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Subjective cognitive concerns, episodic memory and the APOE ε4 allele

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Abstract

Background—Subjective cognitive concerns may represent a simple method to assess likelihood of memory decline among APOE ϵ 4 carriers.

Methods—We examined the relationship of self-reported subjective cognitive concerns, using 7 specific cognitive concerns, with memory and memory decline over 6 years among APOE ϵ 4 carriers and non-carriers from the Nurses' Health Study.

Results—In both groups, increasing subjective cognitive concern score predicted worse baseline memory and faster rates of subsequent memory decline, after adjustment for age, education and depression. The relation with baseline memory appeared statistically stronger in APOE ϵ 4 carriers (P -interaction=0.03). For memory decline, mean differences in slopes of episodic memory (95% CI) for 4 to 7 versus no concern = -0.05 ($-0.10, 0.01$) standard units in APOE ϵ 4 carriers, and -0.04 ($-0.08, -0.01$) standard units in non-carriers.

Conclusions—APOE ϵ 4 carriers with self-assessed cognitive concerns appear to have worse memory, and possibly accelerated memory decline.

Keywords

memory; Apolipoprotein E4; subjective cognitive concerns

1. Introduction

The ϵ 4 allele of the apolipoprotein E (APOE) gene is a strong genetic risk factor for sporadic Alzheimer disease (AD). APOE ϵ 4 carriers have 3 to 15 times greater odds of developing AD for one and two ϵ 4 copies, respectively [1]. Moreover, the APOE ϵ 4 allele is an established risk factor for memory decline [2], which begins early in AD dementia [3, 4]. For example, in the Nurses' Health Study, compared to carriers of two ϵ 3 alleles, those with at least one ϵ 4 allele had an odds ratio of 1.46 (95% CI = 1.10, 1.94) for substantial decline in memory performance [5]. Still, APOE ϵ 4 carrier status only explains a fraction of risk, and there is variability in the rate of memory decline among carriers. Yet, the factors which predict worse memory among APOE ϵ 4 carriers remain largely unknown. Simple approaches to identify carriers with greatest likelihood of memory impairment will be important, both in conducting research to evaluate interventions to reduce dementia and cognitive decline and, eventually, to administer interventions to this group.

There is increasing interest in subjective cognitive concerns (SCC) as a marker of risk of AD progression and cognitive decline. SCC have been found to predict accelerated memory decline [6], increased risk of AD [7–9], and have been associated with the presence of neurobiological markers of AD (eg, grey matter atrophy [10–14], white matter integrity [15], amyloid burden [16, 17] and AD pathology at autopsy [18]). Although APOE ϵ 4 has been associated with a greater prevalence of SCC [19–21], very limited research has addressed whether SCC predict memory decline in APOE ϵ 4 carriers [22].

In a previous cross-sectional report, we found a relationship between SCC, defined by the number of endorsed symptoms on 7 specific concerns, and the current level of cognitive function (including memory) measured by neuropsychological testing [23]. In the present

manuscript, we assessed the relationship of SCC to baseline memory and subsequent verbal memory decline according to APOE $\epsilon 4$ status among women from the Nurses' Health Study.

2. Methods

2.1 Study population

The NHS began in 1976 when 121,700 female registered nurses aged 30–55 years, residing in 11 US states, completed a mailed questionnaire about their health and lifestyle. Follow-up questionnaires have been sent every 2 years since; follow-up rates remain approximately 90% to date. From 1995 to 2001, a cognitive study was initiated in participants who were 70+ years and free of stroke. Among eligible women, 19,415 (93%) completed the first telephone-based cognitive assessment. Follow-up assessments were performed 3 times at 2-year intervals, with high participation rate (>90%). The study was approved by the Partners Human Research Committee (Boston, MA). For the questionnaire information, the return of the completed questionnaire was considered to imply informed consent. For the telephone interview, agreement to complete the interview was considered as consent.

In 2002, a buccal sample was collected from willing participants of the NHS cognitive study, allowing APOE genotyping for 4,304 participants. Characteristics of the participants who provided a buccal sample were generally similar to those of the entire cognitive subcohort. However, they had slightly higher mean cognitive scores [5].

Because APOE $\epsilon 4$ prevalence and its association with dementia differ by race, we excluded the 61 non-Caucasians from the study sample for these analyses. Additionally, we were especially concerned about confounding by depression since it is a major potential correlate of both SCC and cognition; hence, we also excluded the 448 participants with self-reported diagnosis of depression, regular antidepressant use, or a score of 52 or lower on the mental health index (MHI-5 [24]) of the Medical Outcomes Study 36-item Short-Form Survey (SF36) [25] (range 0–100 points) on the closest questionnaire (from the parent Nurses' Health Study) prior to the initial cognitive assessment. We further excluded the 382 participants missing any information on SCC and 38 participants with missing MHI-5; 3,375 subjects were therefore included in these analyses, amongst whom we identified 779 APOE $\epsilon 4$ carriers (i.e., carrying at least one APOE $\epsilon 4$ allele, 23.0% of the sample) and 2,596 non carriers (i.e., no APOE $\epsilon 4$ allele).

2.2 Assessment of subjective cognitive concerns

At the beginning of the telephone cognitive interview, the participants were asked 7 yes/no questions about specific cognitive concerns (listed in Table 1), which were previously found in other cohorts to be useful in patients with possible cognitive impairment [26]. These 7 items were based on reports of a recent change in: memory; remembering a short list; remembering things from one second to the next; remembering recent events; difficulties with understanding or following spoken instructions, a group conversation or the plot of a television program; and trouble finding one's way on familiar streets.

We computed a SCC score as the total number of concerns reported for each individual [23]; thus, SCC scores could range from 0 to 7. Since few women reported more than 4 concerns, we created a score with 5 categories by grouping together all women reporting four or more concerns (0, 1, 2, 3, 4 or more symptoms).

2.3 Objective cognitive assessment

After the assessment of SCC, objective cognitive testing was performed using validated assessments on the telephone. The cognitive battery included: (i) the Telephone Interview of Cognitive Status (TICS); (ii) immediate and (iii) delayed recall of the East Boston Memory Test (EBMT); (iv) delayed recall of the TICS 10-word list; (v) category fluency and (vi) digit span-backwards. Early in the initial wave of cognitive interviews, we administered only the TICS and delayed recall of the TICS 10-word list; in subsequent years, we added these tests to the assessment battery: the East Boston Memory Test (immediate and delayed recall trials), category fluency, and digit span backwards. Thus, the sample size slightly differs across tests but study participation rates were identical for all tests.

For these analyses, we focused on the 4 trials of verbal (episodic) memory, i.e., the immediate and delayed recall trials of the EBMT [27] (range 0–12 points each, higher scores indicating better performance) and the TICS 10-word list (range 0–10 points each, higher scores indicating better performance). We focused on episodic memory because impairment of episodic memory is a strong predictor of AD [3], and particularly accelerated decline in episodic memory in APOE ϵ 4 carriers vs non carriers has been described; indeed, in our own previous research, we found a mean difference in episodic memory decline of -0.08 standard units (95% CI -0.14 , -0.03) over two years in APOE ϵ 4 carriers vs non-carriers [5].

For analyses, we created a composite score of episodic memory, calculated as the average of z-scores of the four trials assessing episodic memory. We calculated z-score memory composites at each of the four time-points by using the distribution of scores at the first cognitive assessment.

2.4 Apolipoprotein E genotyping

Buccal samples were processed using ReturPureGene DNA Isolation Kit (Gentra Systems Minneapolis MN) to extract genomic DNA from human cheek cells. Polymorphisms were genotyped using TaqmanTM (Applied Biosystems, Foster City, CA) assays.

2.5 Other variables

We considered potential confounding variables, including age, educational level, and mental health (which may influence cognition and subjective concerns in older subjects [6, 28]) using the MHI-5 as a continuous variable.

2.6 Statistical analyses

We modeled trajectories of the four repeated episodic memory composite scores using a linear mixed model [29]. The linear mixed model included an intercept that represents the level of cognitive score at baseline and a slope that represents the annual change in scores

over time, as well as a random intercept and random slope to account for inter-individual variability.

In the primary analysis, we examined the relationship between SCC score at the initial cognitive assessment and subsequent episodic memory change, across APOE $\epsilon 4$ carrier status (including in the linear mixed model interaction terms between SCC and APOE $\epsilon 4$ on the intercept and one the slope, respectively), and adjusting for age, educational level and the MHI-5.

In a secondary analysis, to determine whether a specific concern (rather than total number of concerns) may be particularly related to memory decline, we studied associations between each specific concern and episodic memory change, considering the presence (*vs* absence) of each concern separately, mutually adjusting for other concerns and for age, educational level and MHI-5.

We evaluated the robustness of our findings in two additional secondary analyses. We excluded individuals with possible “cognitive impairment” at baseline (i.e., TICS < 31 points, a standard cut-off [30], and the 10% of individuals with worst episodic memory composite scores at baseline in a second analysis), since evidence suggests that those with the very worst cognition may have insight/meta-cognitive deficits that interfere with the ability to provide subjective reports of their memory.

All analyses were conducted using SAS version 9.2 (SAS institute, Inc.) and a P value < 0.05 was considered statistically significant.

3. Results

In our sample, we observed APOE genotype frequencies similar to frequencies generally reported for older Caucasian female populations [31, 32]: $\epsilon 3/3$: $n = 2148$ (63.6%), $\epsilon 3/2$: $n = 427$ (12.7%), $\epsilon 2/2$: $n = 22$ (0.7%), $\epsilon 2/4$: $n = 54$ (1.6%), $\epsilon 3/4$: $n = 666$ (19.6%), $\epsilon 4/4$: $n = 58$ (1.7%). Among APOE $\epsilon 4$ carriers, 7.4% were homozygotes (Table 1). APOE $\epsilon 4$ carriers were similar in mean age, in educational level, and in mean MHI-5, compared to non-carriers. Compared to APOE $\epsilon 4$ non-carriers, women with an APOE $\epsilon 4$ allele had worse scores on the TICS (mean score = 33.8 and 34.0 points in carriers and non-carriers, respectively, $P = 0.02$), the immediate and delayed recalls to the EBMT (mean immediate recall = 9.3 *vs* 9.5 points, $P = 0.04$; mean delayed recall = 8.9 *vs* 9.2 points, $P = 0.002$), the digit span backward test (mean score = 6.6 *vs* 6.8, $P = 0.03$). APOE $\epsilon 4$ carriers had also lower composite verbal memory scores, compared to non-carriers (mean score = -0.06 and 0.02 standard units in carriers and non-carriers, respectively, $P = 0.003$).

APOE $\epsilon 4$ carriers reported slightly more subjective concerns than non-carriers, on average (mean number of subjective cognitive concerns = 1.5 and 1.4 in carriers and non-carriers, respectively, $P = 0.003$). Moreover, APOE $\epsilon 4$ carriers were somewhat more likely to endorse at least one subjective concern compared to non-carriers (e.g., 74.2% reported any subjective concern, *vs* 69.4% among non-carriers, Table 1); the odds ratio for reporting at least one concern in APOE $\epsilon 4$ carriers *vs* non carriers was 1.27 (95% CI 1.06, 1.52) (results not shown in tables). In addition, APOE $\epsilon 4$ carriers were more likely to report multiple

concerns (e.g., 6.4% of APOE $\epsilon 4$ carriers reported 4 or more concerns vs 5.0% of non-carriers, Table 1).

3.1 Association between subjective cognitive concerns score and episodic memory

When we considered initial cognitive performance, we found in both APOE $\epsilon 4$ carriers and non-carriers a trend of increasing SCC score at baseline associated with increasingly worse baseline episodic memory (p for trend < 0.001 in both groups, Table 2). When we considered each level of score as a categorical variable (i.e., 1 concern, 2 concerns, etc.) versus no concern, there was a statistically significant association between most levels of concerns and episodic memory. However, this association appeared generally two to three times as strong among APOE $\epsilon 4$ carriers as among APOE $\epsilon 4$ non carriers (global P -value for interaction = 0.03, Table 2). For example, mean differences in baseline episodic memory score (95% CI) for 1 concern, 2 concerns, 3 concerns and 4 to 7 concerns versus no concerns = -0.16 standard units (-0.29, -0.03), -0.09 (-0.23, 0.05), -0.31 (-0.48, -0.14) and -0.51 (-0.73, -0.30), respectively, in APOE $\epsilon 4$ carriers, and -0.00 standard units (-0.07, 0.07), -0.02 (-0.10, 0.05), -0.11 (-0.20, -0.02) and -0.17 (-0.29, -0.04) in APOE $\epsilon 4$ non-carriers, after adjustment for age, education and MHI-5. Findings did not appear meaningfully different in $\epsilon 4$ homozygotes, although the sample size was limited.

When we considered episodic memory decline subsequent to report of cognitive concerns (Table 2 and Figure), in both APOE $\epsilon 4$ carriers and non-carriers, we found trends of higher SCC score at baseline predicting steadily worse rates of episodic memory decline (p for trend = 0.02 and 0.001 among APOE $\epsilon 4$ carriers and non-carriers, respectively, Table 2 and Figure). In our multivariate model, mean differences in slopes of episodic memory change (95% CI) for 1 concern, 2 concerns, 3 concerns and 4 to 7 concerns were -0.05 (-0.08, -0.01) standard units, -0.06 (-0.09, -0.02), -0.05 (-0.09, -0.01) and -0.05 (-0.10, 0.01), respectively, in APOE $\epsilon 4$ carriers, and -0.00 (-0.02, 0.01), -0.01 (-0.03, 0.01), -0.03 (-0.05, -0.01) and -0.04 (-0.08, -0.01) standard units in APOE $\epsilon 4$ non-carriers. Although findings were qualitatively stronger in carriers (without meaningful difference among $\epsilon 4$ homozygotes, as with initial memory performance), there was no significant interaction between SCC score and APOE on memory change (P for interaction = 0.14). This may be due to the lower statistical power to detect interactions with memory change than baseline memory, since there is more variability in the measurement of memory change.

To help interpret these mean differences, we contrasted the effect of age on cognitive decline in our cohort with the effect of SCC on cognitive decline in our cohort. Specifically, in APOE $\epsilon 4$ carriers, each additional concern was cognitively equivalent to an additional 2.4 years of aging; that is, women with SCC had similar objective memory decline as those 2.4 years older in age. In APOE $\epsilon 4$ non-carriers, each additional concern was cognitively equivalent to an additional 1.7 year of aging.

3.2 Association between specific subjective cognitive concerns and episodic memory change

We secondarily examined whether specific concerns independently predicted episodic memory decline among APOE4 carriers and non-carriers. In a model adjusted for age,

education and depression and including all 7 concerns, we found few significant relationships between any single specific concern and subsequent episodic memory decline (Table 3). Only report of a recent change in memory (the most common concern) was significantly independently related to worse episodic memory change in APOE ϵ 4 carriers (mean difference = -0.07 standard units, 95% CI -0.10, -0.04), but not in non-carriers (mean difference = -0.01 standard units, 95% CI -0.03, 0.00, Table 3; P for interaction <0.001). None of the other single items were significantly related to episodic memory decline in carriers or in non-carriers. However, since substantially more women reported a recent change in memory than the other individual concerns, we had less ability to detect relations for the other concerns.

3.3 Sensitivity analyses

The results were virtually unchanged when we limited the sample to the 646 APOE ϵ 4 carriers and the 2,217 APOE ϵ 4 non-carriers with “normal” cognition at baseline (e.g., with TICS ≥ 31 ; see supplemental Table 1), or when we excluded the 10% of individuals with the worst episodic memory composite scores at baseline (supplemental Table 2), suggesting that the results were not influenced by low baseline cognitive performance among some participants, although few women had extremely low neuropsychological test scores.

4. Discussion

In this large sample of older women, we found a strong relationship between baseline SCC and both concurrently assessed episodic memory and change in memory during the subsequent 6 years of follow-up. Relationships with baseline memory appeared stronger among APOE ϵ 4 carriers, suggesting SCC may be a particularly important marker in those with genetic risk of worse cognition. The relation between SCC and memory change was also qualitatively stronger in APOE ϵ 4 carriers. Our results therefore suggest that self-report of cognitive concerns may be useful for identifying individuals with worse cognition, and potentially greater likelihood of memory decline, particularly among APOE ϵ 4 carriers.

Similar to our findings, in some previous studies, SCC have been prospectively related to memory decline, although the relationship has not been entirely consistent in the literature [33–38]. The studies which failed to identify a relationship were generally of limited sample size and shorter follow-up [36]. Moreover, recent studies have found a relationship of SCC to markers of AD pathology, providing biological support for SCC as a marker of risk for cognitive decline [10–14]. Our own work adds to these previous studies by suggesting that SCC may be of particular utility in those at greater genetic risk for cognitive decline.

Several previous studies of AD biomarkers have reported specifically stronger associations of SCC among APOE ϵ 4 carriers than non-carriers. In a small cross-sectional study, APOE ϵ 4 carriers with SCC referred to a memory clinic had lower hippocampal volumes than those without memory impairment [39]. APOE ϵ 4 carriers with SCC (defined by a single question, ie, reporting occasional forgetting names or forgetting where one placed objects) had greater brain hypometabolism (a marker of loss of synaptic function due to neuronal damage) in the same regions as those affected in AD patients, and increased levels of AD biomarkers in the cerebrospinal fluid, as compared to carriers without subjective memory concerns [40].

The relation of SCC to objective cognitive decline among APOE ϵ 4 carriers has not been previously well-examined. The Amsterdam Longitudinal Study on Aging suggested an additive association of the APOE4 allele and SCC (defined by a single question, ie, “Do you have problems with your memory?”) to cognitive decline (but not episodic memory change [22]). However, APOE ϵ 4 carrier status was not related to decline in episodic memory itself, indicating potential issues in the measurement of episodic memory decline in this study.

An important strength of our study is the large sample size with longitudinal follow-up for episodic memory, which is a strong predictor of AD [3]. In addition, our population-based study rather than clinic-based study, including women enrolled in a general health investigation rather than specifically a cognitive cohort, may have benefits in terms of generalizing findings to those not necessarily focused on their symptoms. Some potential limitations should also be considered. First, cognitive function was slightly better in the subsample with genotyped APOE compared to the entire cohort. This is not likely to have affected the internal validity of our findings, but might lead us to slightly underestimate associations between APOE and memory (ie, if the distribution of cognitive performance were somewhat truncated in our subsample). Our sample was limited to female, mostly non-hispanic Caucasian healthcare professionals, with generally high socio-economic status and health knowledge. This is useful to decrease extraneous variability in study measures, and to enhance the validity of health information, but results may not be generalizable to populations with different demographic features. Furthermore, a telephone assessment of cognitive function may have caused some misclassification. However, in a validation study, our telephone-based cognitive battery performed very well compared with detailed, in-person interviews ($r = 0.81$ comparing the 2 modes of assessment). Moreover, using cognitive scores from our telephone interview, we previously found clear associations with many risk factors for cognitive decline, and the magnitude of associations we found (including for APOE genotype) were generally comparable with those observed using in-person cognitive interviews in other studies [5, 41]; both these aspects establish the high validity of our telephone interview method. Finally, it is possible in our study that the stronger association of SCC to episodic memory among APOE4 carriers was simply due to the greater rate of memory impairment in carriers (and thus greater ability to detect relationships); nonetheless, this phenomenon would be true of any examination of interactions between APOE ϵ 4 (or any other at-risk population) and variables of interest, and we have not uniformly identified strong interactions in our previous research on APOE ϵ 4 and various risk factors of interest [5].

In summary, our study suggests that SCC predict episodic memory performance, particularly among those who are APOE ϵ 4 carriers. Given the ease of collecting SCC from individuals, this may represent a simple tool for identifying those at greatest risk of objective cognitive impairment and, possibly, accelerated cognitive decline, to target for research to evaluate preventive interventions. Certainly, further prospective studies of SCC are needed to confirm if there may be a stronger association with memory decline among APOE ϵ 4 carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure. Trajectories of episodic memory composite score, by increasing number of subjective cognitive concerns reported at baseline among APOE ε4 carriers and non-carriers.*

* Trajectories were estimated using a linear mixed model adjusted for age, educational level and mental health index (MHI-5). Predicted mean evolution of composite episodic memory scores were represented for registered nurses, aged 70 years-old, with a MHI-5 score=83 (ie, the average score in the population), and APOE4 carriers (left) and non-carriers (right), respectively. P-values for trend were calculated using a continuous variable of concerns score in another multivariate linear mixed model.

Table 1

Characteristics of APOE $\epsilon 4$ carriers and APOE $\epsilon 4$ non-carriers in the cognitive sub-study of the Nurses' Health Study

	APOE $\epsilon 4$ carriers (N=779)	APOE $\epsilon 4$ non- carriers (N=2,596)
APOE $\epsilon 4$ homozygotes, N (%)	58 (7.4)	-
Mean (SD) age at first cognitive exam (years)	74.2 (2.3)	74.3 (2.3)
Educational level, N (%)		
Registered nurse	630 (80.9)	2,033 (78.3)
Bachelor	106 (13.6)	411 (15.8)
Master or Doctorate	43 (5.5)	152 (5.9)
Mean (SD) Mental Health Index (MHI-5) score	82.4 (10.4)	82.9 (10.0)
Mean (SD) TICS (points)	33.8 (2.8)	34.0 (2.5)
Mean (SD) Verbal fluency (points)	17.2 (4.6)	17.2 (4.5)
Mean (SD) Digit span Backward (points)	6.6 (2.4)	6.8 (2.4)
Mean (SD) episodic memory (points)		
TICS 10 words list, immediate recall	4.7 (1.7)	4.7 (1.6)
TICS 10 words list, delayed recall	2.2 (2.0)	2.4 (2.0)
East Boston Memory Test, immediate recall	9.3 (1.7)	9.5 (1.6)
East Boston Memory Test, delayed recall	8.9 (1.9)	9.2 (1.7)
Mean episodic memory composite score (standard units)	-0.06 (0.72)	0.02 (0.66)
Subjective cognitive concerns, N (%)		
Recent change in memory	451 (57.9)	1,363 (52.5)
Trouble remembering a short list	232 (29.8)	702 (27.0)
Trouble remembering things from one second to the next	197 (25.3)	603 (23.2)
Trouble remembering recent events	147 (18.9)	398 (15.3)
Difficulty in understanding or following spoken instructions	53 (6.8)	181 (7.0)
Trouble following a group conversation or plot in a TV program	51 (6.6)	139 (5.4)
Trouble finding your way around familiar streets	9 (1.2)	33 (1.3)
Number of subjective cognitive concerns, mean (SD)	1.5 (1.3)	1.3 (1.2)
Subjective cognitive concern score, N (%)		
0	201 (25.8)	793 (30.6)
1	239 (30.7)	785 (30.2)
2	187 (24.2)	585 (22.5)
3	102 (13.1)	303 (11.7)
4-7	50 (6.4)	130 (5.0)

Abbreviations: APOE: Apolipoprotein E; TICS: Telephone-Interview Cognitive Status. Values are percentage of non-missing values or mean (SD).

Mean differences (95% CI) in baseline episodic memory scores and in slopes of memory ^{*} by change increasing number of subjective cognitive concerns reported at baseline among APOE ε4 carriers and non-carriers

Table 2

APOE ε4 carriers (N=779)		APOE ε4 non-carriers (N=2,596)	
	Estimate (95% CI)	P trend	P for interaction
Mean difference in baseline memory			
0 concern	Ref		-
1 concern	-0.16 (-0.29, -0.03)		0.04
2 concerns	-0.09 (-0.23, 0.05)		0.40
3 concerns	-0.31 (-0.48, -0.14)		0.04
4-7 concerns	-0.51 (-0.73, -0.30)		0.006
		<0.001	0.03 [†]
Mean difference in slope of memory change			
0 concern	Ref		-
1 concern	-0.05 (-0.08, -0.01)		0.03
2 concerns	-0.06 (-0.09, -0.02)		0.04
3 concerns	-0.05 (-0.09, -0.01)		0.50
4-7 concerns	-0.05 (-0.10, 0.01)		0.83
		0.02	0.14 [†]

Abbreviations: APOE: Apolipoprotein E.

^{*} Estimations were computed from a linear mixed model adjusted for age, educational level and MHI-5. The linear mixed model included: (i) an intercept (ie, baseline mean memory score for the reference category [70 years-old Registered nurse, reporting no cognitive concern, APOE ε4 non-carrier, with MHI-5 score =83, the average score]); (ii) subjective cognitive concerns score (SCC, in 5 categories), APOE ε4 carrier status (at least one ε4 allele vs no ε4 allele), age (continuous), educational level (in 3 categories) and mental-health index score (MHI-5, continuous) (ie, parameters for effect of each covariate on baseline memory [the intercept]); (iii) SCC × APOE ε4 interaction term (ie, parameter for interaction between SCC and APOE ε4 on the intercept); (iv) a slope (ie, mean annual change in memory for the reference category); (v) the two-way interactions of SCC score, APOE ε4 carrier status, age and educational level with time (ie, parameters for effect of each covariate on memory change [the slope]); (vi) SCC × APOE ε4 × time interaction term (ie, parameter for interaction between SCC and APOE ε4 on the slope); (vii) a random intercept and random slope (ie, subject-specific baseline memory and annual memory change).

[†] Global P value of the type III test (with 4 degrees of freedom) of the interaction term between subjective cognitive concern score and APOE ε4 carrier status on baseline episodic memory and on slope of memory change, respectively. P-values for trend were calculated using a continuous variable of concerns score in another multivariate linear mixed model.

Table 3

Mean differences (95% CI) in slopes of episodic memory change * by specific subjective cognitive concerns reported at baseline among APOE ε4 carriers and non-carriers

	APOE ε4 carriers (N=779)	APOE ε4 non-carriers (N=2,596)
Recent change in memory	−0.07 (−0.10, −0.04)	−0.01 (−0.03, 0.00)
Trouble remembering a short list	0.03 (−0.00, 0.06)	−0.00 (−0.02, 0.01)
Trouble remembering things from one second to the next	0.00 (−0.03, 0.04)	−0.01 (−0.02, 0.01)
Trouble remembering recent events	0.02 (−0.02, 0.05)	−0.01 (−0.03, 0.01)
Difficulty in understanding or following spoken instructions	−0.05 (−0.10, 0.01)	−0.01 (−0.04, 0.02)
Trouble following a group conversation or plot in a TV program	0.01 (−0.05, 0.06)	−0.01 (−0.04, 0.02)
Trouble finding your way around familiar streets	−0.04 (−0.17, 0.09)	−0.03 (−0.09, 0.04)

Abbreviations: APOE: Apolipoprotein E.

* Estimations were computed from a linear mixed model adjusted for age, educational level and MHI-5 and mutually adjusted for other subjective concerns.