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Meta-Analysis of Cognitive Ability Differences by Apolipoprotein E Genotype in Young Humans

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Highlights

- Apolipoprotein (APOE) ε4 has been proposed as an antagonistic pleiotropy gene
- Cognitive associations of the ε4 allele in younger persons yield mixed results
- This meta-analysis examined cognitive associations with APOE ε4 in younger humans
- Findings were non-significant across ~~six of seven~~ **all seven** cognitive domains
- Marginally better performance in executive functioning was observed in ε4 persons
- Overall, findings do not support an antagonistic pleiotropic effect of APOE ε4

Abstract

The apolipoprotein (APOE) ε4 allele has been proposed as an example of an antagonistic pleiotropy gene, conferring a beneficial effect on cognition in early life and a detrimental impact on cognition during later years. However, findings on the cognitive associations of the ε4 allele in younger persons are mixed. This PRISMA conforming study aimed to investigate APOE genotype (e4/non-e4) associations across seven cognitive domains (intelligence/achievement, attention/working memory, executive functioning, memory, language, processing speed and visuospatial abilities) in younger humans using a meta-analytic approach. Of 689 records reviewed, 29 studies (34 data-points) were selected for the quantitative synthesis. Participants' ages ranged from 2-40. Results showed that young ε4 carriers did not statistically differ from non-ε4 carriers across any cognitive domains. Overall, findings do not provide compelling support for an antagonistic pleiotropic effect of the ε4 allele across the lifespan.

Keywords: apolipoprotein E, Alzheimer's disease, cognition, neuropsychology, executive functions, PRISMA

Introduction

The link between the apolipoprotein (APOE) ε4 allele and Alzheimer's disease (AD) is well established in the literature (Farrer et al., 1997; Saunders et al., 1993). Presence of the APOE ε4 allele confers a three- to four-fold increased risk of developing Alzheimer's disease

(AD; Saunders et al., 1993) and has been linked to neuropathological changes associated with AD, including beta-amyloid plaques (Morris et al., 2010; Serrano-Pozo et al., 2015; Strittmatter et al., 1993) and neurofibrillary tangles (Namba et al., 1991). Furthermore, presence of the ε4 allele in healthy non-demented older adults is associated with poorer cognitive performance (Bondi et al., 1995; Caselli et al., 2004; Small et al., 2004), reduced grey matter volume in regions associated with AD (Den Heijer et al., 2002; Scarmeas and Stern, 2006; Soininen et al., 1995), and differences in cerebral activity during resting and task-based functional magnetic resonance imaging (fMRI; e.g., Bondi et al., 2005; Bookheimer et al., 2000; Tuminello and Han, 2011 for review) compared to non-demented older adults without the allele.

In recent years, there has been increased interest in understanding the effect of the APOE ε4 allele on cognition in different age groups, including children and young adults. Findings support differential effects of the ε4 allele on cognition based on the age group under investigation. Compared to healthy older adults in whom cognitive deficits have been consistently reported in ε4 carriers (Small et al., 2004), differences between ε4 and non-ε4 carriers in middle age are reduced or null (Salvato, 2015 for review). Conversely, in young adults and children, some studies report ε4 carriers outperforming non-ε4 carriers on cognitive tasks (Han and Bondi, 2008 for review).

Based on findings suggesting differential cognitive effects of ε4 allele possession throughout the lifespan, Han and Bondi (2008) along with others (Alexander et al., 2007; Jochemsen et al., 2012; Rusted et al., 2013) proposed the antagonistic pleiotropy hypothesis of APOE ε4. Antagonistic pleiotropy is a theory of senescence in which "individual loci/alleles have different effects on fitness at different ages" (Albin, 1993; Williams, 2001). Specifically, these alleles are thought to have a positive, beneficial effect on fitness in early life and a

negative, detrimental impact on fitness during later years in the context of aging (Albin, 1993). Han & Bondi (2008) suggested that ε4 is one such allele, conferring advantages on cognitive tasks early in life but resulting in cognitive and neural disadvantages in late life. Although this is theoretically compelling, findings regarding cognition in younger ε4 carriers are mixed. While some studies provide support for better cognition in young ε4 carriers compared to non-ε4 carriers (Bloss et al., 2010; Puttonen et al., 2003; Schultz et al., 2008; Wright et al., 2003; Yu et al., 2000), other studies fail to find support (Deary et al., 2003; Dennis et al., 2010; Filbey et al., 2006; Jorm et al., 2007; Luciano et al., 2009; Richter-Schmidinger et al., 2011) and some even report poorer cognitive performances in young ε4 carriers (Acevedo et al., 2010; Bloss et al., 2008; Calderon-Garciduenas et al., 2016).

Mixed findings regarding cognitive effects of the ε4 allele in younger persons likely relate to methodological variability between research studies. In a review of the literature, Tuminello & Han (2011) discuss the implications of some studies including high-risk groups in their samples and suggest that accounting for additional variables that can affect cognition is an important factor that can impact study results. For example, other AD risk factors such as family history of AD (e.g., see Bloss et al., 2008) and presence of other AD-related genes (e.g., Green et al., 2014) may interact with APOE genotype to impact cognition. Additionally, studies vary with regards to their definition of young ε4 and non-ε4 carriers, with some examining very wide age ranges (e.g., Stening et al., 2016; Suri et al., 2015) and others including restricted ranges (Bunce et al., 2011; Bunce et al., 2014; Dell'Acqua et al., 2015).This can potentially be an important source of variability if the ε4 allele exerts a beneficial effect on cognition during a restricted time period in early life (Tuminello and Han, 2011).

An additional source of variability between studies is classification of ε4 and non-ε4 participants. While some studies exclude ε4 carriers who also possess the ε2 allele (e.g., Calderon-Garciduenas et al., 2016; Dennis et al., 2010; Filbey et al., 2006; Jorm et al., 2007), others do not (e.g., Acevedo et al., 2010; Luciano et al., 2009; Marchant et al., 2010; Puttonen et al., 2003; Richter-Schmidinger et al., 2011; Schultz et al., 2008; Wright et al., 2003; Yu et al., 2000). The ε2 allele has been associated with reduced cognitive decline among healthy older persons (Farrer et al., 1997; Shinohara et al., 2016), reduced clinical and pathological progression in AD (Serrano-Pozo et al., 2015), and increased longevity and survival among older adults (Corder et al., 1996). It is therefore considered a protective factor against AD. The presence of both ε2 and ε4 alleles may have either opposing influences or synergistic effects in young age, depending on the role of the ε4 allele on cognition in young age. Thus, differential inclusion of ε2-ε4 heterozygotes may produce variability in findings across studies.

A final source of variability between studies relates to the specific neuropsychological tests and cognitive domains under investigation. One possibility is that the ε4 allele confers benefits in some domains of cognition but not in others due to a differential influence of the allele on underlying neural systems. Han and Bondi (2008) suggest that benefits on cognitive tasks in young ε4 carriers may be mediated by increased recruitment of frontal-executive neural networks. This is supported by imaging work implicating the frontal-executive system as a focus of compensatory recruitment in healthy older ε4 carriers (Bondi et al., 2005; Han and Bondi, 2008; Kukolja et al., 2010; Seidenberg et al., 2009; Tuminello and Han, 2011; Wierenga et al., 2010) and studies that provide evidence for increased recruitment of frontal systems in young ε4 carriers (Filbey et al., 2010; Filbey et al., 2006). However, findings regarding frontal involvement in young and older ε4 carriers are mixed (Trachtenberg et al., 2012; Tuminello and

Han, 2011). For example, some studies of young ε4 carriers do not support increased frontal system recruitment in young ε4 carriers, instead finding evidence for increased recruitment of task-related regions (e.g., Dennis et al., 2010; Filippini et al., 2009; Tuminello and Han, 2011 for review). To the degree that the ε4 allele results in increased recruitment of neural networks underlying specific cognitive functions, performance differences between ε4 and non-ε4 persons may arise for some cognitive domains but not others.

A recent meta-analysis by Ihle and colleagues (Ihle et al., 2012) sought to integrate findings across studies reporting on associations between APOE ε4 and cognition in younger persons. The authors did not find an association between presence of the ε4 allele and cognition in persons between the ages of 5 and 35. Based on a potential association between the ε4 allele and frontal-executive networks (Han and Bondi, 2008), the authors also conducted post-hoc analyses to investigate whether tasks requiring increased executive demands would moderate the association between possession of the ε4 allele and performance on cognitive measures. Findings were non-significant. The authors conclude that the antagonistic pleiotropy hypothesis of APOE ε4 should be treated with caution.

Findings of Ihle et al. (2012) are informative and important. However, for several reasons, an updated meta-analysis is needed. Most relevant is the fact that new studies have been published since the 2012 meta-analysis. Additionally, although Ihle et al. investigated moderating effects of executive demands, the authors did not specifically examine other cognitive domains which may reveal associations with the ε4 allele and acknowledge this as a limiting factor in their study. Finally, Ihle and colleagues also analyzed studies that included ε2-ε4 heterozygote participants, which can introduce confounds due to well-established protective factors of the ε2 allele. Thus, the aim of the present meta-analysis is to update and extend

findings of Ihle et al. with these considerations in mind. To this end, we embarked on a systematic literature review of studies that report associations between cognition and APOE in younger persons (infancy to age 40) and quantitatively integrated these findings using meta-analytical techniques across seven cognitive domains.

Methods

Literature Search

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009). In accordance with PRISMA guidelines, the project was registered with PROSPERO, the international prospective register of systematic reviews (registration number: CRD42017079478). The literature search was conducted on October 13, 2017 with no imposed date restriction. The search term "(APOE or Apolipoprotein e) and (cognition or cognitive function or neuropsychology or neuropsychological tests)" was applied to PubMed and PsychINFO databases, with APOE used as a common abbreviation for apolipoprotein E. Age limits were selected in the search engine menu in order to restrict results to the age range of interest. For PubMed, child (birth to 18) and adult, ages 19-44, were selected. For PsychInfo, we selected 30s, young adulthood, adolescence, childhood, school age, preschool, infancy, and neonatal.

Inclusion/Exclusion Criteria

Inclusion criteria were as follows: 1) human subject research, 2) participant age range of less than or equal to 40 years of age, 3) non-clinical samples (i.e., not meeting criteria for a medical or mental health condition that could impair cognition), 4) report of at least one neuropsychological or cognitive outcome measure, and 5) report of cognitive outcomes stratified

by ε4 and non-ε4 groups. We excluded studies that 1) focused on animal research, 2) focused on another topic (e.g., brain injury, cancer), 3) were duplicate studies, 4) did not report data separately for APOE ε4 and non-ε4 groups, 5) included ε2-ε4 heterozygotes, 6) were not empirical, peer-reviewed research articles (e.g., dissertation, books, abstract only, conference presentations, case studies) or 6) lacked cognitive outcomes. The decision to exclude APOE-ε2 carriers from the ε4 group was made due to the potential confound of protective effects that are conferred by the allele (Farrer et al., 1997).

Data extraction and risk of bias

Two authors (GHW and SDH) independently reviewed all individual titles and abstracts of citations yielded from the search. Disagreements that arose for citations were discussed until an agreed-upon decision was reached. Full-text articles were downloaded and reviewed whenever there was a question regarding one of the selection criteria. Risk of bias was assessed at the study level for selective reporting, incomplete outcome data, quality of experimental design (e.g., inadequate sample size per genotype group, demographic considerations, IRB approval for research procedures), and undue influence of funding sources. Studies judged to indicate a potential risk of bias were excluded from review. Each article was reviewed by GHW and SDH for potential risk of bias with disagreements settled through discussion.

Data Analysis

Outcomes in the present study were neuropsychological or cognitive test scores (e.g., experimental designs, fMRI tasks) stratified by genotype group (ε4 vs. non-ε4). The ε4 group included homozygotes of the ε4 allele as well as more commonly occurring ε3/ε4 heterozygotes.

The non-ε4 group consisted of ε3 homozygotes, ε2 homozygotes, and ε2/3 heterozygotes. Tests were grouped into the following seven categories to assess for any specific effects by domain: achievement/intelligence, attention/working memory, executive functioning, language, memory, processing speed, and visuospatial abilities. To examine whether ε4 and non-ε4 groups differ across each of the seven domains, Hedges' g (Hedges, 1981) were calculated with random effects models, which assume that the true effect size might differ from study to study. Thus, results are weighted based on study sample size, allowing inferences to be extended beyond the studies included in the meta-analysis (Hedges and Vevea, 1998). Statistical analyses were conducted using Comprehensive Meta Analysis (CMA) software, version 3.3.070 (Biostat, Englewood, NJ). Forest plots were visualized using CMA, and results were deemed significant at an alpha of $p<.05$. Follow-up analyses were conducted excluding studies that included sub-groups of ε4 and non-ε4 carriers with an additional risk factor for AD or cognitive impairment (e.g., positive family history of AD). As a quality control measure, if fewer than five studies were available for a particular analysis, the analysis was not conducted due to lack of adequate data. This was not the case for any of the analyses.

Heterogeneity, which refers to the variability or diversity of studies included in a systematic review, can impact the robustness and generalizability of the results (Higgins et al., 2003; Thompson, 1994). Heterogeneity was considered via statistical calculation of Q, Tau, Tau^2, and I^2. Q provides a measure of absolute heterogeneity of effects with a corresponding *p*-value (Cochran, 1954). Tau and Tau^2 provide measures of the standard deviation and variance of true effects respectively (Borenstein et al., 2010), and provide a basis for comparison across studies. I^2 refers to a ratio of true effect variance to observed error variance (Higgins et al., 2003).

Table 1 lists the measures extracted from articles that were used in the present review according to each cognitive domain. Per meta-analysis convention, if more than one measure was reported in a single study for a given cognitive domain, outcomes were pooled and the mean effect size was used. If a study further subdivided ε4 and non-ε4 participants into subgroups based on a common factor (e.g., sex), each subgroup was considered to be a separate data point.

Results

Study Selection

Search of databases yielded 689 records with an additional 32 records identified through other sources (e.g., reference lists of review articles). Following removal of duplicates, 635 records were screened by reviewing titles and abstracts. Of these, 79 were removed based on the title (e.g., case study, non-English language, irrelevant topic) and 412 were removed after reading the abstract (e.g., animal study, clinical sample, out of age range, review paper, dissertation, book). Thus, 144 full-text articles were assessed for eligibility and 101 were excluded following full-text review. Most of these studies (*n*=63) were excluded for being outside of the pre-specified age range. These were studies in which the age range was unclear based on reading the abstract alone. Sixteen studies included ε2 carriers in the ε4 group, 13 did not report cognitive outcomes, and nine focused on APOE genotype in the context of a disease state or health condition (e.g., cancer, stroke, brain injury, cardiovascular disease). After these exclusions, 43 articles remained in the qualitative synthesis. Further assessment of records revealed three studies that met criteria for risk of bias, two due to small sample sizes per genotype group and one due to methodological

concerns. Three studies were excluded because they reported identical data as other studies that were included in the quantitative synthesis. In these cases, the studies that provided more cognitive outcome data were selected. Ten articles reported data in a different format than the format necessary for the quantitative synthesis or were missing values (means and/or standard deviations) for relevant cognitive measures. In an attempt to include these studies, emails were sent to corresponding authors requesting data. Two authors responded by the date of preparation of this manuscript and were included in the final quantitative synthesis. In sum, 29 studies remained in the quantitative meta-analysis. Five of the 29 included studies that subdivided genotype groups by other factors (e.g, sex) yielding a total of 34 data points to be included in the quantitative synthesis. Figure 1 presents the flowchart for determining study inclusion into the meta-analysis.

APOE ε4 vs. APOE non-ε4

Demographic data per study are presented in Table 2. Comparing performance of ε4 and non-ε4 persons on measures across all domains combined revealed a summary effect size that did not significantly differ from zero (p=.98). Examining each of the seven domains separately also revealed no differences between groups for the domains of achievement/intelligence, attention/working memory, language, memory, processing speed, and visuospatial abilities (all ps $\geq$ .22). With regard to executive functioning, a marginal trend arose in which ε4 persons scored higher than non-ε4 persons (13 studies, H_g= .251, SE_g= .152, 95% CI= -0.05 to 0.56, p=.098). Heterogeneity was found to be in the high range for executive functioning (Q = 48.68, p < .001, I^2 = 75.35, Tau = 0.45, Tau^2 = 0.20). Figure 2 presents the forest plot for the domain of

executive functioning. Forest plots for all other domains can be visualized in Supplementary Materials (Figures 1-7).

Follow-up analysis

To investigate whether inclusion of "high-risk" groups would impact study findings, we re-analyzed data excluding the positive family history sub-sample from Bloss et al. (2008), the high prenatal mercury exposure sub-sample from Ng et al. (2013), and data from Green et al. (2014) who investigated differences between ε4 and non-ε4 carriers who also had the CLU-C genotype. This was relevant for the combined domains analysis and for analyses of achievement/intelligence, executive functioning, language, processing speed, and visuospatial abilities. Findings remain non-significant across all domains combined, and the domains of achievement/intelligence, language, processing speed, and visuospatial abilities after excluding data points reflecting high-risk sub-samples. For executive functioning, only the Green et al. (2014) study was removed. In doing so, the summary effect is no longer marginal (12 studies, H_g= .241, SE_g= .162, 95% CI= -0.08 to 0.56, p=0.14). Heterogeneity remains high (Q = 47.86, p < .001, I^2 = 77.02, Tau = 0.47, Tau^2 = 0.22).

Discussion

This meta-analysis examined associations between cognition and presence of the APOE ε4 allele in younger persons. Findings were ~~largely~~ non-significant, suggesting that in children and young adults, ε4 and non-ε4 carriers perform similarly on cognitive tests. Findings from the present meta-analysis converge with a previous meta-analysis conducted by Ihle et al. (2012), providing further support against the antagonistic pleiotropic hypothesis of the ε4 allele as originally proposed by Han and Bondi (2008).

Examining cognitive differences between ε4 and non-ε4 persons separately across each of seven cognitive domains allowed for interrogation of associations between APOE ε4 and specific areas of functioning. Based on fMRI research suggesting functional differences in executive-frontal neural networks in young and older ε4 carriers (for review see Han and Bondi, 2008; Tuminello and Han, 2011), we postulated whether specific cognitive domains would show differences above others. Findings were non-significant across ~~the majority of~~ **all** domains assessed including achievement/intelligence, attention/working memory, language, memory, **executive functioning**, processing speed, and visuospatial abilities. ~~However,~~ **In regard to executive functioning, a non-significant** marginal difference arose ~~in the domain of executive functioning,~~ such that ε4 carriers outperformed non-ε4 carriers on measures of executive functioning. This finding diverges from Ihle et al. (2012), who approached the question differently. In their meta-analysis, Ihle et al. subdivided tasks into those involving high executive demands and those involving low executive demands and did not find evidence of differences between ε4 and non-ε4 carriers on tasks with high executive demands.

Executive functioning reflects a range of abilities (e.g., set-shifting, inhibition, decision making) that are assessed with a variety of different cognitive tests, but all are believed to be frontally mediated. Han and Bondi (2008) speculated as part of their antagonistic pleiotropy hypothesis that "frontal-executive cognitive processes might mediate the APOE ε4 advantage in youth and the compensatory mechanisms invoked later in life." The marginal finding of better scores on measures of executive functioning in young ε4 carriers relative to non-ε4 carriers aligns well with this aspect of the antagonistic pleiotropy hypothesis **initially proposed by Han & Bondi. However, for several reasons, we now caution against interpreting this marginal finding as support for the antagonistic pleiotropy hypothesis.** First, evidence for associations

between the ε4 allele and frontal-executive neural networks is inconclusive. While a small number of fMRI studies support increased recruitment of frontal executive networks in young ε4 carriers (Filbey et al., 2010; Filbey et al., 2006), a larger group of studies instead report increased neural recruitment of regions specific to the administered task (Dennis et al., 2010; Filippini et al., 2009; Tuminello and Han, 2011). In the literature review and reassessment of the antagonistic pleiotropy hypothesis, Tuminello & Han (2011) suggest that the preponderance of studies supporting increased frontal recruitment in younger ε4 carriers is likely due to utilization of frontally mediated tasks (e.g., Filbey et al., 2010 used a working memory task). The authors **propose** a revision of the antagonistic pleiotropy hypothesis to account for these findings, **suggesting that compensatory neural recruitment in young ε4 carriers occurs in task-related regions rather than frontally-mediated regions. Thus, our finding of better performance in the domain of executive functioning but not in other cognitive domains does not seem to be supported by fMRI studies or the most recent revision of the antagonistic pleiotropy hypothesis (Tuminello & Han, 2011).**

~~A larger body of literature has investigated neural effects of the ε4 allele in older individuals. Some studies report increased neural recruitment of frontal systems in older ε4 carriers and suggest that it reflects compensation for deficiencies in other systems (Bondi et al., 2005; Bookheimer et al., 2000; Kukolja et al., 2010; Seidenberg et al., 2009; Tuminello and Han, 2011; Wierenga et al., 2010). However, as with the fMRI literature in young ε4 carriers, findings with regard to older ε4 carriers are mixed (Scarmeas and Stern, 2006; Tuminello and Han, 2011; Trachtenberg et al., 2012), and it remains unclear the degree to which the ε4 allele impacts frontal-executive systems in older adults as proposed by Han and Bondi (2008) in their antagonistic pleiotropy hypothesis.~~

~~Although the present study's marginal finding supports the antagonistic pleiotropy hypothesis and the notion that the ε4 allele influences frontal-executive systems~~, **A second reason to caution against over-interpretation of this marginal finding** ~~Thus, we caution over-speculation of the marginal difference between ε4 and non-ε4 carriers on measures of executive functioning, especially given the~~ **relates to** the high heterogeneity statistics of this analysis. High heterogeneity in meta-analyses suggests that the variability between studies is not due only to chance but also to the measurement of different effects across studies (Higgins et al., 2003; Thompson, 1994). This limits the generalizability of findings of a meta-analysis (Higgins et al., 2003; Thompson, 1994), although some have suggested that certain heterogeneity estimates are less reliable with smaller sample sizes of studies (Huedo-Medina et al., 2006; Ioannidis et al., 2007; von Hippel, 2015). One potential reason for high heterogeneity in this domain relates to the broad range of abilities that fall under executive functioning and the difficulty of isolating such abilities due to lower order processes that are also necessary for completing executive tasks (i.e., task impurity; Miyake and Friedman, 2012). Nevertheless, in light of high heterogeneity and a marginal trend towards significance, the executive functioning finding reported in the present meta-analysis should be interpreted with extreme caution and necessitates replication, ideally with a larger sample of studies, in order to clarify whether this finding may represent a true effect. A possibility that remains to be addressed is the notion that the ε4 effect is specific to one component of executive functioning. Future studies may consider further subdividing executive tasks into component processes to investigate this possibility.

Overall, the present findings do not support an antagonistic pleiotropic effect of the ε4 allele as it relates to cognition in younger age ranges. One possibility that the present study cannot rule out is a differential effect of the ε4 allele on cognition later in the lifespan.

Exaggerated cognitive decline in older ε4 carriers compared to non-ε4 carriers is well-established in the literature (see Tuminello and Han, 2011 for review). However, one study reported higher cognitive performances in oldest-old ε4 carriers compared to oldest-old non-ε4 carriers (Carrion-Baralt et al., 2009). Additionally, other studies do not find exaggerated cognitive decline in ε4 compared to non-ε4 carriers when examining oldest-old persons as is typically found in young-old carriers (Juva et al., 2000; Kozauer et al., 2008; Welsh-Bohmer et al., 2009), suggesting that the effect of ε4 on cognition is age specific. As a result of such findings, some have suggested that the ε4 allele may exhibit antagonistic pleiotropy effects particularly in young-old and old-old age (Carrion-Baralt et al., 2009; Tuminello and Han, 2011), with a negative impact on cognition in young-old individuals and a positive impact in the oldest old. Future research can examine this in greater detail.

Visual examination of forest plots highlights the variable effect sizes found across studies within each cognitive domain assessed, and estimated heterogeneity parameters confirm this observation (see Supplemental Materials). Qualitatively, studies differed across many factors and this may have contributed to the high level of inconsistency between studies. One source of variability between studies is the specific age range under investigation. While some studies impose a very restrictive age range (e.g., 20-24 years old, Bunce et al., 2011; Bunce et al., 2014; age 14, Dell'Acqua et al., 2015), others examined a much wider age range of young ε4 and non-ε4 carriers (e.g., 20-40 years old, Suri et al., 2015; 18-30 years old, Kunz et al., 2015). Tuminello & Han (2011) suggest that pleiotropic effects of the ε4 allele in younger persons may be restricted to a narrow age range, and thus assessing associations across a wide range of ages may contribute to inconsistencies between studies. ~~Although we were interested in examining age (child vs. young adult) as a moderator, this was not possible due to a small number of studies in~~

~~each age group per cognitive domain.~~ **To further explore this possibility, we examined the impact of age on differences between ε4 and non-ε4 groups for all measures combined. We did this by calculating a weighted average of the average ages provided for ε4 and non-ε4 groups. Five studies were excluded because they provided age ranges, rather than averages, in their sample characteristics. Age did not explain a significant portion of the variance in cognitive differences between ε4 and non-ε4 carriers (p=0.99), arguing against pleiotropic effects specific to narrower age ranges. Due to small numbers of studies within each cognitive domain, we could not investigate age as a moderator for each cognitive domain separately due to the propensity of Type 1 errors in meta-regression analyses (Higgins & Thompson, 2004).**

A second source of variability relates to the specific allele composition of ε4 and non-ε4 carriers assessed. Some studies included ε2 hetero- or homozygotes in their non-ε4 group (e.g., (Alexopoulos et al., 2011; Bloss et al., 2008; Dennis et al., 2010) while others only included ε3 homozygotes (e.g., Bloss et al., 2010; Matura et al., 2016; Matura et al., 2014; Wierenga et al., 2013). Although we excluded studies that included ε2-ε4 participants, we opted not to exclude studies that included ε2 carriers in their non-ε4 group due to the already small number of studies meeting criteria for inclusion in the meta-analysis. Differences between studies with regard to the non-ε4 groups may contribute to variability in findings across studies, especially given the protective effect on cognition associated with the ε2 allele (Corder et al., 1996; Farrer et al., 1997; Serrano-Pozo et al., 2015; Shinohara et al., 2016). Relatedly, we included both ε3-ε4 and ε4-ε4 participants in the ε4 group, also potentially introducing a source of variability to the findings. Examining a dose-response effect of the ε4 allele was not possible due to the small number of studies under consideration in the present meta-analysis.

A final important source of variability between studies is the decision by some studies to include high-risk subgroups of ε4 and non-ε4 carriers (e.g., family history of AD, Bloss et al., 2008; presence of CLU-C genotype, Green et al., 2014; prenatal mercury exposure, Ng et al., 2013). Inclusion of other factors that can contribute to cognitive differences between groups makes interpretation of associations between ε4 and cognition difficult (Tuminello and Han, 2011). Excluding the three studies (Bloss et al., 2008; Green et al., 2014; Ng et al., 2013) that included high-risk groups did not change the outcome of the majority of analyses. However, excluding Green et al. (2014) from the executive functioning analysis reduced the marginal effect to a null effect, further warranting cautious interpretation of this marginal finding.

High heterogeneity across studies is one limitation of this meta-analysis. Other limitations include the small number of studies meeting inclusionary criteria, highlighting the fact that studies examining the cognitive effects of the ε4 allele in healthy young persons are few and far between. A second related limitation is the lack of power to **fully** assess for moderating variables such as age and sex. This should be a consideration for future meta-analyses that aim to examine the relationship of the ε4 allele with cognition in younger persons. A final limitation is the wide age range considered in the study, ranging from toddlers to 40 year olds. This was unavoidable given the already small number of studies under consideration.

Findings from the meta-analysis largely do not support the ε4 allele as a pleiotropic gene, replicating findings of an earlier report by Ihle et al. (2012). The present meta-analysis also extends findings of Ihle et al. by showing that differences between young ε4 and non-ε4 carriers were null across ~~six of seven~~ all cognitive domains assessed including achievement/intelligence, attention/working memory, language, memory, processing speed, and visuospatial abilities. A marginal trend arose in which ε4 carriers outperformed non-ε4 carriers on measures of executive

functioning, but further replication is needed in light of high heterogeneity between studies and a small number of studies considered. ~~If this is a replicable effect, it supports a potential pleiotropic role of the ε4 allele on frontal-executive neural systems.~~ Importantly, high variability between studies reported in the present meta-analysis highlights the need for more research in this area, particularly with greater consistency in the parameters implemented across studies.

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*Studies included in the meta-analysis are denoted with an asterisk.

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Figures 1. PRISMA Flow Diagram

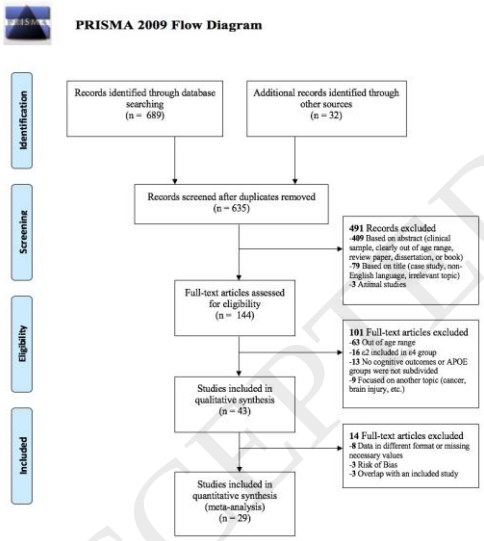
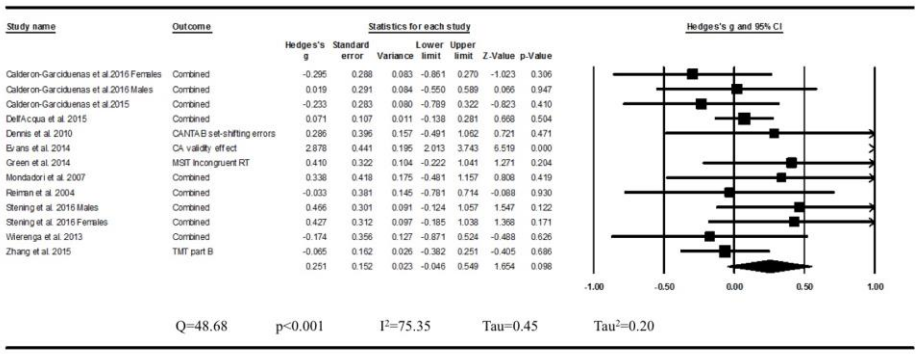


Figure 2. Forest plot for domain of executive functioning. Difference in means reflects APOE ε4 carriers minus APOE non-ε4 carriers. Rhombus midpoint is Hedges' g and the left and right points span the lower and upper limit.

Executive Functioning



Study name	Outcome	Statistics for each study							Hedges's g and 95% CI
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Calderon-Garciduenas et al.2016 Females	Combined	-0.295	0.288	0.083	-0.861	0.270	-1.023	0.306	
Calderon-Garciduenas et al.2016 Males	Combined	0.019	0.291	0.084	-0.550	0.589	0.066	0.947	
Calderon-Garciduenas et al.2015	Combined	-0.233	0.283	0.080	-0.789	0.322	-0.823	0.410	
DellAcqua et al. 2015	Combined	0.071	0.107	0.011	-0.138	0.281	0.668	0.504	
Dennis et al. 2010	CANTAB set-shifting errors	0.286	0.396	0.157	-0.491	1.062	0.721	0.471	
Evans et al. 2014	CA validity effect	2.878	0.441	0.195	2.013	3.743	6.519	0.000	
Green et al. 2014	MSIT Incongruent RT	0.410	0.322	0.104	-0.222	1.041	1.271	0.204	
Mondadori et al. 2007	Combined	0.338	0.418	0.175	-0.481	1.157	0.808	0.419	
Reiman et al. 2004	Combined	-0.033	0.381	0.145	-0.781	0.714	-0.088	0.930	
Stening et al. 2016 Males	Combined	0.466	0.301	0.091	-0.124	1.057	1.547	0.122	
Stening et al. 2016 Females	Combined	0.427	0.312	0.097	-0.185	1.038	1.368	0.171	
Wierenga et al. 2013	Combined	-0.174	0.356	0.127	-0.871	0.524	-0.488	0.626	
Zhang et al. 2015	TMT part B	-0.065	0.162	0.026	-0.382	0.251	-0.405	0.686	
		0.251	0.152	0.023	-0.046	0.549	1.654	0.098	

Q=48.68 p<0.001 I^2=75.35 Tau=0.45 Tau^2=0.20

Table 1. List of cognitive measures by domain.

Domain	Abbreviation	Test
Achievement/Intelligence		
	CAT-6 Language	California Achievement Test-6 - Language
	CAT-6 Math	California Achievement Test-6 - Math
	CAT-6 Reading	California Achievement Test-6 - Reading
	CAT-6 Spelling	California Achievement Test-6 - Spelling
	CDIIT Global Score	Comprehensive Development Inventory for Infants and Toddlers - Global Score
	HAWIE-R IQ	Hamburg Wechsler Intelligence Scale Revised Test - Full Scale IQ
	IQ	Unknown source[1]
	MWTB-IQ	Mehrfachwahl Wortschatz Intelligenz Test B - IQ
	NART	National Adult Reading Test - Total Words
	SRA Numeric ability	SRA Test of Educational Ability - Spanish, Numeric Ability
	SRA Reasoning ability	SRA Test of Educational Ability - Spanish, Reasoning Ability
	SRA Verbal ability	SRA Test of Educational Ability - Spanish, Verbal Ability
	WAIS Full-Scale iQ	Wechsler Adult Intelligence Scale (unspecified edition) - Full Scale IQ
	WISC-III Full-Scale IQ	Wechsler Intelligence Scale for Children Third Edition - Full Scale IQ
	WISC-IV Perceptual Reasoning Index	Wechsler Intelligence Scale for Children Fourth Edition - Perceptual Reasoning Index
	WISC-IV Verbal Comprehension Index	Wechsler Intelligence Scale for Children Fourth Edition - Verbal Comprehension Index
	WISC-R Performance IQ	Wechsler Intelligence Scale for Children Revised - Performance IQ
	WISC-R Verbal IQ	Wechsler Intelligence Scale for Children Revised - Verbal IQ
Attention/Working Memory		
	2-back	n-back task - 2-back accuracy
	3-back	n-back task - 3-back accuracy
	CANTAB Spatial Span Length	Cambridge Neuropsychological Test Automated Battery - Spatial Span Length
	CANTAB Spatial Working Memory	Cambridge Neuropsychological Test Automated Battery - Spatial Working Memory
	IGD Working Memory Score	Inventory for Memory Diagnostics - Working Memory Score
	PMT cards sorted	Prospective Memory Task - number of cards sorted
	RVIP detections	Rapid Visual Information Processing Task - mean detections per minute
	RVIP false alarms	Rapid Visual Information Processing Task - false alarms
	TMT part A	Trail Making Test - Part A
	WAIS-R Arithmetic	Wechsler Adult Intelligence Scale Revised - Arithmetic
	WAIS-R Digit Span	Wechsler Adult Intelligence Scale Revised - Digit Span
	WAIS-R Orientation	Wechsler Adult Intelligence Scale Revised - Orientation
	WISC-R Arithmetic	Wechsler Intelligence Scale for Children Revised - Arithmetic

	WISC-R Digit Span	Wechsler Intelligence Scale for Children Revised - Digit Span
	WMS-III Digits Backward	Wechsler Memory Scale Third Edition - Digits Backward
	WMS-III Letter Number Span	Wechsler Memory Scale, Third Edition - Letter Number Span
	WMS-III Letter Number Span	Wechsler Memory Scale, Third Edition - Spatial Span
	WMS-III Spatial Span	Wechsler Memory Scale Revised - Backward Digit Span
	WMS-R Concentration/Attention Score	Wechsler Memory Scale Revised - Concentration and Attention Score
Executive Functioning		
	CA validity effect	Covert Attention Task Validity Effect
	CANTAB set-shifting errors	Cambridge Neuropsychological Test Automated Battery - Intra-extra dimensional set shifting errors
	COWAT	Controlled Oral Word Association Test
	DKEFS Design Fluency switching	Delis-Kaplan Executive Function System - Design Fluency, switching score
	DKEFS Letter Fluency	Delis-Kaplan Executive Function System - Letter Fluency
	DKEFS TMT switching	Delis-Kaplan Executive Function System - Trail Making Test, switching score
	Kramer Card Sorting	Kramer Card Sorting - number of correct concepts
	MSIT Incongruent RT	Multi-Source Interference Task - Incongruent Trials RT
	Nonverbal Fluency	Nonverbal Fluency
	Stroop interference condition	Stroop interference condition
	TMT part B	Trail Making Test - Part B
	Verbal Fluency-FAS	Verbal Fluency - letters F-A-S
	Verbal Fluency-S words	Verbal Fluency - S words
	WISC-IV Similarities	Wechsler Intelligence Scale for Children Fourth Edition - Similarities
	WISC-IV Matrix Reasoning	Wechsler Intelligence Scale for Children Fourth Edition - Matrix Reasoning
	WISC-R Similarities	Wechsler Intelligence Scale for Children Revised - Similarities
	WISC-R Mazes	Wechsler Intelligence Scale for Children Revised - Mazes
Language		
	BNT	Boston Naming Test
	CDIIT Language	Comprehensive Development Inventory for Infants and Toddlers - Language
	Spot-the-Word	Spot-the-Word Task
	SRB Synonyms	Dureman–Sälde battery - Synonyms
	WAIS-R Information	Wechsler Adult Intelligence Scale Revised - Information
	WISC-IV Vocabulary	Wechsler Intelligence Scale for Children Revised - Vocabulary
	WISC-R Comprehension	Wechsler Intelligence Scale for Children Revised - Comprehension
	WISC-R Information	Wechsler Intelligence Scale for Children Revised - Information
Memory		
	AVLT total learning	Auditory-Verbal Learning Test - total learning

AVLT long-term recall	Auditory-Verbal Learning Test - long-term recall
BVMT-R total learning	Brief Visuospatial Memory Test Revised - total learning
CANTAB Paired Associate Learning	Cambridge Neuropsychological Test Automated Battery - paired associate learning
CANTAB Pattern Recognition	Cambridge Neuropsychological Test Automated Battery - paired recognition memory
CANTAB Spatial Recognition	Cambridge Neuropsychological Test Automated Battery - spatial recognition memory
Complex Figure Test recall	Complex Figure Test - recall
CVLT I immediate Recall	California Verbal Learning Test, immediate recall
CVLT I delayed Recall	California Verbal Learning Test, delayed recall
CVLT-German immediate recall	California Verbal Learning Test - German, immediate recall
CVLT-German trial 1 immediate recall	California Verbal Learning Test - German, Trial 1 immediate recall
CVLT-German short delay recall	California Verbal Learning Test - German, short delay recall
CVLT-German delayed recall	California Verbal Learning Test - German, delayed recall
CVLT-II Trials 1-5	California Verbal Learning Test-II - Trials 1-5 total learning
CVLT-II long delay free recall	California Verbal Learning Test-II - long delay free recall
Episodic Memory Task immediate recall	Episodic Memroy Task - immediate written recall (created by authors)[2]
fMRI Face-Name immediate retrieval	fMRI Face-Name paradigm - immediate retrieval
fMRI Face-Name delayed retrieval	fMRI Face-Name paradigm - delayed retrieval
fMRI neutral scenes encoded	fMRI Neutral Scenes - percent encoded
fMRI neutral scenes retrieved	fMRI Neutral Scenes - percent retrieved
fMRI Picture Encoding false alarms	fMRI Picture Encoding Task - subsequent item memory false alarm rate
fMRI Picture Encoding hits	fMRI Picture Encoding Task - subsequent item memory hit rate
fMRI post-scan memory test	fMRI post-scan memory test - global performance
fMRI Spatial Memory drop error	fMRI Spatial Memory Paradigm - degree of drop error
IGD learning ability	Inventory for Memory Diagnostics - learning ability score
IGD delayed recall	Inventory for Memory Diagnostics - delayed recall score
PMT detections	Prospective Memory Task - detections
VAT cued recall	Verbal Associative Learning Test – cued recall
VAT recognition	Verbal Associative Learning Test – recognition
WMS Logical Memory I	Wechsler Memory Scale (unknown version) - Logical Memory I
WMS Logical Memory II	Wechsler Memory Scale (unknown version) - Logical Memory II
WMS Visual Reproduction I	Wechsler Memory Scale (unknown version) - Visual Reproduction I
WMS Visual Reproduction II	Wechsler Memory Scale (unknown version) - Visual Reproduction II
WMS-R Verbal Memory	Wechsler Memory Scale Revised – Verbal Memory score
WMS-R Visual Memory	Wechsler Memory Scale Revised – Visual Memory score
WMS-R Delayed Recall	Wechsler Memory Scale Revised – Delayed Recall score
WMS-R General Memory	Wechsler Memory Scale Revised – General Memory score

	WMS-R Logical Memory I	Wechsler Memory Scale Revised - Logical Memory I
	WMS-R Logical Memory II	Wechsler Memory Scale Revised - Logical Memory II
Processing Speed		
	CANTAB Choice RT	Cambridge Neuropsychological Test Automated Battery - Choice RT
	CANTAB Rapid Visual Info Processing	Cambridge Neuropsychological Test Automated Battery - Rapid Visual Information Processing Task
	Simple RT	Simple RT
	Choice RT	Choice RT
	Letter Digit Substitution Test	Letter Digit Substitution Test
	MSIT Congruent Trials RT	Multi-Source Interference Task - congruent trials RT
	Processing speed composite	Sorting Task and Visual Attention Task - RT, combined z-scores
	Symbol-Digit Modalities Test	Symbol-Digit Modalities Test
	WISC-R Coding	Wechsler Intelligence Scale for Children Revised - Coding
Visuospatial Abilities		
	Complex Figure Test Copy	Complex Figure Test - copy
	Luria Mental Rotation	Luria Mental Rotation
	RCFT Copy	Rey Complex Figure Test - copy
	WAIS-R Block Design	Wechsler Adult Intelligence Scale Revised - Block Design
	WISC-R Block Design	Wechsler Intelligence Scale for Children Fourth Edition - Block Design
	WISC-R Block Design	Wechsler Intelligence Scale for Children Revised - Block Design
	WISC-R Object Assembly	Wechsler Intelligence Scale for Children Revised - Object Assembly
	WISC-R Picture Arrangement	Wechsler Intelligence Scale for Children Revised - Picture Arrangement
	WISC-R Picture Completion	Wechsler Intelligence Scale for Children Revised - Picture Completion

[1]Authors (Green et al. 2014; Shaw et al. 2007) do not cite source of IQ score
[2]This task was created by Dowell et al., 2013

Table 2. Demographic data for participants in APOE ε4 versus APOE non-ε4 analysis.

Study	Study Characteristics		*N*		Age				Sex		Education				
			ε4	non-ε4	ε4		non-ε4		ε4	non-ε4	ε4		non-ε4		Education Metric
	Recruitment Age Range	Genotype Breakdown			*M*	*SD*	*M*	*SD*	%F	%F	*M*	*SD*	*M*	*SD*	
Alexopoulos et al. 2011	College-aged	ε2/2, ε2/3 vs. ε3/4, ε4/4	16	17	24.20	4.10	24.70	3.20	56%	71%	16.56	2.07	17.35	2.69	Years
Bloss et al. 2008 – familyhx[1]	11-16	ε2/3, 3/3 vs. ε3/4, ε4/4	24	85	13.42	1.40	13.42	1.22	50%	56%	16.46	2.17	16.35	2.09	Mother-years
Bloss et al. 2008 +familyhx[1]	11-16	ε2/3, 3/3 vs. ε3/4, ε4/4	24	85	13.42	1.40	13.42	1.22	50%	56%	16.46	2.17	16.35	2.09	Mother-years
Bloss et al. 2010	11-16	ε3/3 vs. ε3/4, ε4/4	33	90	13.34	1.32	13.28	1.30	55%	61%	16.46	2.17	16.28	2.15	Mother-years
Bunce et al. 2011	20-24	ε3/3 vs. ε3/4, ε4/4	530	1291	(20-24)	-	(20-24)	-	50%	53%	14.56	1.59	14.56	1.55	Years
Bunce et al. 2014	20-24	ε2/2, ε2/3 vs. ε3/4, ε4/4	426	189	(20-24)	-	(20-24)	-	-	-	-	-	-	-	-
Calderón-Garcidueñas et al.2016 Female[1]	Children	ε3/3 vs. ε3/4	36	69	12.70	6.70	11.89	4.10	53%	43%	11.62	1.90	11.07	2.30	Mother-years
Calderón-Garcidueñas et al.2016 Males[1]	Children	ε3/3 vs. ε3/4	36	69	12.70	6.70	11.89	4.10	53%	43%	11.62	1.90	11.07	2.30	Mother-years
Calderón-Garcidueñas et al.2015	Children	ε3/3 vs. ε3/4, ε4/4	22	28	13.62	4.80	13.36	5.00	50%	43%	11.62	1.74	11.07	2.12	Mother-years
Dell'Acqua et al. 2015	14 year olds	ε3/3 vs. ε3/4	114	372	14.40	0.50	14.40	0.50	41%	45%	-	-	-	-	-
Dennis et al. 2010	Young Adult	ε2/3, ε3/3 vs. ε3/4, ε4/4	12	12	21.80	3.30	20.80	2.90	58	75%	-	-	-	-	-
Dowell et al. 2013	18-30	ε3/3 vs. ε3/4, ε4/4	21	20	21.40	2.20	20.90	1.40	62%	70%	-	-	-	-	-
Evans et al. 2014	18-30	ε3/3 vs. ε3/4, ε4/4	21	20	21.40	2.20	20.90	1.40	62%	70%	15.10	0.20	15.10	0.30	Years
Filippini et al. 2009	20-35	ε3/3 vs. ε3/4, ε4/4	18	18	28.40	4.90	28.60	3.90	39%	44%	19.60	2.00	19.50	1.50	Years
Green et al. 2014 CLU-C sample[2]	College-aged	ε3/3 vs. ε3/4, ε4/4	23	16	24.00	5.49	25.25	5.87	17%	6%	-	-	-	-	-
Jorm et al. 2007	20-24	ε2/3, ε3/3 vs. ε3/4	517	1524	(20-24)	-	(20-24)	-	-	-	-	-	-	-	-
Kunz et al. 2015	18-30	ε3/3 vs. ε3/4	38	37	22.34	0.45	22.76	0.49	53%	51%	16.05	0.37	16.19	0.38	Years
Matura et al. 2016	20-39	ε3/3 vs. ε3/4, ε4/4	25	25	26.75	5.31	25.83	3.61	44%	44%	17.67	2.12	17.58	2.43	Years
Matura et al. 2014	20-38	ε3/3 vs. ε3/4, ε4/4	25	25	26.60	5.20	26.20	4.10	44%	44%	17.70	2.10	17.60	2.60	Years
Mondadori et al. 2007	Young Adult	ε2/3, ε3/3 vs. ε3/4, ε4/4	13	10	22.60	3.50	21.60	1.70	46%	60%	14.30	1.70	13.80	1.50	Years
Ng et al. 2013 High Mercury[3]	Age 2	ε3/3 vs. ε3/4, ε4/4	14	59	2.00	0.00	2.00	0.00	50%	39%	50%	-	57.6%	-	Mother %college edu
Ng et al. 2013 Low Mercury[3]	Age 2	ε3/3 vs. ε3/4, ε4/4	12	51	2.00	0.00	2.00	0.00	67%	49%	50%	-	56.9%	-	Mother %college edu
Nichols et al. 2012 scanned cohort	19-40	ε3/3 vs. ε3/4	23	57	27.00	4.90	27.00	5.30	40%	58%	17.00	1.50	17.00	2.40	Years

Nichols et al. 2012 non-scanned cohort	18-40	ε3/3 vs. ε3/4	48	122	(18-40)	-	(18-40)	-	67%	54%	-	-	-	-	-
O'Dwyer et al. 2012	20-38	ε3/3 vs. ε3/4, ε4/4	22	22	26.90	5.30	26.70	4.00	41%	41%	17.00	4.30	16.80	4.50	Years
Reiman et al. 2004	20-39	ε2/3, ε3/3 vs. ε3/4	12	15	30.70	5.40	31.20	5.00	75%	80%	16.00	1.70	16.10	1.50	Years
Ruiz et al. 2010	13-18.5	ε2/3, ε3/3 vs. ε3/4	76	336	NA	NA	NA	NA	49%	51%	-	-	-	-	-
Shaw et al. 2007	<21yo	ε3/3 vs. ε3/4, ε4/4	65	145	NA	NA	NA	NA	51%	42%	-	-	-	-	-
Sinclair et al. 2015	18	ε3/3 vs. ε3/4	542	1215	18.00	0.00	18.00	0.00	51%	56%	23.2%	-	20.9%	-	Mother % w/ degree
Stening et al. 2016 Female	19-35	ε3/3 vs. ε3/4, ε4/4	16	39	23.20	3.20	23.60	3.60	100%	100%	14.60	1.90	14.80	1.90	Years
Stening et al. 2016 Male	19-35	ε3/3 vs. ε3/4, ε4/4	19	36	25.30	3.90	23.60	2.80	0%	0%	16.10	1.80	14.70	1.30	Years
Suri et al. 2015	20-40	ε3/3 vs. ε3/4, ε4/4	18	17	23.88	4.75	24.11	4.96	56%	53%	17.05	2.18	17.50	2.89	Years
Wierenga et al. 2013	College-aged	ε3/3 vs. ε3/4, ε4/4	15	15	23.60	3.10	23.30	3.00	80%	53%	14.90	0.30	15.00	0.50	Years
Zhang et al. 2015	16-39	ε3/3 vs. ε3/4, ε4/4	47	200	26.90	5.90	27.44	6.40	55%	47%	11.30	3.75	11.02	3.59	Years

[1]Study reports cognitive data separately by subgroup but demographics are reported for full sample.
[2]Study examines CLU-C and non-CLU-C; only CLU-C was considered because CLU-nonC ε4 group only included three participants
[3]Study of toddlers who were exposed to mercury while in the womb.
Note: n=study sample size; sd=standard deviation, M=mean, edu=education, %F = percent female; ε4= at least one Apolipoprotein ε4 allele; non-ε4 = Apolipoprotein ε2 and/or ε3 carriers