele in the total sample. When considering sex, a pattern of lower mean IQ performance per *APOE*ε4 allele is observable in females but not for males, although notably the sample sizes for *APOE*ε4/ε4 are small.

3.1. Multilevel regression models I and II

*APOE*ε4 associations with longitudinal IQ performance at the year 7, 12, and 16 assessments were evaluated via multilevel regression models fitted to longitudinal IQ scores ($N = 1321$, 48.86% male; age range 6.50–17.99 years), adjusting for sex, age, adopted status, study sample, and the number of ε2 alleles. Parameters from the full multilevel main effects model fitted with covariates (Model

Table 2
IQ Assessments by study

Assessment	Year 7	Year 12	Year 16
WISC − R	CAP/LTS	CAP	
WISC − III		LTS	
WAIS − R			CAP
WAIS − III			LTS

Key: CAP, Colorado Adoption Project; LTS, Longitudinal Twin Study.

Table 3
APOE genotype frequencies in analysis sample by study

APOE	rs429358	rs7412	CAP		LTS	
			N	Percent	N	Percent
ε22	T/T	T/T	6	1.27	9	1.06
ε23	T/T	C/T	50	10.59	104	12.25
ε24	C/T	C/T	13	2.75	16	1.88
ε33	T/T	C/C	283	59.96	524	61.72
ε34	C/T	C/C	110	23.31	189	22.26
ε44	C/C	C/C	10	2.12	7	0.82
Current *N*	1321		472		849	

Key: CAP, Colorado Adoption Project; LTS, Longitudinal Twin Study.

Table 4
Age and IQ test performance by *APOE*ε4 alleles across assessments at years 7, 12, and 16

	Variable	*APOE*ε4 = 0			*APOE*ε4 = 1			*APOE*ε4 = 2		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Total Sample										
Year 7	Verbal IQ	865	106.31	14.32	296	105.72	14.65	15	107.40	10.44
	Performance IQ	866	110.78	12.54	296	108.68	13.62	15	110.53	10.33
	Full Scale IQ	865	109.24	12.99	296	107.77	13.50	15	109.60	7.87
	Age	871	7.42	0.37	296	7.45	0.36	15	7.38	0.40
Year 12	Verbal IQ	839	105.89	13.19	288	105.58	12.76	14	108.07	14.07
	Performance IQ	839	105.85	13.75	287	104.36	13.59	13	109.62	8.44
	Full Scale IQ	839	106.38	12.95	287	105.40	12.74	13	109.08	10.87
	Age	841	12.44	0.39	288	12.45	0.36	14	12.40	0.42
Year 16	Verbal IQ	873	103.70	12.58	288	102.94	11.58	14	103.43	10.91
	Performance IQ	873	104.25	12.44	288	103.22	11.88	14	105.86	14.20
	Full Scale IQ	873	104.17	11.75	288	103.20	10.63	14	104.71	10.31
	Age	873	16.36	0.44	289	16.36	0.43	14	16.55	0.41
Males										
Year 7	Verbal IQ	430	105.81	14.49	146	107.03	14.17	8	106.88	11.31
	Performance IQ	430	111.14	12.72	146	110.82	13.08	8	115.38	10.93
	Full Scale IQ	430	109.13	13.29	146	109.72	13.11	8	111.88	7.88
	Age	432	7.47	0.39	146	7.51	0.36	8	7.54	0.40
Year 12	Verbal IQ	407	106.61	13.36	142	107.55	13.41	7	114.57	11.31
	Performance IQ	407	104.89	13.80	142	106.12	13.49	7	111.71	6.32
	Full Scale IQ	407	106.29	12.84	142	107.56	13.33	7	114.71	7.95
	Age	409	12.48	0.40	142	12.51	0.38	7	12.58	0.45
Year 16	Verbal IQ	421	104.49	13.05	147	104.46	11.13	6	109.50	11.36
	Performance IQ	421	103.97	12.94	147	104.99	12.40	6	114.83	14.96
	Full Scale IQ	421	104.54	12.05	147	104.98	10.86	6	112.33	8.96
	Age	421	16.39	0.48	148	16.41	0.44	6	16.64	0.47
Females										
Year 7	Verbal IQ	435	106.81	14.14	150	104.44	15.04	7	108.00	10.21
	Performance IQ	436	110.42	12.37	150	106.60	13.86	7	105.00	6.53
	Full Scale IQ	435	109.34	12.70	150	105.87	13.64	7	107.00	7.57
	Age	439	7.37	0.33	150	7.39	0.35	7	7.19	0.35
Year 12	Verbal IQ	432	105.20	13.01	146	103.66	11.83	7	101.57	14.22
	Performance IQ	432	106.75	13.66	145	102.64	13.52	6	107.17	10.48
	Full Scale IQ	432	106.45	13.06	145	103.28	11.81	6	102.50	10.56
	Age	432	12.40	0.38	146	12.39	0.33	7	12.21	0.31
Year 16	Verbal IQ	452	102.96	12.10	141	101.36	11.87	8	98.88	8.58
	Performance IQ	452	104.51	11.96	141	101.38	11.07	8	99.13	9.67
	Full Scale IQ	452	103.82	11.46	141	101.34	10.10	8	99.00	7.27
	Age	452	16.32	0.40	141	16.31	0.40	8	16.47	0.39

I) are presented in Table 5 (fixed effects) and Table S2 (random effects). With respect to prediction by *APOE* genotype, 1-tailed tests were selected for ε4 under Model I given the hypothesized directionality. Results suggested that for each ε4 allele, Full scale IQ scores were lower by 1.91 points compared to ε33 homozygotes ($p = 0.0051/2 = 0.0026$, 1-tailed); this corresponds to an estimated d effect size of −0.13 using the expected SD for IQ scores of 15 (i.e., 1.91/15). Consistent effects were observed for Verbal ($B = -1.60$, $p = 0.0224/2 = 0.0112$, 1-tailed; $d = -0.11$) and Performance IQ ($B = -1.78$, $p = 0.0118/2 = 0.0059$, 1-tailed; $d = -0.12$). False Discovery Rate (FDR) adjusted 1-tailed p-values remain significant: Full scale IQ, $p = 0.0077$; Verbal IQ, $p = 0.0112$; and Performance IQ, $p = 0.0089$.

Fig. 1 presents expected mean Full Scale IQ scores as a function of the number of *APOE*ε4 alleles in the total sample.

Next, to evaluate sex differences with respect to *APOE* effects, an interaction term with sex and *APOE*ε4 alleles was entered and evaluated under Model II using a 2-tailed test (see Table 5, Model II), adjusting for the interaction of sex and ε2 alleles. For Verbal IQ, the ε4 by sex interaction was significant ($p = 0.0324$, 2-tailed), suggesting the ε4 effect may be larger in females than males, whereas the main effect of ε4, now reflecting male performance, was nonsignificant. Specifically, the ε4 effect was −0.23 ($se = 0.95$; $d = -0.02$) in males and −2.95 ($se = 1.38$; $d = -0.20$) in females. The ε4 effects for Performance IQ and Full Scale IQ may be especially pronounced for females (ε4 x Sex $p \leq 0.0132$, 2-tailed), whereas the main effect of ε4, reflecting differential male performance, was nonsignificant. For Full Scale IQ, the ε4 effect was −0.33 ($se = 0.92$; $d = -0.02$) in males and −3.41 ($se = 1.35$; $d = -0.23$) in females (see Fig. 1). For Performance IQ, the ε4 effect was −0.13 ($se = 0.97$; $d = -0.01$) in males and −3.48 ($se = 1.40$; $d = -0.23$) in females. FDR adjusted 2-tailed p-values for the ε4 × Sex effects remain significant: Full scale IQ, $p = 0.0198$; Verbal IQ, $p = 0.0324$, and Performance IQ, $p = 0.0198$.

Fig. 1 also presents expected performance differences for Full Scale IQ by the number of *APOE*ε4 alleles in males and females.

3.2. Sensitivity analyses

We performed a sensitivity test to evaluate whether *APOE* effects are determinable at the youngest assessment at year 7 alone ($N = 1176–1177$; see Supplementary Tables S3-S4); a further benefit was that the WISC-R battery was implemented for both study samples. We observed significant main effects of *APOE* for Performance and Full Scale IQ (FDR adjusted 1-tailed $p = 0.0156$ for both) with consistent, but nonsignificant, effects for Verbal IQ (FDR adjusted 1-tailed $p = 0.0749$) (see Table S3, Model I). Although the models including sex interactions did not achieve significance (all $p \geq 0.0973$; see Table S3, Model II), the pattern of effect sizes was consistent to that observed in the models fitted to longitudinal IQ above.

We also performed a follow-up sensitivity analysis of the longitudinal IQ performance models, with the inclusion of additional

Table 5
Multilevel fixed effects: *APOE*ε4 effects on IQ across year 7, year 12, and year 16 assessments

Fixed Effects	Model I				Model II			
	B	se	LL	UL	B	se	LL	UL
Verbal IQ								
Intercept	106.42	0.64[c]	105.16	107.67	105.89	0.69[c]	104.54	107.23
Study	−6.28	0.88[c]	−8.01	−4.55	−6.21	0.88[c]	−7.95	−4.48
Adopted	−3.64	0.98[c]	−5.55	−1.72	−3.56	0.98[c]	−5.47	−1.64
Sex	−2.36	0.71[c]	−3.75	−0.96	−1.30	0.87	−3.00	0.39
Age	−0.36	0.03[c]	−0.43	−0.30	−0.36	0.03[c]	−0.43	−0.30
ε2	−0.42	0.86	−2.12	1.27	0.30	1.22	−2.09	2.69
ε4	−1.60	0.70[a,d]	−2.97	−0.23	−0.23	0.95	−2.09	1.63
Sex*ε2	–	–	–	–	−1.37	1.60	−4.50	1.77
Sex*ε4	–	–	–	–	−2.95	1.38[a,e]	−5.65	−0.25
Performance IQ								
Intercept	105.76	0.61[c]	104.56	106.96	105.33	0.66[c]	104.02	106.63
Study	−8.17	0.81[c]	−9.76	−6.58	−8.11	0.81[c]	−9.70	−6.51
Adopted	−1.56	1.06	−3.63	0.51	−1.47	1.06	−3.55	0.60
Sex	−1.16	0.70	−2.53	0.22	−0.30	0.86	−1.99	1.38
Age	−0.79	0.03[c]	−0.86	−0.72	−0.79	0.03[c]	−0.86	−0.72
ε2	−0.17	0.84	−1.82	1.48	−0.64	1.24	−3.06	1.79
ε4	−1.78	0.71[a,d]	−3.16	−0.39	−0.13	0.97	−2.03	1.77
Sex*ε2	–	–	–	–	0.85	1.65	−2.38	4.08
Sex*ε4	–	–	–	–	−3.48	1.40[a,e]	−6.23	−0.73
Full Scale IQ								
Intercept	106.60	0.61[c]	105.41	107.80	106.11	0.65[c]	104.82	107.39
Study	−7.81	0.83[c]	−9.44	−6.17	−7.75	0.83[c]	−9.38	−6.11
Adopted	−2.97	0.99[b]	−4.92	−1.02	−2.90	0.99[b]	−4.84	−0.95
Sex	−2.05	0.69[b]	−3.41	−0.70	−1.06	0.84	−2.71	0.59
Age	−0.63	0.03[c]	−0.69	−0.58	−0.63	0.03[c]	−0.69	−0.58
ε2	−0.45	0.83	−2.09	1.18	−0.35	1.19	−2.67	1.98
ε4	−1.91	0.68[b,d]	−3.25	−0.58	−0.33	0.92	−2.14	1.48
Sex*ε2	–	–			−0.22	1.56	−3.28	2.84
Sex*ε4	–	–			−3.41	1.35[a,e]	−6.05	−0.77

$N = 1321$. Study (CAP = −.5, LTS = .5), Adopted (0 = Not, 1 = Adopted), Sex (Male = 0, Female = 1); Age was centered at 16 years; ε2 = number of alleles (0,1,2); ε4 = number of alleles (0,1,2). Model I refers to main effects models with *APOE* and Model II includes interaction effects with sex and *APOE*.
[a] $p < .05$ LL and UL = lower and upper 95% confidence interval.
[b] $p < .01$.
[c] $p < .001$.
[d] $p < .05$ 1-tailed, FDR corrected.
[e] $p < .05$ 2-tailed, FDR corrected.

covariates, that is, a sex by study interaction and self-reported race and ethnicity. Adding these covariates did not alter conclusions for longitudinal IQ across assessment years 7, 12, and 16 as detailed above with all tests remaining significant at adjusted FDR *p*-values: Model I, 1-tailed $p = 0.0064$ to $p = 0.0041$; and Model II, 2-tailed $p = 0.0397$ to $p = 0.0264$ (see Supplementary Tables S5-S6).

3.2.1. Tests of nonadditivity

We explored the possibility of nonadditive effects in Model I, given hints of nonadditivity in the mean IQ patterns by *APOE*ε4 alleles. We fitted Model I.a, with all covariates, entering recoded additive effects for ε2 and ε4 alleles (see Supplementary Table S7, Model I.a). Subsequently, we added the dominance effect for ε2 alleles. Results suggested that the ε2 dominance effect was negative and significant for Verbal, Performance, and Full Scale IQ (p =0.0003, 0.0247, and 0.0006, respectively, 2-tailed), suggesting reduced performance for ε2 heterozygotes (ε2/ε3, ε2/ε4) than expected from an additive model (see Supplementary Tables S6, Model I.b). FDR-adjusted 2-tailed *p*-values for the ε2 dominance effects remained significant ($p = 0.0247$ to 0.0009). Moreover, the additive effect for ε2 became significant and positive for Verbal ($p = 0.0090$) and Full Scale IQ ($p = 0.0159$), with the same direction for Performance IQ ($p = 0.1015$), suggesting a benefit in IQ performance for ε2/ε2 homozygotes. FDR-adjusted 2-tailed *p*-values remained significant for Verbal and Full Scale IQ, both $p = 0.0239$. Last, we added the ε4 dominance effect, which allows ε4 heterozygotes (ε2/ε4, ε3/ε4) to deviate from that expected under an additive model. Results suggested that adding the ε4 dominance effect was not significant (all $p \geq 0.2917$) (see Supplementary Table S7, Model I.c). The more parsimonious Model I.b best represents the contributions

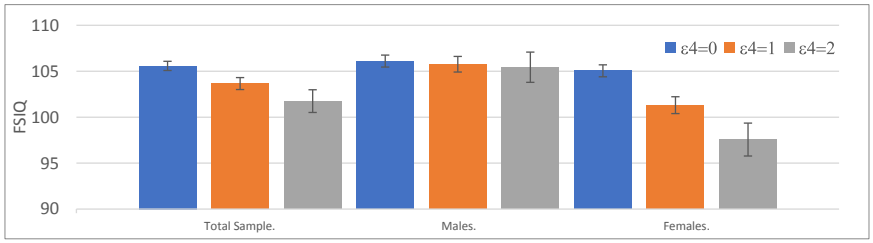

Fig. 1. Mixed Model estimates: *APOE*ε4 effects on Full Scale IQ based on child and adolescent assessments (years 7, 12, and 16). Analyses adjusted for nesting of individuals within family type, number of *APOE*ε2 alleles, sex, age, adoption status, and study (CAP or LTS). *APOE*ε3/ε3 was the referent group. The "Total Sample" estimates were averaged across sex (i.e., sex = 0.5), with all other effects at centered values. Standard errors are shown.

of additive (ε2 and ε4) and nonadditive (ε2) influences. Supplementary Figure S1 displays Full scale IQ by *APOE* genotypes, based on Models I.a and Model I.b, as well as covariate-adjusted least-squares means. See supplement for further details.

4. Discussion

APOE genotypes may be associated with general cognitive performance earlier than midlife. We observed small detriments in IQ performance across childhood and adolescence with nearly a 2-point decrement for each ε4 allele compared to those with APOE ε3/ε3 genotypes. Performance and Verbal IQ showed consistent effects, with the smaller effect sizes for Verbal IQ. Hence, *APOE*ε4 genotypes may be associated with lower IQ as early as childhood. Moreover, *APOE* may show stronger (or earlier) effects on IQ in females than males, particularly for Performance and Full Scale IQ.

The role of *APOE* on cognition between childhood and early adulthood is inconclusive, with most childhood studies cross-sectional in design (Calderon-Garciduenas et al., 2016; Chang et al., 2016; Ihle et al., 2012; Khan et al., 2014) and limited in assessments of IQ (Taylor et al., 2011). A recent large cross-sectional imaging and neuropsychological study of individuals aged 3–20 years (Chang et al., 2016) suggested potential differences in brain and cognitive development for those with particular *APOE* genotypes. For example, those with *APOE*ε2/ε4 evidenced smaller hippocampal volumes, and those with ε4/ε4 evidenced lower hippocampal fractional anisotropy at age 8 and younger (Chang et al., 2016). In addition, differential executive functioning and working memory performance were reported for *APOE*ε4/ε4 and attentional processing for *APOE*ε2/ε4 (Chang et al., 2016); however, the authors did not test associations with broader constructs. The Lothian Birth Cohort included a single childhood cognitive ability assessment with follow-ups in late adulthood at age 70 and beyond; they report a nonsignificant negative *APOE* ε4 effect for their measure of general verbal cognitive ability and reasoning assessed at age 11 (Luciano et al., 2009). In the present study, the weakest effect we observed was for Verbal IQ with larger *APOE* ε4 effects for Performance and Full Scale IQ. Notably absent from a recent large-scale GWAS of intelligence is implication of the *APOE* region (Savage et al., 2017); only about 5.7% of the nearly 280,000 samples included in this GWAS were from children or young adults. In this, and in similar GWAS, age and sex tend to be treated as covariates, and not leveraged per se to evaluate whether particular variants or gene sets are associated at certain age periods. Cautions in relying on imputations of *APOE* genotypes from GWAS have also been noted, although in recent years, imputation has become more reliable (Radmanesh et al., 2014; Roses et al., 2016).

Opportunities to evaluate earlier life cognitive functioning are uncommon in studies of cognitive aging, yet cognitive development across childhood and adolescence may represent a salient period when cognitive reserves are being formed. Cognitive reserve theories suggest that individuals may differ in their capacity to withstand aging-related pathologies because of cognitive processing optimizations that boost functioning and may allow individuals to weather aging and disease-related neural changes (Barulli and Stern, 2013). Likewise, early origin theories of late-life cognitive health (Barnett et al., 2013; Liu et al., 2010), stimulated in part by the "Barker hypothesis" of prenatal and early-life developmental determinants of adult-onset disease risk, have led to interests in modifiable features and life course mediators and moderators of cognitive aging and dementia. Our results suggest that cognitive differences associated with *APOE* may emerge early and become magnified later in the life course, and if so, childhood represents a key period of intervention to invest in and boost reserves.

*APOE*ε4 effects may be larger in females than in males, particularly for Full Scale IQ and Performance IQ. Recent cross-sectional work described in children ages 3–20 years (Chang et al., 2016) treated sex as a covariate but did not evaluate sex as a moderator of observed *APOE* effects. A report of 5995 British 8-year-old children from the ALSPAC study failed to find *APOE* associations with cross-sectional WISC Verbal, Performance, or Full Scale IQ (Taylor et al., 2011). However, trends for sex-stratified effects were observed where females with rare *APOE* genotypes, ε2/ε2 and ε4/ε4, showed higher average scores than ε3/ε3 females, whereas those with ε2/ε4 and ε3/ε4 genotypes showed worse scores than ε3/ε3 females for Verbal ($p = 0.03$) and Total IQ ($p = 0.02$). Moreover, a recent cross-sectional study evaluating 105 12-year-old children ($SD = 5.4$ years) living in Mexico City reported findings of an increased vulnerability to poorer performance in female carriers of *APOE*ε4 on Total and Performance IQ, consistent with our report (Calderon-Garciduenas et al., 2016). Recent literature suggests that differential risks for MCI and AD in females may appear in proscribed age periods and may not extend over the lifespan (Neu et al., 2017). Our findings suggest that such windows may extend to earlier stages of development, particularly for reasoning traits represented by performance IQ, before any notable cognitive differences raise clinical concerns. It will be important to track whether such early differences may become amplified perhaps due to differential cognitive reserves (Pettigrew et al., 2013; Runge et al., 2014), although early-life cognitive differences associated with *APOE* have yet to be directly linked to later cognitive reserves.

Explorations of nonadditive effects suggest a possible advantage for *APOE*ε2/ε2 individuals, followed by ε3/ε3, and the lowest performance among those who carry one or more ε4 alleles. Although the observed patterns by genotype are consistent with patterns of dementia risk (Farrer et al., 1997; Neu et al., 2017), and congruent with possible cognitive advantages and detriments observed in child samples (Chang et al., 2016) (c.f., females, Taylor et al., 2011), we note the ε2/ε2 and ε4/ε4 genotypes are relatively rare and necessitate some caution in interpretation of their means relative to the other more common genotypes. Further examination of differential benefits and vulnerabilities of *APOE* genotypes and sex moderation in larger samples, where it can be fully interrogated, is warranted.

The point estimates and *d*-effect size estimates we observed indicate that the effects on IQ are small per APOE ε4 allele, up to a few points. In terms of clinical relevance, a difference of a few points, while small, may be potentially relevant in terms of cognitive reserve for which any disadvantages could become magnified later in adulthood (c.f., Barulli and Stern, 2013; Liu et al., 2010). This bears further study. Moreover, childhood IQ is predictive of biological age as well as the pace of aging at midlife (Belsky et al., 2017; Schaefer et al., 2016), with lower childhood IQ associated with increased biological aging, as well as increased cardiovascular disease risks before age 65 (Hart et al., 2004) even after adjusting for covariates, suggesting that there may be physical health pathways to consider. With respect to *APOE*, this would include cholesterol-lipid pathways. Finally, for further perspective, the small differences in IQ that we observed are similar to the effect sizes noted in a recent meta-analysis of over 600,000 individuals from 42 studies across the lifespan suggesting that each additional year of achieved education may be causally associated with a 1 to 5 IQ point gain (Ritchie and Tucker-Drob, 2018). Echoing Ritchie and Tucker-Drob (2018), here in the context of *APOE*ε4, a few points may not be consequential for any one individual but could be meaningful in terms of early interventions to allay accelerated cognitive aging or dysfunction in a population sense.

Cognitive decline is a devastating and feared aspect of aging, yet its developmental origins have become a focus only recently. Cognitive development during childhood and adolescence may

contribute to the formation of crucial cognitive reserves that may hold a unique saliency to later cognitive functioning. Understanding the emergence and phenomena of differential cognitive growth in early life and differential maintenance in functioning in adulthood is critical to evaluating the promise of interventions. Additional longitudinal studies are warranted to consider early origins of cognitive health and the possibility of developmental effects that emerge in this age span. To this end, we are in the process of collecting additional Full Scale IQ and specific cognitive abilities data on the entire CATSLife sample between 28–46 years of age with an expected completion in 2020.

Disclosure

The authors report no conflicts of interest.

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Data Statement: Analysis code and outputs are provided at the Open Science Framework platform (https://osf.io/fn9gk/?view_only=f50599adacfc4abdbfda47aa926387eb). We will make available all data used in this manuscript, except where participant directives do not permit us to do so. Data will be made available publicly after the current CATSLife testing is completed and, in the interim, can be reanalyzed in a collaborative effort with our group by qualified investigators.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.04.011

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