IQ, Educational Attainment, Memory and Plasma Lipids: Associations with Apolipoprotein E Genotype in 5995 Children

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Background: Apolipoprotein E (APOE) genotype (ε2/ε3/ε4; rs429358 ε4 allele; rs7412 ε2 allele) is strongly associated with both lipid levels and Alzheimer’s disease. Although there is also evidence of milder cognitive impairment in later life in carriers of the APOE ε4 allele, there have been few studies investigating the impact of APOE genotype on cognitive function in children.

Methods: We determined APOE genotype in 5995 children from the Avon Longitudinal Study of Parents and Children and investigated associations between APOE genotype and plasma lipids (at age 9), IQ (at age 8), memory (at ages 8 and 10), and performance in school attainment tests (at ages 7, 11, and 14).

Results: Observed genotype group counts were consistent with Hardy–Weinberg equilibrium (χ² p value = .84). There were strong relationships between APOE genotype and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, which follow the same patterns as in adults. There was no strong evidence to suggest that APOE genotype was associated with IQ (all p values ≥ .46), memory function (p ≥ .35), or school attainment test results (p ≥ .28).

Conclusion: Although APOE genotype does have strong associations with lipid levels in childhood, there does not seem to be meaningful effects on cognitive performance, suggesting that any detrimental effects of the ε4 allele on cognitive function are not important until later life.

Key Words: APOE, children, cognitive function, IQ, lipids, memory

There are two well-known coding polymorphisms of apolipoprotein E (APOE), resulting in arginine > cysteine amino acid changes at positions 130 (rs429358) and 176 (rs7412). These changes determine alleles ε2/ε3/ε4, having frequencies of 8%, 78%, and 14%, respectively, in the UK population. The APOE ε4 allele represents a major susceptibility factor for late onset Alzheimer’s disease (LOAD), with carriers having approximately a three-fold risk (over tenfold for homozygotes) of developing LOAD compared with noncarriers. The mechanism linking APOE genotype and LOAD remains obscure, although isoform-dependent effects on β amyloid deposition and clearance, synaptic signaling, and inflammatory responses have been reported.

The APOE ε4 allele might also be associated with domain-specific cognitive decline in normal aging. Memory decline in particular has been noted in several studies, including one study of almost 6000 elderly adults, as being more marked in ε4 carriers. A recent model predicted that long-term memory decline in ε4 carriers began at age 50–60 years compared with noncarriers. The mechanism linking APOE genotype and LOAD remains obscure, although isoform-dependent effects on β amyloid deposition and clearance, synaptic signaling, and inflammatory responses have been reported.

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The influence of APOE alleles on cognition at an early age would be of particular interest, because it would potentially aid mechanistic understanding. There have been relatively few studies of APOE in relation to cognition in children; most of these have been small and therefore of limited power to detect differences between individual genotype groups. Deary et al. (24), in a retrospective study of 173 participants in the Lothian study, found no difference in performance by ε4 carrier status in the Moray House IQ test at age 11 years, and Turic et al. (25) similarly found no differences in APOE genotype distribution in 101 high-IQ and 101 average-IQ children.
In a study of 109 11–16-year-olds in California, Bloss et al. (26) found some evidence that cognitive function was lower only in e4 carriers who also had a family history of Alzheimer’s disease. However, in children, total spatiotemporal wave activity patterns have been shown to differ between e3 homozygotes and e4 carriers (27). In addition, a magnetic resonance imaging study of 239 healthy children showed that e4 carriers had lower cortical thickness in the left entorhinal region of the brain compared with noncarriers (27). There is also evidence that the e4 allele might actually be protective for brain development and cognitive function in early childhood. Infants carrying the e4 allele performed better in mental development tests in a study in Mexico, and amongst children in Brazil, who had had heavy diarrhea burdens in their first 2 years of life, e4 carriers showed better verbal fluency than noncarriers (28,29). This has led some to hypothesize that e4 might be an example of antagonistic pleiotropy, with the e4 allele being beneficial in early life but detrimental later in life (29,30). This could be due to the higher cholesterol levels seen in e4 carriers, because cholesterol is essential for neurodevelopment (31).

The purpose of this study was to obtain more precise estimates of the effects of all six APOE genotypes on cognitive performance in childhood, in the context of the prevailing childhood blood lipid profile. We analyzed APOE genotype in relation to IQ at age 8, memory tasks at ages 8 and 10, and school age educational performance tests (at ages 7, 11, and 14) in children from the ALSPAC study (Avon Longitudinal Study of Parents and Children). In parallel, we analyzed the APOE genotype in relation to plasma lipid profiles.

Methods and Materials

Study Population

The ALSPAC study (http://www.bristol.ac.uk/alspac) is a prospective study, established to explore child health and development (32). The initial ALSPAC sample consisted of 14,541 pregnant women from Bristol, United Kingdom, with expected delivery dates between April 1991 and December 1992, resulting in 14,062 live births. At age 7, a further 548 eligible children were added to the sample, making a total sample size of 14,610 for analyses. Detailed information on the children has been collected via questionnaires since birth and at annual clinic visits since the age of 7.

Genotyping

DNA Samples. Deoxyribonucleic acid samples were available for this study for 7091 children (63% of the 11,343 ALSPAC children with DNA samples available). Genotyping of the three main allelic variants (e3, e4, and e2) of APOE was undertaken by integrated single-label liquid phase assay. Full details of the method have been published previously (1). Polymerase chain reaction products were analyzed with a 384-well LightTyper instrument (Roche Diagnostics, GmbH, Indianapolis, Indiana), and genotypes were determined with Light-Typer software, Ver. 1. Duplicate DNA samples (identities unknown during genotyping) were analyzed to validate the assay, and a random sample (of 100 wells) was called independently by two investigators as a validation of genotype calling.

Lipids. Nonfasting blood samples were taken during clinic visit at age 9 (age range 8.8–11.7 years). Plasma lipids (total cholesterol, triglycerides, and HDLc) were measured by modification of the standard Lipid Research Clinics Protocol with enzymatic reagents for lipid determinations (33). The LDLc was estimated with the Friedewald equation (34).

Cognitive Function Measures

Clinic Assessments. The IQ was measured at a clinic held when the children were 8.5 years of age (mean: 8.7 years; range: 7.5–9.4 years) with the Wechsler Intelligence Scale for Children (35). A shorter version of the scale was used in which alternate items (always starting with Item 1 on the standard form) were used for 9 of 10 subtests. Scores from the verbal and performance subscales were used as outcome measures as well as overall IQ score. A measure of speech and language, the Wechsler Objective Language Dimensions (WOLD) test (36) was administered at the same clinic. Reading level was assessed at clinic at age 7.5 years (mean: 7.5 years; range: 6.9–8.0 years) with measures based on the Wechsler Objective Reading Dimensions (WORD) test (37).

Short-term memory at age 8 was measured in clinic with an adaptation of the Nonword Repetition Test (38). Children were asked to repeat 12 nonsense words of three, four, and five syllables after hearing them on an audio cassette. The outcome measure is the number of words repeated correctly. Working memory at age 10 was assessed in clinic via the Counting Span Working Memory Task (39). This test involved counting and recalling numbers of dots on screens, which were administered in sets of two, three, four, and five screens. Two scores were recorded from this test; the span score represents the number of correctly recalled sets, with a maximum score of 5 in increments of .5, and the global score represents the total number of screens correct, with a maximum of 42 (40).

School Assessments. In addition to clinic measures of cognitive function, we used the results of nationally administered school-based tests (SATS) (for more detailed information see website: http://curriculum.qcda.gov.uk/). These are undertaken in Year 2 (key stage 1, age 6–7 years), Year 6 (key stage 2, age 10–11 years), and Year 9 (key stage 3, age 13–14 years). For key stage 1, English (reading and writing) and math scores were categorized into three groups: below average (W, 1), average (2a, 2b, 2c), and above average (3+) on the basis of the expected attainment for this age group. For key stages 2 and 3, total scores obtained in the tests for the three core subjects (English, math, and science) were used as the outcome measure.

Statistical Analysis

Individuals of known nonwhite ethnic origin (n = 547) were excluded from all analyses. Where siblings and multiple births were present, the first-born in the study was kept, and the others (n = 172) were dropped from all analyses.

Hardy–Weinberg equilibrium tests were performed on the entire sample of genotyped children (excluding siblings and those of nonwhite ethnicity) and on the samples with available lipid or cognitive function measures to assess the possibility of sampling bias due to nonattendance at clinic.

Means and SDs of total cholesterol, LDLc, and HDLc levels were calculated for each genotype. Geometric means and interquartile ranges are presented for triglycerides, due to skewed distributions.

Age− (in months) and gender-adjusted associations between genotypes and total cholesterol; LDLc; HDLc; triglycerides (log-transformed); total, verbal, and performance IQ; WORD and WOLD scores; memory tests; and key stage 2 and 3 test scores were assessed by linear regression. In all regression models, each APOE genotype was considered separately with e3 homozygotes as the reference group. Heterogeneity of associations of APOE genotypes with each outcome were assessed by analysis of covariance models and p values reported. Chi-square tests were used to look at associations between APOE genotypes and key stage 1 test results. Direct associations between plasma lipids (as continuous variables and in quartiles) and cognitive function measures were assessed by linear regression, adjusted for age, gender, and maternal education and household socioeconomic status.

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Ethical Approval
Ethical approval was obtained from the ALSPAC Law and Ethics Committee and local research ethics committees. Parental consent and assent of the child were obtained for all measurements made.

Results
In total, 95% of samples were successfully genotyped. The number of children with genotype information available for the analyses was 5995, after excluding children of known non-white ethnicity and siblings. Lipid measures on a subset of 2875 of those genotyped and IQ measures for a subset of 3925 of those genotyped were available. There was no strong evidence of a gender difference in genotype distribution ($p = .16$) or of deviation from Hardy-Weinberg equilibrium for the whole sample ($\chi^2 = 1.42, p = .84$) or when the sample was restricted to children with genotype and lipid data ($n = 2875, \chi^2 = 4.53, p = .34$) or genotype and IQ data ($n = 3925, \chi^2 = 1.97, p = .74$).

Lipids
Levels of total cholesterol and LDLc increased according to the number of $\varepsilon 4$ alleles and decreased according to the number of $\varepsilon 2$ alleles ($p < .0001$) (Table 1). Conversely, levels of HDLc decreased according to the number of $\varepsilon 4$ alleles and increased according to the number of $\varepsilon 2$ alleles ($p < .0001$). A U-shaped curve was found for triglycerides where levels increased according to the number of $\varepsilon 2$ and $\varepsilon 4$ alleles. Tables S1 (male subjects) and S2 (female subjects) in Supplement 1 describe lipid levels in relation to APOE genotype for boys and girls. Girls demonstrated higher levels of total, LDLc, and triglycerides.

Lipids and IQ
Information on lipids and IQ was available for 3713 children (Table 2). The IQ decreased by 93 points for each mmol/L increase in LDLc ($p = .04$), but this attenuated to .58 points ($p = .15$) after adjustment for maternal education and household social class. The 2254 children who had APOE information demonstrated a similar pattern. Associations of quartiles of lipid measures with IQ and lipids (as continuous measures and quartiles) with other cognitive function measures are shown in Tables S3–S5 in Supplement 1.

Individuals in the second and fourth quartiles of LDLc demonstrated lower IQ scores than those in the lowest quartile, but these associations did attenuate after adjustment for maternal education and social class (Table S3 in Supplement 1). There was some evidence that being in the highest quartiles of either total cholesterol or LDLc was associated with lower scores in key stage 2 math and the nonword repetition memory test (Table S5 in Supplement 1). These associations remained after adjustment for maternal education and household socioeconomic position.

Cognitive Function
There was little evidence to suggest that IQ, WORD, and WOLD test results were associated with APOE genotype (Table 3). However, on each measure, children who carried $\varepsilon 2/2$ and $\varepsilon 4/4$ genotypes tended to have slightly higher scores. For example, total IQ was 3.6 points higher for children who carried $\varepsilon 2/2$ compared with those who carried $\varepsilon 3/3$ and 2.6 points higher for $\varepsilon 4/4$ compared with $\varepsilon 3/3$. Memory scores, including nonword repetition task results, were not associated with APOE genotype (Table 4). The SATS scores were essentially unrelated to APOE genotype (Table 5 and S6 in Supplement 1).

However, there was a consistent pattern that $\varepsilon 2/2$ and $\varepsilon 4/4$ girls had higher IQ scores (from 3 to 7 points) compared with $\varepsilon 3/3$ girls (Table S7 in Supplement 1). These genotypes were also associated

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All Children, n = 3713

| Lipid                      | Coeffa (IQ points) | 95% CI        | p    | Coeffa (IQ points) | 95% CI        | p    |
|----------------------------|--------------------|---------------|------|--------------------|---------------|------|
| Total cholesterol (mmol/L) | −.69               | (−1.46, .09)  | .08  | −.45               | (−1.17, .26)  | .22  |
| LDLC (mmol/L)              | −.92               | (−1.79, .06)  | .04  | −.59               | (−1.38, .21)  | .15  |
| HDLc (mmol/L)              | −.07               | (−1.74, 1.60) | .93  | −.27               | (−1.82, 1.27) | .73  |
| Triglyceridea (mmol/L)     | .54                | (−.64, 1.73)  | .37  | .35                | (−.74, 1.44)  | .53  |

Children with APOE Genotype Data, n = 2254

| Lipid                      | Coeffa (IQ points) | 95% CI        | p    | Coeffa (IQ points) | 95% CI        | p    |
|----------------------------|--------------------|---------------|------|--------------------|---------------|------|
| Total cholesterol (mmol/L) | −.78               | (−1.78, 23)   | .13  | −.70               | (−1.64, .23)  | .14  |
| LDLC (mmol/L)              | −.98               | (−2.10, .15)  | .09  | −.85               | (−1.89, .20)  | .11  |
| HDLc (mmol/L)              | −.79               | (−2.95, 1.38) | .48  | −.64               | (−2.65, 1.37) | .53  |
| Triglyceridea (mmol/L)     | 1.15               | (−.37, 2.67)  | .14  | .62                | (−.80, 2.03)  | .39  |

Table 2. Associations of Plasma Lipids with Total IQ

Abbreviations as in Table 1.

aCoefficients from linear regression represent increase in IQ points/mmol/L increase in lipid measure.
bAge, gender, maternal education, household social class adjusted.
cTriglyceride is log-transformed.

table 3. Associations of APOE Genotype with IQ, WORD, and WOLD Tests

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | 3.62   | (−2.20, 9.44) | n/a  |
| e2/e3    | .29    | (−1.24, 1.83) | n/a  |
| e2/e4    | .85    | (−2.56, 2.04) | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | .37    | (−1.61, .88)  | n/a  |
| e4/e4    | 2.24   | (−1.29, 5.77) | n/a  |

Performance IQ, n = 3940

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | 2.78   | (−3.29, 8.85) | .91  |
| e2/e3    | .83    | (−.76, 2.43)  | n/a  |
| e2/e4    | 1.27   | (−2.06, 4.60) | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | .93    | (−.35, 2.21)  | n/a  |
| e4/e4    | 2.41   | (−1.22, 6.04) | .46  |

WORD, n = 4391

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | 1.46   | (−1.59, 4.50) | n/a  |
| e2/e3    | −.31   | (−1.15, .52)  | n/a  |
| e2/e4    | −.44   | (−2.21, 1.33) | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | −.27   | (−.94, .40)   | n/a  |
| e4/e4    | 1.02   | (−.92, 2.96)  | .64  |

WOLD, n = 3940

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | .36    | (−.35, 1.06)  | n/a  |
| e2/e3    | −.03   | (−.21, .15)   | n/a  |
| e2/e4    | .08    | (−.29, .46)   | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | −.06   | (−.21, .09)   | n/a  |
| e4/e4    | .28    | (−.14, .69)   | .56  |

Table 3. Associations of APOE Genotype with IQ, WORD, and WOLD Tests

APOE, apolipoprotein E; WORD, Wechsler Objective Reading Dimensions; WOLD, Wechsler Objective Language Dimensions; CI, confidence interval.

aFrom linear regression adjusted for gender and the age of child in months.
bThe p values for heterogeneity from analysis of covariance model.
cCoefficients represent change in IQ score in IQ points.
dCoefficients represent point changes in WORD and WOLD scores.

Discussion

We have undertaken a composite analysis including APOE genotype and serum lipid, IQ, and educational measures in a large population-based sample of children. Lipid profiles differed by APOE genotype in characteristic patterns corresponding with the wider literature, which has largely focused on adults (21). There was strong statistical evidence for these genotype-specific differences in total cholesterol, HDLc, triglycerides, and calculated LDLc, and the data define with high precision the population patterns for this test.

Table 4. Scores in Memory Tests at Ages 8 and 10 by APOE Genotype

| Test                                    | Coeffa | 95% CI        | p    |
|-----------------------------------------|--------|---------------|------|
| NonWord Repetition Task, n = 3937       |        |               |      |
| e2/e2                                   | .43    | (49, 1.35)    | n/a  |
| e2/e3                                   | −.06   | (−.30, .18)   | n/a  |
| e2/e4                                   | −.08   | (−.58, .41)   | n/a  |
| e3/e3                                   | n/a    | n/a           | n/a  |
| e3/e4                                   | −.09   | (−.28, .11)   | n/a  |
| e4/e4                                   | −.08   | (−.62, .46)   | .86  |

Counting Span Task Global Score, n = 3667

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | −.83   | (−3.56, 1.90) | n/a  |
| e2/e3    | .02    | (−.73, .77)   | n/a  |
| e2/e4    | .30    | (−1.29, 1.89) | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | .32    | (−.28, .92)   | n/a  |
| e4/e4    | .98    | (−.79, 2.75)  | .75  |

Counting Span Task Span Score, n = 3667

| Genotype | Coeffa | 95% CI        | p    |
|----------|--------|---------------|------|
| e2/e2    | −.11   | (−.42, .20)   | n/a  |
| e2/e3    | −.01   | (−.08, .08)   | n/a  |
| e2/e4    | .02    | (−.16, .20)   | n/a  |
| e3/e3    | n/a    | n/a           | n/a  |
| e3/e4    | .05    | (−.02, .12)   | n/a  |
| e4/e4    | .18    | (−.02, .37)   | .35  |

Nonword repetition task from age 8 clinic, counting span task from age 10 clinic. APOE, apolipoprotein E; CI, confidence interval.

aAdjusted for gender and age.
bThe p values for heterogeneity from analysis of covariance model.

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Because of the wide range of cognitive function measures investigated within ALSPAC (both clinic measures and the results of nationally administered tests), our study provides good evidence that having an e4 allele is not detrimental to cognitive performance in childhood or adolescence. This study was sufficiently powered to detect differences of 1.9 and 2.0 IQ points in e4/e3 and e2/e3 genotypes, respectively, compared with e3 homozygotes but only differences of 5.1 and 8.5 IQ points in e4 and e2 homozygotes, respectively. Furthermore, it might be expected that the e4 allele would have an additive effect on cognitive function (i.e., having one e4 allele has a weaker effect than having two), but the effects are in the same direction—as is demonstrated for both lipids and LOAD (21,44)—but we did not observe this pattern in our results. In addition, the e2 allele did not exert any effect in the common e2/3 heterozygote group. This lack of association with cognitive function measures in ALSPAC is consistent with the findings of previous smaller studies in children of a similar age (24,25) and suggests that the preclinical effects of Alzheimer’s disease do not start in childhood. The human ancestral allele for APOE is widely accepted to be e4, the sequence observed in other primates and from which two most commonly been found to be associated with cognitive decline in adults and Alzheimer’s disease, no differences were evident for the main genotype groups for IQ, memory, and educational measures of children, although there were possible differences for rare genotype subgroups.

The total and LDLc values for the different genotypes in our cohort (age 9) are similar although slightly lower than the average values observed in a population based-sample of 3–18-year-olds in Finland in 1980 and a sample of 11-year-old Greek schoolchildren (41,42). A study on the same Finnish population found that the characteristic differences in lipid levels by APOE genotype were present at age 3 but not in newborns, suggesting that these associations develop in the first few years of life (43). For HDLc level, genotype differences were less marked in our sample than differences in LDLc and total cholesterol, but there was clear evidence of an increase with e2 alleles and a decrease with e4 alleles, which was not obvious in the Finnish population (41). The lipid data act as a positive control for our genotyping and database operations, confirming that the absence of significance with cognitive measures in our study does not reflect technical limitations.

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It might be, as is suggested by the results of studies of normal cognitive aging in older adults, that APOE is only associated with certain domains of cognitive function, and so general measures such as IQ and attainment tests have not captured specific differences. However, memory function, one of the domains that has most commonly been found to be associated with APOE genotype in older people (12,46), did not differ between APOE genotype groups at ages 8 and 10.

The minor homozygote groups (e4/4 and e2/2) displayed the greatest magnitude associations (both positive) with IQ, and e2/2 homozygotes also displayed the greatest magnitude associations with key stage 2 test scores, especially in girls (Tables S7 and S8 in Supplement 1). Given the small numbers in these groups, the confidence intervals are wide and are consistent with there being no effect. However, the results might suggest some cognitive advantages in these groups. Such a scenario could be biologically plausible if lipid levels during childhood affect brain development, a hypothesis that has been put forward with regard to the e4 allele and cholesterol levels and for which there is some evidence in the literature (28,29). Lipid levels are affected both by environmental factors, such as diet, and by genetic variants such as APOE. The APOE
genotype therefore acts as a genocopy for environment-affected lipid levels. Among rare lipoprotein disorders, microsomal triglyceride transfer protein genotypes the effects on the central nervous system of both genetic- and environment-driven forms of vitamin E deficiency (47–49). Higher triglyceride levels are observed in both e4 and e2 carriers compared with e3 (Table 1) and numerous important substances such as polyunsaturated fatty acids (50), palmitate (51), fish oils (i.e., N-3 fatty acids) (52), and fat-soluble vitamins such as vitamin E (47)—which have recognized importance in brain development—are also carried by lipoprotein particles. Further studies would be required with larger numbers in the minor homozygote groups to obtain robust conclusions for them.

Our genetic observations are consistent with the attenuation of the association between LDLc and IQ (Table 2), after adjustment for the confounding factors maternal education and socioeconomic status. Further studies would be required with larger numbers in the male subjects and female subjects. Mortensen and Hogh (9) found a genotype might have a different effect on cognitive function in different populations, but the effect of genotype on IQ has been found in many studies. The effect of the genotype on IQ scores in higher LDLc quartiles was attenuated after adjustment for confounding factors and residual effects were inconsistent (e.g., lower IQ in second and fourth quartiles of LDLc compared with the first and third). It would be possible in the future, with a large number of genetic variants influencing LDLc (55), to use Mendelian randomization tests (56) of whether there is causal association between circulating LDLc and cognitive function.

We found some evidence of an interaction between genotype and gender in the IQ analyses, which raises the possibility that APOE genotype might have a different effect on cognitive function in male subjects and female subjects. Mortensen and Hogh (9) found a decline in IQ scores in e4 carriers from age 70 to 80 in women but not men, although the study sample comprised only 163 people. However, although associations between APOE genotype were stronger when our analyses were stratified by gender than in the sample as a whole, there was no consistent pattern across the different cognitive measures, and evidence for these associations would not remain after Bonferroni correction for the number of statistical tests performed. Thus, support for a gender difference in the association between cognitive measures and APOE is limited.

In conclusion, although the estimates for the homozygote groups are less precise, due to relatively small numbers we can be confident that—at least for the three major genotype groups (e3/e3, e3/e4, and e2/e3) that represent 94% of this population—APOE genotype has no major influence on cognition in childhood and adolescence. However, given the strong associations with lipid profiles in these children, APOE genotype should be considered important in the context of the origins of cardiovascular disease.

Supplementary material cited in this article is available online.
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