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APOE ε4 influences cognitive decline positively in *APP* and negatively in *PSEN1* mutation carriers with autosomal-dominant Alzheimer's disease

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Abstract

Background and purpose: The aim was to investigate the effect of *APOE* ε4 allele on cognitive decline in adAD. Presence of the *APOE* ε4 allele reduces age of symptom onset, increases disease progression, and lowers cognitive performance in sporadic Alzheimer's disease (AD), while the impact of the *APOE* ε4 allele in autosomal-dominant AD (adAD) is incompletely known.

Methods: Mutation carriers (MCs; *n* =39) and non-carriers (NCs; *n* =40) from six adAD families harbouring a mutation in the *APP* (28 MCs and 25 NCs) or the *PSEN1* genes (11 MCs and 15 NCs) underwent repeated cognitive assessments. A timeline of disease course was defined as years to expected age of clinical onset (YECO) based on history of disease onset in each family. The MC and NC groups were comparable with regard to demographics and prevalence of the *APOE* ε4 allele. The relationship between cognitive decline and YECO, YECO[2], education, *APOE*, and *APOE*-by-YECO interaction was analysed using linear mixed-effects models.

Results: The trajectory of cognitive decline was significantly predicted by linear and quadratic YECO and education in MCs and was determined by age and education in NCs. Adding *APOE* ε4 allele (presence/absence) as a predictor did not change the results in the MC and NC groups. The outcome also remained the same for MCs and NCs after adding the *APOE*-by-YECO interaction as a predictor. Analyses of *APP* and *PSEN1* MCs separately showed favourable *APOE*-by-YECO interaction in *APP* (less steep decline) and unfavourable interaction in *PSEN1* (steeper decline), linked to the *APOE* ε4 allele.

Conclusion: The *APOE* ε4 allele influences cognitive decline positively in *APP* and negatively in *PSEN1* mutation carriers with adAD, indicating a possible antagonistic pleiotropy.

KEYWORDS
APOE, *APP/PSEN1*, autosomal-dominant Alzheimer's disease, cognition, longitudinal

INTRODUCTION

Presence of the *APOE* ε4 allele (ε4+) is associated with a younger age of symptom onset in a dose-related manner in sporadic Alzheimer's disease (sAD) compared to absence of an *APOE* ε4 allele (ε4−), as shown by the earliest onset in *APOE* ε4 homozygotes, followed by heterozygotes, with the latest onset in non-carriers of the *APOE* ε4 allele [1]. In sAD, *APOE* ε4+ has been related to higher regional density of plaque and tangle brain pathology [2], an increased amount of white matter hyperintensities [3], dose-dependent hippocampal thinning [4], increased cerebrospinal fluid biomarker abnormality [5], elevated positron emission tomography-measured beta-amyloid binding [6], and decreased glucose metabolism [7]. Furthermore, it has been shown that *APOE* ε4+ has a negative impact on cognition in sAD, as well as in cerebrovascular disease and type 2 diabetes [8, 9]. In addition, it has been shown that *APOE* ε4+ is associated with impaired episodic memory in non-demented older adults compared to *APOE* ε4− [10, 11]. Some studies have also documented negative influences in cognitive domains other than memory [12]. Together, the effects of *APOE* ε4 on sAD indicate a multifactorial disorder related to allelic variation in *APOE*, aging, cerebrovascular disease, traumatic brain injury, the immune system, mitochondrial functioning, and infection. All these risk factors may act collectively to cause Alzheimer's disease (AD) pathology in sAD [13].

Studies of the Colombian family (the *PSEN1* E280A mutation) have reported a reduced age of onset due to presence of the ε4 allele [14], while other studies have reported a lack of significant negative influence on age of onset depending on *APOE* ε4+ [15, 16] and no effect on cognitive decline [17, 18]. In children with a family history of AD, significant negative effects of *APOE* ε4+ on cognition have been reported when comparing children with and without the ε4 allele [19].

Presence of the *APOE* ε4 allele has been shown to have differential effects on memory performance depending on age. Studies in young adults and children have found better cognitive performance in cognitive tasks in *APOE* ε4 carriers compared to ε4 non-carriers, which could be indicative of antagonistic pleiotropy [20, 21]. In a study of embryonic development, the ε4 allele was present less frequently in spontaneously aborted embryos versus controls, suggesting that the presence of ε4 has protective effects during embryogenesis [22]. In addition, there are reports of favourable effects of *APOE* ε4+ on tasks of attention in young healthy individuals [23]

and there was a favourable effect of *APOE* ε4+ across ages in a short-term memory task with brief retention intervals [24]. Similarly, adults with a high parasite burden living in the Amazon carrying *APOE* ε4 performance across cognitive domains was positively affected in adults with a high versus low parasite burden of living [25]. A recent study using transgenic mice (*APP/PSEN1*) suggested that the *APOE* gene has two opposing roles, one favourable in aging and another related to beta-amyloid toxicity and impairment [26], corresponding to the originally proposed antagonistic pleiotropy in aging [27].

In summary, previous reports regarding the effects of *APOE* ε4 on cognition in various populations are mixed. Age, various diseases, type of AD, and challenging environments may be involved. The objective of the present longitudinal study was to investigate the effect of the *APOE* ε4 allele on cognitive decline in mutation carriers (MCs) and non-carriers (NCs) from autosomal-dominant AD (adAD) families, departing from four hypotheses. First, the presence of *APOE* ε4 has a negative effect on cognition in adAD MCs. Second, *APOE* ε4 effect interacts with time of disease development in adAD MCs. Third, the *APOE* effect on cognitive decline is different in *APP* and *PSEN*1 owing to a differential cognitive trajectory [28]. Fourth, there is no *APOE* and *APOE*-by-time interaction in NCs.

METHODS

Participants

Adult members from six families carrying a mutation of early-onset adAD were invited to a comprehensive clinical examination at the Memory Clinic, Karolinska University Hospital Huddinge, Sweden. Three families carried an *APP* mutation (Swedish, Arctic and London), and three families carried a *PSEN1* mutation (I143T, M146V and H163Y; see details in Appendix S1). No family carried a *PSEN2* mutation. All individuals who accepted a clinical examination were enrolled in the study (39 mutation carriers [MCs] and 40 non-carriers [NCs]). All participants were invited to follow-up examinations: 59 individuals had two examinations, 33 individuals had three examinations, and 22 had four or more examinations, with a total of 229 examinations.

The demographic characteristics of the participants are presented in Table 1. The participant groups (MCs and NCs from *APP*

TABLE 1 Baseline demographic and clinical characteristics in *APP* and *PSEN1* mutation carriers and non-carriers in autosomal-dominant Alzheimer's disease

Characteristic	Carriers		Non-carriers	
	APP	*PSEN1*	*APP*	*PSEN1*
N (female/male)	28 (10/18)	11 (4/7)	25 (11/14)	15 (7/8)
Age, mean±SD years	47.9±11.2	35.6±9.6	47.4±9.9	33.8±11.1
YECO, mean±SD	−7.1±11.0	−11.3±11.4	−7.5±9.7	−8.2±11.8
Education, mean±SD years	10.9±2.5	12.0±3.0	10.8±2.9	10.6±1.5
APOE ε4 (presence/absence)	13/15	6/5	7/18	6/9
MMSE score, mean ±SD	25.3±4.6	26.7±5.2	28.7±1.7	29.5±0.8

Abbreviation: MMSE, Mini Mental State Examination; YECO, years to expected clinical onset.

and *PSEN1* families) were comparable in demographic and basic clinical characteristics (Appendix S1).

Diagnosis

The clinical diagnosis was decided by a consensus meeting of medical professionals based on all available reports, excluding information on the mutation status as described above [28] (details are presented in Appendix S1).

At baseline, eight MCs were diagnosed with dementia [29] and as having AD [30], and nine MCs were diagnosed with mild cognitive impairment (MCI) [31]. All the remaining 22 MCs were asymptomatic. At the last examination, 26 MCs were diagnosed with AD dementia and 13 were still asymptomatic. No NC was diagnosed with AD, MCI, or any other disease affecting the brain, either at baseline or at any follow-up examination.

Advancement of disease

The advancement of disease was calculated as present age minus the family-specific age of clinical onset of disease (years to expected age of clinical onset [YECO]) in line with previous research [16, 28]. This measure is invariant within families and is significantly associated with the observed age of onset and parental age of onset [16, 28].

Assessment of cognition

Cognitive assessment focused on tests within five domains: verbal (Similarities test), visuospatial (Block Design test), episodic memory (Rey Auditory Verbal Learning Test [RAVLT]), executive function (Digit Symbol test), and attention (Trailmaking Test A [TMTA]) as described above [28] (details are presented in Appendix S1).

APOE genotyping

The *APOE* genotyping method is described in Appendix S1.

Statistical analysis

Details of statistical analyses are presented in Appendix S1.

RESULTS

Baseline

Most participants were below 50 years of age (5–10 years ahead of clinical onset). Test results were poorer in MCs versus NCs for four out of the five tests (Block Design, RAVLT, Digit Symbol, and TMTA;

p values <0.01). Participants in *APP* and *PSEN1* families did not differ in any of the cognitive tests (*p* values >0.1). Furthermore, there was no significant gene (*APP/PSEN1*)-by-mutation (MC/NC) interaction on any of the five tests (*p* values >0.1). These results, which were obtained after taking demographic characteristics (age, sex and education) into account, indicate that MCs and NCs from *APP* and *PSEN1* families were comparable at baseline.

Longitudinal cognitive change

Firstly, longitudinal cognitive change was analysed using linear mixed models in relation to linear and curvilinear measures of disease advancement (YECO and YECO^2) and years of education separately in MCs and NCs (results are presented in Table S1). In MCs, the model of cognitive decline was significant in all five tests (Similarities, Block Design, RAVLT, Digit Symbol and TMTA; *p* values <0.001 or *p* values <0.01) covering five cognitive domains (verbal, visuospatial, episodic memory, executive function, and attention, respectively). The decline was highly significant for linear and curvilinear predictors (Table S1). Education was a strong positive predictor in four tests in MCs (*p* values <0.001 or *p* values <0.01; Table S1).

In NCs, there was a significant cognitive decline in two tests – linear in the Digit Symbol test and curvilinear in the Similarities test (*p* values <0.05), while there was no significant change in the other cognitive tests (*p* values >0.1). Education was a strong positive predictor in all five tests (*p* values <0.05).

These results indicate that MCs had extensive and disease-related changes across time in all domains according to relatively large beta weights, while NCs had minor time-related cognitive changes in two tests (Similarities and Digit Symbol) as indicated by the relatively small beta weights (Table S1).

Next, the effect of *APOE* on cognition was analysed by adding *APOE* to the previous analyses (presence vs. absence of the ε4 allele) as a fourth predictor (Table 2). The outcome showed that *APOE* was not a significant predictor in any of the five cognitive tests in MCs (*p* values >0.1). This finding contradicts the first hypothesis that *APOE* is a main factor in MCs. In NCs, *APOE* ε4+ was a significant negative predictor for performance in the TMTA measuring information processing speed (*p* <0.05), while *APOE* was not a significant factor in the other four tests (*p* values >0.1). The results indicate that the negative effect of *APOE* ε4+ in NCs may have implications for normal aging as *APOE* ε4 may be a possible covariate of the typical decline of processing speed in aging. In addition, the effects of the linear and curvilinear time (YECO and YECO^2) were significant and negative on all cognitive tests in MCs, in agreement with the previous results.

In NCs, the time effect was significant and negative in two tests (Digit Symbol and Similarities test) in agreement (Table 2). Years of education was a significant and strong positive predictor for performance in four tests in MCs and in all five tests in NCs (Table 2).

In the third analysis, the *APOE* ε4-by-YECO interaction was added as a fifth predictor to the previous analysis with three predictors. An overview of the outcome is presented separately for MCs and NCs (Table 3). The outcome showed that the *APOE*-by-YECO

TABLE 2 Outcome of linear mixed-effect models on cognitive tests (dependent variable) and predictors (years to expected clinical onset [YECO], YECO^2, education, and *APOE* ε4 presence/absence) showing estimates, standard errors and *p* values of significant predictors in mutation carriers and non-carriers

Domain/Test	Carriers (n = 39)				Non-carriers (n = 40)			
	YECO	YECO^2	Educ	APOE	YECO	YECO^2	Educ	APOE
	est	est	est	est	est	est	est	est
	[SE]	[SE]	[SE]	[SE]	[SE]	[SE]	[SE]	[SE]
	p	p	p	p	p	p	p	p
Verbal/Sim	−0.140 [0.021] <0.001	−0.006 [0.001] <0.001	+0.244 [0.084] <0.01	ns	ns	−0.001 [0.001] <0.05	+0.250 [0.049] <0.001	ns
Visuospatial/BD	−0.172 [0.021] <0.001	−0.005 [0.001] <0.001	+0.272 [0.090] <0.01	ns	ns	ns	+0.236 [0.076] <0.01	ns
Episodic memory/RAVLT	−0.162 [0.020] <0.001	−0.005 [0.001] <0.001	+0.137 [0.064] <0.05	ns	ns	ns	+0.146 [0.062] <0.05	ns
Executive function/DiSy	−0.182 [0.020] <0.001	−0.005 [0.001] <0.001	+0.239 [0.081] <0.01	ns	−0.017 [0.008] <0.05	ns	+0.170 [0.059] <0.01	ns
Attention/TMTA	−0.019 [0.004] <0.001	−0.001 [0.001] <0.01	ns	ns	ns	ns	+0.020 [0.006] <0.01	−0.068 [0.032] <0.05

Abbreviations: BD, Block Design test; est, estimate; DiSy, Digit Symbol test; RAVLT, Rey Auditory Verbal Learning Test; ns, not significant; Sim, Similarities test; TMTA, Trailmaking Test A; YECO, years to expected clinical onset.

interaction was not significant in any of the five cognitive tests in MCs (*p* values > 0.1). Furthermore, the main effect of *APOE* was not significant in any cognitive test (*p* values > 0.1) in MCs. The effect of education was significant and strong in four tests (*p* values < 0.05) as in the second analysis. This pattern of results for MCs was identical to the pattern of results in the previous step.

In NCs, there was no significant interaction effect in any test (*p* values > 0.1), and the main effect of *APOE* was significant in one test (TMTA), in agreement with the result in the previous analysis (Table 3). The lack of significant time-related effect in NCs was consistent with the previous analyses, and the significant positive effects of education in almost every cognitive test in NCs were also consistent with the previous analyses (Table 3).

In the fourth and final analysis, the effect on cognition using the five previous predictors (YECO, YECO^2, education, *APOE*, and *APOE*-by-YECO interaction) was analysed separately in *APP* and *PSEN1* MCs (Table 4). In *APP* MCs, there were two significant and positive *APOE*-by-YECO interaction effects in the Similarities test (verbal domain; *p* < 0.05) and the TMTA (attention domain; *p* < 0.05). The significant positive beta weights for *APOE*-by-YECO interaction were unexpected. The positive *APOE*-by-YECO interactions in all five tests in *APP* MCs imply that the marked time-related (YECO and YECO^2) cognitive decline is counteracted to some extent by the *APOE*-by-YECO interaction due to presence of the ε4 allele. *APOE* as a main factor was not significant as found in the previous

steps. Compared to the results in the previous analysis, the significant negative time-related effect on YECO and the positive effect of education on cognitive decline remained significant with marked estimates, while the effect on YECO^2 remained significant with less strong estimates.

In *PSEN1* MCs, there was one significant and negative *APOE*-by-YECO interaction in the Block Design test (visuospatial domain; *p* < 0.01 [Table 4]). The beta weights were negative in this test as well as in three other cognitive tests (RAVLT, Digit Symbol and TMTA), although not significant. The implication of negative *APOE*-by-YECO interaction is that the marked time-related (YECO and YECO^2) cognitive decline in *PSEN1* MCs is reinforced by the *APOE*-by-YECO interaction, that is, presence of the ε4 allele. The effect of *APOE* as a main factor was significant and negative in one cognitive test (RAVLT; *p* < 0.01).

Comparison of the significant *APOE*-by-YECO interaction effects, positive in *APP* and negative in *PSEN1* MCs, implies that the *APOE* ε4 allele influences cognitive decline differently by showing a favourable influence in *APP* MCs and a harmful influence in *PSEN1* MCs for unknown reasons.

To examine these results more closely, the *APOE*-by-YECO interaction effects on cognitive decline due to *APOE* ε4+/ε4− across the five tests were visualized separately in *APP* and *PSEN1* MCs (Figure 1). In *APP* MCs (left column), the cognitive decline across all five tests was less pronounced when the *APOE* ε4 was present

TABLE 3 Outcome of linear mixed-effect models on cognitive test results (dependent variables) and predictors (years to expected clinical onset [YECO], YECO², education, *APOE* ε4 presence/absence, and YECO-by-APOE interaction) showing estimates, standard errors and *p* values of significant predictors in mutation carriers and non-carriers

Domain/Test	YECO est [SE] p	YECO² est [SE] p	Educ est [SE] p	APOE est [SE] p	*APOE* × YECO est [SE] p
Carriers, *n* = 39					
Verbal/Sim	−0.156 [0.024] <0.001	−0.005 [0.001] <0.001	+0.237 [0.083] <0.001	ns	ns
Visuospatial/BD	−0.176 [0.023] <0.001	−0.005 [0.001] <0.001	+0.248 [0.081] <0.01	ns	ns
Episodic memory/RAVLT	−0.159 [0.023] <0.001	−0.005 [0.001] 0.001	+0.137 [0.064] <0.05	ns	ns
Executive function/DiSy	−0.169 [0.023] <0.001	−0.005 [0.001] <0.001	+0.235 [0.081] <0.01	ns	ns
Attention/TMTA	−0.036 [0.005] <0.001	−0.001 [0.001] <0.001	ns	ns	ns
Non-carriers *n* = 40					
Verbal/Sim	ns	−0.002 [0.001] <0.05	+0.245 [0.050] <0.001	ns	ns
Visuospatial/BD	ns	ns	+0.239 [0.077] <0.01	ns	ns
Episodic memory/RAVLT	ns	ns	+0.152 [0.064] <0.05	ns	ns
Executive function/DiSy	ns	ns	+0.164 [0.060] <0.01	ns	ns
Attention/TMTA	ns	ns	+0.020 [0.006] <0.01	−0.071 [0.034] <0.05	ns

Abbreviations: BD, Block Design test; est, estimate; DiSy, Digit Symbol test; RAVLT, Rey Auditory Verbal Learning Test; ns, not significant; Sim, Similarities test; TMTA, Trailmaking Test A; YECO, years to expected clinical onset.

compared to absent. In *PSEN1* MCs (right column), the cognitive decline was more pronounced across all tests when the *APOE* ε4 allele was present compared to absent.

DISCUSSION

The aim of this study was to explore how cognitive decline in adAD is affected by the presence or absence of the *APOE* ε4 allele and the *APOE*-by-YECO interaction term in addition to disease advancement (YECO, YECO²) and years of education in *APP* or a *PSEN1* MCs and NCs from six adAD families.

The results showed that linear and curvilinear disease advancement (YECO) were powerful predictors of cognitive decline in MCs, in agreement with previous research on cognition in adAD [16, 28, 32]. In addition, years of education was a powerful positive predictor that mitigates cognitive decline [33]. In contrast, there was no or only minimal change in cognition across time in NCs in most tests, a typical finding in middle-aged normal individuals [34]. The results of the three-predictor model of cognitive decline in adAD was considered as a point of departure for investigating the possible additive contribution of *APOE* ε4 for prediction of cognitive decline in adAD.

The outcome after adding *APOE* (presence/absence of ε4) as a predictor to the three previously used predictors showed that *APOE*

TABLE 4 Outcome of linear mixed-effect models on cognitive test results (dependent variables) and predictors (years to expected clinical onset [YECO], YECO^2, education, *APOE* ε4 presence/absence, and YECO-by-*APOE* interaction) showing estimates, standard errors and *p* values of significant predictors in *APP* and *PSEN1* mutation carriers

Domain/Test	YECO	YECO^2	Educ	APOE	*APOE* × YECO
	est	est	est	est	est
	[SE]	[SE]	[SE]	[SE]	[SE]
	p	*p*	*p*	*p*	*p*
APP mutation carriers, *n* = 28					
Verbal/Sim	−0.136 [0.032] <0.001	ns	ns	ns	+0.099 [0.047] <0.05
Visuospatial/BD	−0.201 [0.041] <0.001	−0.006 [0.001] <0.001	ns	ns	+0.079 [0.046] *p* = 0.09
Episodic memory/RAVLT	−0.126 [0.029] <0.001	ns	+0.168 [0.077] <0.05	ns	+0.058 [0.045] *p* > 0.10
Executive function/DiSy	−0.150 [0.029] <0.001	ns	+0.219 [0.095] <0.05	ns	+0.067 [0.043] *p* > 0.10
Attention/TMTA	−0.031 [0.006] <0.001	ns	ns	ns	+0.024 [0.009] <0.05
PSEN1 mutation carriers, *n* = 11					
Verbal/Sim	−0.186 [0.039] <0.001	−0.007 [0.001] <0.001	ns	ns	+0.006 [0.028] *p* > 0.10
Visuospatial/BD	−0.044 [0.020] <0.05	ns	ns	ns	−0.084 [0.026] *p* < 0.01
Episodic memory/RAVLT	−0.184 [0.036] <0.001	−0.078 [0.001] <0.001	ns	−1.367 [0.398] <0.01	−0.052 [0.026] *p* = 0.053
Executive function/DiSy	−0.206 [0.040] <0.001	−0.008 [0.001] <0.001	+0.329 [0.142] <0.05	ns	−0.056 [0.029] *p* = 0.058
Attention/TMTA	−0.031 [0.010] <0.01	−0.001 [0.001] <0.001	ns	ns	−0.002 [.007] *p* > 0.10

Abbreviations: BD, Block Design test; est, estimate; DiSy, Digit Symbol test; RAVLT, Rey Auditory Verbal Learning Test; ns, not significant; Sim, Similarities test; TMTA, Trailmaking Test A; YECO, years to expected clinical onset.

did not contribute significantly to cognitive decline in any test in MCs. Similar findings of nonsignificant *APOE* ε4 effects on cognition in adAD have been obtained previously [17, 18, 35]. A few studies, for instance, one study in children with a family history of AD, have reported contrasting results [19]. Compared to previous research in sAD showing a negative effect of *APOE* ε4, the lack of a clear negative effect in adAD in the present study and other studies suggests that different mechanisms exist, one in sAD and another in adAD. It could be that presence of the *APOE* ε4 allele is a negative factor for sAD because it influences the cerebrovascular system, while this is not the case or is less so in adAD. It is well documented that *APOE* ε4 is related to the vascular system, and it could be speculated that

manifest and incident disease(s) in the vascular system may be partly responsible for the *APOE* effect in sAD and MCI [8, 9, 13, 20, 21]. An alternative interpretation could be that *APOE* is age-related. In support of the age-related *APOE* hypothesis, a longitudinal study on memory in normal aging and preclinical AD [11] showed that the *APOE* ε4 effect shifted from positive to negative when participants were aged 50–60 years [11]. In addition, *APOE* is involved in many biological systems, not only the cerebrovascular system, which implies that other mechanisms could explain the lack of significant *APOE* ε4 effects on cognition in adAD MCs in the present study [20, 21].

In NCs, presence of the *APOE* ε4 allele was a significant negative factor for cognitive function in the attention domain (TMTA
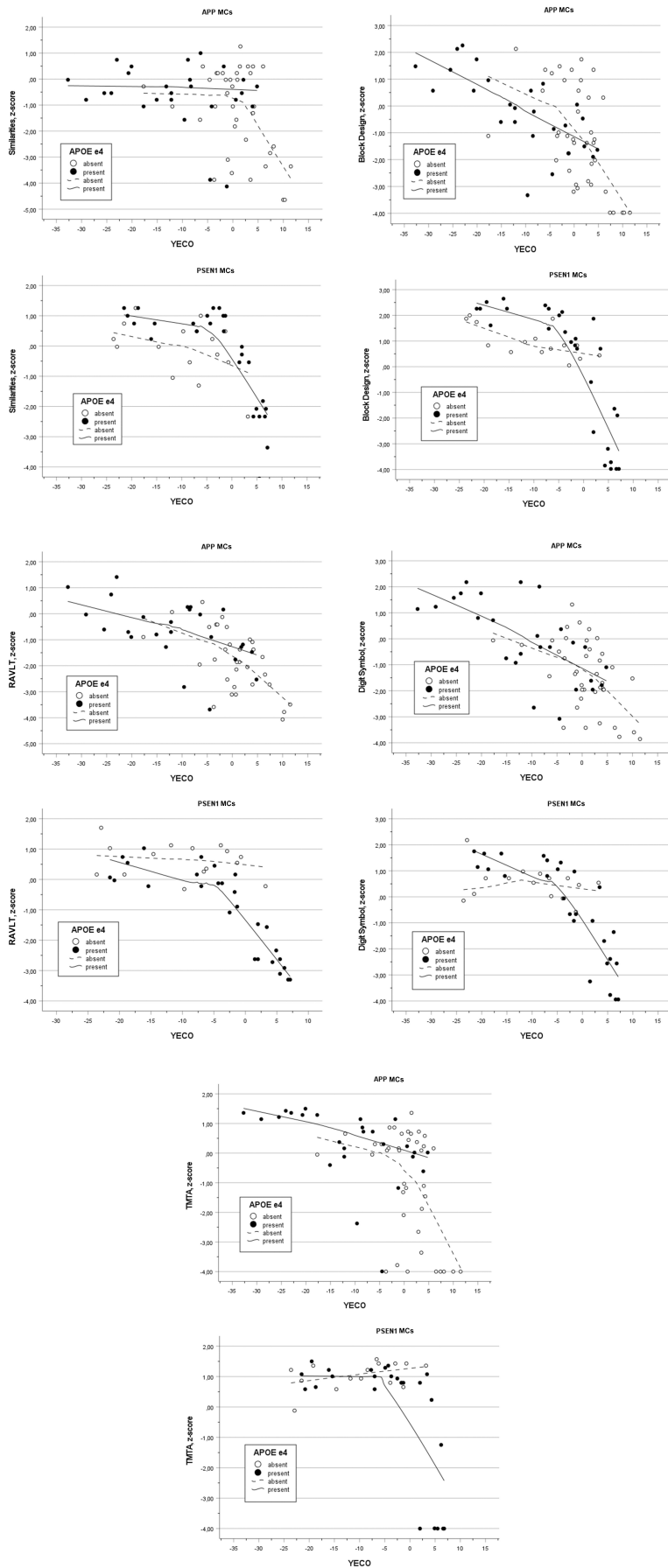
FIGURE 1 Longitudinal cognitive decline across time of disease advancement (years to expected clinical onset [YECO]) on five tests in *APP* and *PSEN1* mutation carriers (MCs) divided into *APOE* subgroups, showing *APP* MCs with and without the ε4 allele in the left column and *PSEN1* MCs with and without the ε4 allele in the right column. RAVLT, Rey Auditory Verbal Learning Test; Sim, Similarities test; TMTA, Trailmaking Test A

test), which is indicated by a decline in cognitive processing speed in normal aging [34, 36], but not in other cognitive domains. The time-related predictors (YECO and YECO^2) were nonsignificant, except for one test (Digit Symbol) that indexed the executive domain and another test (Similarities) that indexed the verbal domain; the statistical power of these associations was small compared to the corresponding power of these predictors in MCs. The detrimental effect of *APOE* ε4 on attention (TMTA) in NCs could be compared to similar findings in normal aging [36]. Similar negative effects have been reported in numerous studies of normal aging [37–39].

The addition of *APOE*-by-YECO interaction as a fifth predictor did not contribute significantly to the model in any cognitive tests, either in MCs or in NCs. These results run counter to the hypothesis that the *APOE* effect increases across time as presented in the Introduction. However, it has been demonstrated that the cognitive trajectories are different in *APP* and *PSEN1* MCs [28], which motivated the corollary hypothesis that the effect of *APOE* and *APOE*-by-YECO interaction may depend on the mutated adAD gene (*APP* and *PSEN1*).

The main result was the differential effect of the *APOE*-by-YECO interaction on cognitive decline in MCs when *APP* and *PSEN1* MCs were compared. The beta weights of the *APOE*-by-YECO interaction were positive in all five cognitive tests and significant in two tests (Similarities and TMTA) in *APP* MCs (i.e., favourable). In contrast, the *APOE*-by-YECO interaction was negative in four cognitive tests (the exception was the verbal Similarities test) and significant in one test (Block Design) in *PSEN1* MCs, that is, it was unfavourable. This pattern of results, observed as contrasting mean level of trajectories across YECO in most tests for *APOE* ε4 in *APP* versus *PSEN1*, was an unexpected and novel finding (Figure 1). Specifically, the cognitive decline started relatively early and continued slowly in the preclinical disease course in the cognitive tests in *APP* MCs when *APOE* ε4 was present. In contrast, the trajectory of cognitive decline was biphasic, slow in the early preclinical part of the disease course, and steep around the estimated clinical onset in *PSEN1* MCs when *APOE* ε4 was present. These findings indicate that *APOE* ε4+ was a favourable factor with regard to cognition in *APP* MCs and an unfavourable factor for cognitive decline in *PSEN1* MCs. When *APOE* ε4 was absent, the cognitive decline was pronounced across the disease course in *APP* MCs, while cognitive decline was markedly smaller in *PSEN1* MCs, and possibly not significantly different from normal aging. Together, these findings could be conceived of as a double dissociation and a gene–gene interaction (*APP*/*PSEN1* vs. ε4+/ε4−).

A possible interpretation of the different cognitive trajectories in *APP* and *PSEN1* linked to *APOE* ε4 presence versus absence indicates opposing roles of *APOE* ε4 in *APP* and *PSEN1* genes. The pattern was similar across cognitive domains, indicating cognitive independence. The pattern was also unrelated to demographic features, as the groups were comparable. Furthermore, there was no difference in mean years to estimated clinical onset. So far there is no explanation of the finding other than a gene–gene interaction with unknown players. However, the *APOE*-by-YECO interaction on cognitive decline in *APP* and *PSEN1* MCs must be regarded as uncertain because the group sample sizes are small. A reliable conclusion awaits information from larger future studies on this topic. Meanwhile, it is an intriguing pattern of observations that can be related to the antagonistic pleiotropy phenomenon [40].

The antagonistic pleiotropy phenomenon has been observed in different contexts (high-parasite environments), aging (cognitively normal middle-aged and adults), populations (fetal development, children and adults), and specific cognitive tasks (short vs. long exposure in short-term memory/attention and episodic memory vs. non-memory) [11, 16, 20–25] in agreement with a recent suggestion that *APOE* has opposing roles in aging and neurodegeneration based on mice studies [26]. A possible explanation for antagonistic pleiotropy is that the *APOE* ε4 allele may lead to increased resistance to toxic agents, or may contribute to brain repair [20, 21, 41].

The findings of the present study can be summarized in relation to the hypotheses. The first hypothesis, that the presence of *APOE* ε4 has a negative effect on cognition in MCs, was not confirmed. The second hypothesis, that there is a possible time-related interaction (*APOE*-by-YECO) in cognition in MCs, was not confirmed. The third hypothesis, that *APOE* and the *APOE*-by-YECO interaction term have differential effects on cognition in *APP* and *PSEN1* MCs, was partly confirmed. The fourth hypothesis, that *APOE* and the *APOE*-by-YECO interaction term have no effect on cognition in NCs, was confirmed with one exception: the TMTA attention domain showed a decrease in performance.

It is advantageous that the present study included MCs and NCs from six adAD families, followed with repeated examinations of cognition and covering more than 40 years of natural disease course. The main drawback is the small sample size, laying the study open to random influences on results.

To conclude, the results indicate that presence of the *APOE* ε4 allele influences cognitive decline positively in *APP* MCs (relatively slow progression) and negatively in *PSEN1* MCs (pronounced progression). When *APOE* ε4 was absent, the opposite pattern was obtained, pronounced progression in *APP* MCs and slow or minimal progression in *PSEN1* MCs. These results indicate opposing roles of the *APOE* ε4 allele on cognition in *APP* and *PSEN1* that may reflect an antagonistic pleiotropic phenomenon.

AUTHOR CONTRIBUTIONS

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FUNDING INFORMATION

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author or the principal investigator (Caroline Graff).

ETHICAL APPROVAL

All participants provided written informed consent to participate in the study, which was conducted according to the declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional Human Ethics Committee of Stockholm, Sweden.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.