The Impact of *APOE* and Smoking History on Cognitive Function in Older, Long-Term Breast Cancer Survivors

Tim Ahles

ahlest@mskcc.org

Memorial Sloan-Kettering Cancer Center https://orcid.org/0000-0002-7936-2818

Irene Orlow

Memorial Sloan Kettering Cancer Center

Elizabeth Schofield

Memorial Sloan Kettering Cancer Center

Yuelin Li

Memorial Sloan Kettering Cancer Center

Elizabeth Ryan

Memorial Sloan Kettering Cancer Center

James C. Root

Memorial Sloan Kettering Cancer Center

Sunita K. Patel

City of Hope Beckman Research Institute

Katrazyna McNeal

Memorial Sloan Kettering Cancer Center

Alexandra Gaynor

Memorial Sloan Kettering Cancer Center

Heidi Tan

City of Hope Beckman Research Institute

Vani Katheria

City of Hope Beckman Research Institute

Jessica Vazquez

City of Hope Beckman Research Institute

Sergio Corrales-Guerrero

Memorial Sloan Kettering Cancer Center

Keimya Sadeghi

Memorial Sloan Kettering Cancer Center

Tiffany Traina

Memorial Sloan Kettering Cancer Center

Arti Hurria

City of Hope Beckman Research Institute

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Abstract

Purpose

To determine whether older breast cancer survivors score lower on neuropsychological tests compared to matched non-cancer controls and to test the hypotheses that survivors who were APOE ε4 carriers would have the lowest cognitive performance, but that smoking history would decrease the negative effect of ε4 on cognition.

Methods

Female breast cancer survivors who had been diagnosed and treated at age 60 or older and were 5 – 15 year survivors (N=328) and age and education matched non-cancer controls (N=160) were assessed at enrollment and at 8, 16 and 24 month follow ups with standard neuropsychological and psychological assessments. Blood for *APOE* genotyping was collected and smoking history was assessed at enrollment. Participants were purposely recruited so that approximately 50% had a history of treatment with chemotherapy or no chemotherapy and approximately 50% had a smoking history.

Results

After adjusting for age, cognitive reserve, depression and fatigue, breast cancer survivors scored significantly lower on all domains of cognitive function. A significant two-way interaction demonstrated that the negative effect of ε4 on cognitive performance was stronger among survivors. A significant three-way interaction supported the hypothesis that smoking history had a protective effect on cognitive function in ε4 carriers that was more pronounced in the controls than the survivors.

Conclusions

The results support the long-term cognitive impact of breast cancer diagnosis and treatments on older, disease-free survivors, particularly for ε4 carriers. The results also emphasize the importance of assessing smoking history when examining *APOE* and cognition and are an example of the complex interactions of age, genetics, health behaviors and disease history in determining cognitive function.

Introduction

Research has demonstrated that breast cancer treatments negatively impact cognitive function (1–9). As the population of long-term breast cancer survivors continues to grow, an important research question is the impact of the cancer diagnosis and treatment on the trajectory of cognitive aging in older long-term, disease-free breast cancer survivors who were diagnosed and treated as older adults. Increasing human (10–11) and animal research (12–13) suggests that cancer treatments accelerate aging on a biological

level. One question is whether there is a steeper trajectory of cognitive aging (accelerated aging hypothesis) in older breast cancer survivors or whether they experience cognitive change due to cancer treatment and then demonstrate a trajectory of cognitive aging that parallels aging individuals without a cancer history (phase shift hypothesis, 1, 14-15).

These two hypotheses are not mutually exclusive; some survivors may demonstrate a phase shift pattern whereas others carrying key risk factors may demonstrate an accelerated cognitive aging pattern. Apolipoprotein E (APOE), a complex glycolipoprotein that facilitates the uptake, transport, and distribution of cholesterol and other lipids, has been studied extensively in relation to cognitive functioning (16). The isoform ε4 has been associated with more pronounced cognitive decline with aging, following insult to the brain, and with a variety of disorders with prominent cognitive dysfunction (e.g., Alzheimer's disease, 16-17). The isoform ε4's effect on cognitive decline is attributed to reduced neuronal and vascular repair, increased oxidative stress and inflammation, decreased production of neural progenitor cells, impairment of the blood brain barrier, and morphologic differences in brain structure (17-19).

APOE ε4 has been associated with poorer cognitive outcomes in patients with breast cancer and lymphoma (20–21), testicular cancer (22) and brain tumors (23). However, research has suggested that the negative impact of APOE ε4 on cognitive function is impacted by smoking history (24–27). In breast cancer and brain tumor populations, ε4 carriers without a smoking history demonstrated the expected decline in cognitive function whereas those with a smoking history did not (21, 23). One possible mechanism explaining the apparent protective effect of smoking on cognitive decline is the correction of a nicotinic receptor deficit and associated decrease in dopaminergic activity in ε4 carriers, particularly in individuals who begin smoking at an early age (28).

This study examined the trajectory of cognitive aging in older long-term breast cancer survivors who were diagnosed and treated as older adults compared to matched non-cancer controls and addresses three questions: 1) do survivors demonstrate lower cognitive performance compared to controls and is the trajectory over time more consistent with the phase shift or accelerated aging hypothesis; 2) is the impact of ε4 on cognitive function more significant for survivors compared to controls; and 3) does a smoking history reduce the negative cognitive impact of ε4?

Methods

Participants. Breast cancer survivors were identified through the survivorship clinics at Memorial Sloan Kettering Cancer Center (MSK) and City of Hope Comprehensive Cancer Center (COH), supplemented at each site by recruitment through the Army of Women. Survivors were eligible if they were diagnosed with stage 0-III breast cancer, treated at age 60 or above, were 5 to 15-year disease-free survivors at the time of enrollment and provided informed consent. Survivors were excluded based on the following criteria: score of 11 or greater (indicating risk of dementia) on the Blessed Orientation-Memory-Concentration (BOMC) Test (29), previous history of cancer (except non-melanoma skin cancer), treatment with chemotherapy for non-cancer conditions, neurobehavioral risk factors, including history of neurologic disorder (*e.g.*,

seizure or dementia), alcohol/substance abuse, head trauma requiring hospitalization or evidence of structural brain changes on imaging; and severe psychiatric disorder (*e.g.*, schizophrenia, bipolar disorder). Recruitment was targeted so that approximately 50% had a history of treatment with chemotherapy (MSK=81, COH=79) or no chemotherapy (MSK=87, COH=81) and approximately 50% had a smoking history.

Female non-cancer controls (MSK=77, COH=85) who met the same inclusion criteria (except for diagnosis of cancer) and exclusion criteria were recruited through community advertisement and the Army of Women. Non-cancer controls were frequency matched on age and education. All methods and procedures were approved by the institutional review boards of MSK and COH.

Toward the end of the study, the age at diagnosis was lowered to 55 to increase the number of survivors who had been treated with chemotherapy. Twenty-three participants between 55-60 were recruited (11 treated with chemotherapy, 5 not treated with chemotherapy, and 7 controls).

Cognitive Assessments. Assessments occurred at enrollment and at 8, 16, and 24-month follow-ups. The assessment battery included standardized neuropsychological tests. The neuropsychological measures were categorized into domains based on previous studies (9) and clinical judgement of the neuropsychologists involved with the study (JR, ER, SP) informed by a factor analysis.

Each test score was first standardized (z-score) according to the healthy control group, and then a mean of standardized scores within the domain calculated for each participant. Individual test scores were checked for deviation from a normal distribution, and for those that differed the Box-Cox algorithm (30) was used to determine a suitable power transformation prior to group comparisons and domain score calculations. Table 2 lists the neuropsychological tests and self-report measures administered. Smoking history was assessed utilizing questions from the CDC-Behavioral Risk factor Surveillance System (43).

Biospecimens procurement and APOE **typing.** The main objective was to type the *APOE* gene polymorphisms that, in combination, encode the APOE ε4 isoform. For this, genomic germline DNA was extracted from blood and saliva, and sequenced. DNA extraction, sequencing details, and quality control methods can be found in the Supplementary Material. APOE isoforms ε2, ε3, and ε4 were annotated according to combinations of the *APOE* rs429358 and rs7412 alleles (23, 44–45).

Data Analysis. Both descriptive and inferential statistics were used in this analysis. Retention, baseline demographics such as smoking status, and mean domain scores over time are all described. Group differences with respect to these variables are based on Chi-square and t-tests. The general statistical framework for the main analysis was Bayesian hierarchical linear modeling (HLM), regressing the repeated-measures of cognitive performance domain scores on indicators of survivorship, APOE status, and smoking history, with adjustment for time, age, cognitive reserve (WRAT), and covariates that differed by survivorship at first assessment (Depression and Fatigue, 46). Random per-person intercepts were included to account for within-person variations. Bayesian computation generally involved 4 Markov Chain Monte Carlo (MCMC) chains of 4000 iterations each with the first 2000 as the burn-in iterations,

which yielded a total of 8000 samples from the posterior draws. Convergence of the MCMC chains was evaluated by the recommended $\widehat{R} \leq 1.01$ diagnostic metric (46–47). Standard “weakly informative” priors were used (48), “priors that convey some generally useful information but clearly less than we actually have for the particular problem under study” (49). Posterior median parameter estimates, along with 95% highest density region (HDR) are reported. For modeled group comparisons, the posterior distribution for each participant is estimated, median values for each participant in a group aggregated, and the mean and HDRs calculated from these aggregate distributions. The rstanarm package in R (version 4.0.4) was used for the Bayesian analysis.

Statistical Power: Data in our prior research (21) indicated that an N=160 in each of the three cohorts (and N=126 complete cases), then a simulation approach (50) yielded an estimated statistical power of 90% to test the 3-way interaction between APOE4 status, chemotherapy, and smoking history on post-enrollment changes in neurocognitive outcomes.

Results

Retention for the 490 initially enrolled participants (Figure 1) was high (69% of participants completed the 24-month assessment) and did not differ significantly between survivors and controls (p=0.34). Specifically, 84% of participants completed at least 2 assessments, 73% completed 3, and 59% completed all 4. Completion of the 24-month assessment did not vary significantly by participant age or clinical site but did differ by WRAT (p=0.01) and Time 1 domain scores (all p<0.01); those who completed had slightly higher WRAT and domain scores.

Table 1 provides a description of the sample. Survivors and controls were well matched on education, but survivors not treated with chemotherapy were significantly older than survivors treated with chemotherapy and controls. The majority of participants were retired (72%) or unemployed (5%) and most were married (70%).

Table 1
Participant characteristics by treatment group

	No. of Patients (%)				
Characteristic	Overall	Chemo	No Chemo	Control	p-value
	(n = 490)	(n = 160)	(n = 168)	(n = 162)	
Age, M (SD) [n = 489]	72.6 (6.0)	70.9 (5.1)	74.6 (5.9)	72.1 (6.4)	<.001
Race					
White	415 (85%)	129 (81%)	141 (84%)	145 (90%)	.282
Black	37 (8%)	16 (10%)	15 (9%)	6 (4%)	
Asian/ PI	17 (3%)	8 (5%)	5 (3%)	4 (2%)	
Other	14 (3%)	5 (3%)	5 (3%)	4 (2%)	
Missing	7 (1%)	2 (1%)	2 (1%)	3 (2%)	
Ethnicity					
Hispanic	49 (10%)	18 (11%)	12 (7%)	19 (12%)	.310
Non-Hispanic	432 (88%)	138 (86%)	153 (91%)	141 (87%)	
Missing	9 (2%)	4 (3%)	3 (2%)	2 (1%)	
Education					
Less than college	196 (40%)	67 (42%)	71 (42%)	58 (36%)	.382
College or more	292 (60%)	92 (58%)	96 (57%)	104 (64%)	
Missing	2 (0%)	1 (1%)	1 (1%)	0 (0%)	
Smoking Hx					
Yes	224 (46%)	85 (53%)	74 (44%)	65 (40%)	.049
No	264 (54%)	74 (46%)	93 (55%)	97 (60%)	
Missing	2 (0%)	1 (1%)	1 (1%)	0 (0%)	
Endocrine Therapy					
Ever (n = 314)	234 (75%)	110 (72%)	124 (77%)	NA	.298
At Assessment 1 (n = 319)	80 (25%)	52 (34%)	28 (17%)	NA	<.001
Cancer Characteristics					
ER Positive (n = 297)	237 (80%)	111 (73%)	126 (88%)	NA	.001

	No. of Patients (%)				
PR Positive (n = 292)	190 (65%)	84 (55%)	106 (76%)	NA	<.001
HER2 (FISH) Positive (n = 266)	32 (12%)	25 (17%)	7 (6%)	NA	.006
Tumor size (cm), M (SD)	1.7 (1.4)	2.2 (1.5)	1.2 (1.2)	NA	<.001
Years since diagnosis, M (SD)	8.0 (2.7)	8.1 (2.7)	8.0 (2.6)	NA	.574
Baseline Psych [n = 488]					
FSI Disruption, M (SD)	8.1 (11.0)	9.5 (12.4)	8.9 (10.8)	5.9 (9.3)	.008
STAI State Sum, M (SD)	25.8 (7.3)	26.8 (8.3)	25.5 (6.9)	25.0 (6.6)	.076
CESD Sum, M (SD)	6.8 (7.1)	7.9 (8.8)	6.6 (6.1)	5.9 (5.9)	.043

Genotyping was available for 472 participants. Over one fifth (22%) of the participants were ε4 carriers (23% survivors vs. 18% controls, p=0.21); of these, only 4 were homozygous for ε4. Overall, 46% of participants had a history of smoking (49% survivors vs. 40% controls, p=0.09). Of those with a smoking history, 95% started by the age of 25, with median start age of 17 years. Almost all (85%) of the participants with a smoking history reported quitting more than 10 years prior to study enrollment.

Survivors had significantly lower scores on all domains, even after adjusting for practice effects and covariates (i.e., age, CESD, FSI, WRAT). These group differences persisted over time. Observed deficits in survivors collapsed over assessment time points, as compared to controls, were -0.22, -0.15, and -0.19 for Language, Attention, Processing Speed, Executive Function (APE), and Learning and Memory domains, respectively. Median adjusted estimates for deficits in survivors, as compared to controls, were -0.20, -0.14, and -0.14 points, respectively. However, no significant differences were seen when comparing survivors treated with chemotherapy vs. those not exposed to chemotherapy.

Figure 2 plots the observed average domain scores over time (left panel). A small practice effect due to repeated test administration was observed. At each assessment, domain scores increased, on average, 0.04, 0.02, and 0.14, for Language, APE, and Learning and Memory, respectively. This practice effect did not differ significantly between survivors and controls for APE or Learning and Memory domains, but differed significantly for the Language domain, with healthy controls exhibiting a slightly stronger practice effect compared to controls (p=0.01).

Also plotted in Figure 2, right panel, are the model-estimated median domain scores, stratified by ε4 status and cohorts, collapsed over assessment time points to facilitate the visual inspection of the group differences. As shown in the figure, the ε4+survivor cohort had the lowest average domain scores compared to ε4-survivors or healthy controls of either ε4 status. The overall pattern of the model-estimated medians suggested the possibility of interactions between APOEε4 status and cohorts to

address the first two research questions outlined in the Introduction. Thus, the domain scores were evaluated in a model on survivorship, APOEε4 status, the survivorship and APOEε4 interaction, and controlling for time and covariates, as described above. The APOEε4 status by cohort interaction term addressed whether or not APOEε4 was associated with a greater cognitive impact in cancer survivors than controls. It was evaluated by a contrast between ε4 carriers and ε4 non-carriers across the survivors and controls. The bar plot on the Learning and Memory domain shows that ε4+ survivors had a visibly lower score than ε4- survivors. Specifically, ε4- survivors had a median score of 0.09, whereas ε4+ survivors had a considerably worse median score at −0.11. This translates to a contrast of −0.11 − 0.09 = −0.20 (i.e., ε4+ survivors fared worse than ε4- survivors). By comparison, the difference was smaller in the non-cancer control cohort, where the ε4- controls had a median score of 0.23 and ε4+ controls had a median score of 0.18,, which represented a difference of 0.18 − 0.23 = −0.05. Thus, the two-way interaction involved the scaled contrast of these two differences, which was (−0.20 − (−0.05))/4 = −0.04. The corresponding 95% Bayesian HDI was between (-0.06, -0.01), indicating that as compared to the controls, ε4+ survivors fared worse than ε4-survivors in the Learning and Memory domain, and the posterior confidence on this difference was above 95%. Next, we examined the APE domain (middle bar plot), where a similar detrimental effect was also found in ε4+survivors (median contrast = -0.04, 95% HDR: -0.05, -0.03). The language domain (top) had a stronger effect size (median contrast = -0.05, 95% HDI: -0.07, -0.03), as the ε4 effect was reversed amongst controls. Within both the APE and Learning and Memory domains, although there were large main effects associated with both APOE status and survivorship, the ε4 effect was stronger among survivors even after adjustment for covariates.

We next assessed the 3-way interaction between APOE status, survivorship, and smoking history with adjustment for covariates. This 3-way interaction addressed the additional research question that smoking confers a differential protective effect for ε4+ survivors, who in the analyses above showed a greater vulnerability than ε4- survivors. For instance, in the Language domain, the 3-way interaction contrast had a median of 0.20 (95% HDR: 0.15, 0.24). This contrast effectively represents that the difference between ε4+survivors with a smoking history compared to ε4+ survivors without a smoking history may be significantly different than the difference between ε4+ control with a smoking history compared to ε4+ controls without a smoking history, and this difference of differences was greater than zero above a 95% posterior confidence. Figure 3 provides a visualization of this complex 3-way interaction. Similarly, a statistically reliable effect was found in the APE domain (APE median contrast = 0.10, 95% HDR: 0.07, 0.13) and Learning & Memory (median contrast = 0.10, 95% HDI: 0.04, 0.15), although these effect sizes were only half of that in the Language domain. Note that ε4+ smokers scored visibly greater than ε4+ non-smokers, across survivorship status and domain.

Specific interpretation of the 3-way interaction effects is best assessed via 2-way interactions stratified by survivorship; the compensatory effect of smoking on the effect of APOE ε4 carriage was largely driven by controls. For example, the median estimate for the 2-way interaction for the APE domain among survivors was 0.04 (95% HDI = -0.25, −0.34), while the median estimate among controls was 0.48 (95% HDI = 0.04, 0.92). Specific contrasts between smokers and non-smokers of each ε4+ group are given in Table 2. For controls, smoking had a protective effect on ε4-status nearly twice that of survivors (median for controls:

0.43 vs. median for survivors: 0.23). That is, smoking protected both survivors and controls, but the protective effect was stronger for controls. The difference was even more pronounced for Learning and Memory (median for controls: 0.36 vs. median for survivors: 0.04). Mean scores by APOE ε-status, survivorship, and smoking history, based on the Bayesian HLM models controlling for smoking, WRAT, CESD, and FSI, are depicted in Figure 3.

Table 2
Neuropsychological and Self-Report Measures

Cognitive Reserve	**Wide Range Achievement Test 4 (WRAT4 Reading) (31)**
Language	Category Fluency (32); Boston Naming Test (33), Controlled Oral Word Association Test (34)
Attention, Processing Speed, Executive Function	Digit Symbol (33); Trail Making A and B (35); DKEFS Color-Word Naming (36); NAB Digits Forward and Backward (37-38); NAB Driving Scenes (37-28).
Learning and Memory	NAB List Learning (37-38) Trial 1, Semantic Clustering, List A Immediate, List A Delayed, Long Delay, List B Immediate, New Recognition Index; Logical Memory Part 1 and Story B (WMS-R, 39).
Self-Report Questionnaires	Center for Epidemiological Study – Depression, (40); Spielberger State Anxiety Inventory, (41); Fatigue Symptom Inventory, 42); Smoking history: CDC-Behavioral Risk factor Surveillance System (43).

Discussion

The results demonstrated that survivors performed more poorly on all three domains of cognitive function over time. No significant differences were seen for patients treated with chemotherapy compared to those not exposed to chemotherapy suggesting that multiple aspects of cancer treatment impact cognitive function including long-term endocrine therapy. Finally, the patterns of change of domain scores over time were consistent with the phase shift hypothesis (1, 14–15).

Examination of the impact of APOE isoforms revealed the expected main effect of APOE ε4 carriage on cognitive performance but also a significant two-way interaction between survivors vs. controls and APOE ε-status. APOE ε4+ survivors had significantly lower scores across all three cognitive domains supporting role of ε4 as a risk factor for persistent, post-treatment cognitive decline.

The hypothesis that smoking history confers a protective effect on cognitive performance in ε4 carriers was supported by the 3-way interaction of survivors *vs.* controls, APOE status and smoking history for the APE domain, with a similar pattern for the other two domains that was not quite as strong. The compensatory effect of smoking history in ε4 carriers was most dramatic for controls suggesting that a history of cancer and cancer treatment diminishes the compensatory effect of smoking in ε4 carriers. However, the relative difference between survivors and controls (i.e., survivors performing worse) was maintained.

A compensatory mechanism may explain the protective effect of smoking on cognitive function in ε4 carriers, with smoking/exposure to nicotine correcting a deficit in nicotinic receptor activity in these individuals (24–27). Animal studies have suggested that exposure to nicotine in young animals has a prolonged effect in correcting deficits in the nicotinic receptor, lasting into adulthood (28). In our study, the majority of smokers began smoking as teenagers, which may be a critical period for correcting the nicotinic receptor deficit in ε4 carriers. Studies examining *COMT* genotype further support the role of lower levels of dopamine as a risk factor for post-treatment cognitive decline (51–53). Clearly, we are not advocating smoking in adolescence; however, these findings suggest that interventions that promote nicotinic receptor activity may be effective in improving cognitive function (e.g., nicotine patches, 54-55). These results emphasize the importance of assessing smoking history when examining APOE and cognition and are an example of the complex interactions of age, genetics, environmental exposures and disease history.

However, among cognitively normal elders, Durazzo et al (56) found a that ε4+ former smokers performed worse on a number of cognitive tasks. Further, current smoking has been associated with cognitive aging (57). Taken together, these studies suggest that future research needs to more precisely assess factors that may influence the relationship between smoking, APOE status and cognitive aging e.g., age at smoking onset, pack years of smoking, current vs former smokers, and age at smoking cessation.

Strengths of the study include a large sample of long-term breast cancer survivors who were diagnosed and treated as older adults and matched controls recruited at two comprehensive cancer centers. Further, by studying a survivor group, we were able to purposely recruit survivors with approximately a 50-50 split in exposure to chemotherapy vs no chemotherapy and smoking vs non-smoking history.

Limitations include a sample of primarily Caucasian, highly educated, high socioeconomic status participants; thereby, limiting generalizability. Additionally, there are potential gender differences in the association between APOE and cognitive aging that could not be assessed in this population (58–59). Finally, evidence suggests that other *APOE* gene variants may influence cognitive function (60–61). We will explore the potential contribution of other variants in future analyses.

The results support the long-term cognitive impact of breast cancer diagnosis and treatments on older, disease-free survivors, particularly for ε4 carriers. The results also emphasize the importance of assessing smoking history when examining *APOE* and cognition and support the potential for interventions that enhance nicotinic receptor activity.

Declarations

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Author Contributions: Tim Ahles, Arti Hurria, Irene Orlow, Elizabeth Ryan and James Root contributed to the study conception and design. Statistical analyses were conducted by Yuelin Li and Elizabeth Schofield. Data collection and material preparation were performed by Katrazyna McNeal, Heidi Tan, Vani Katheria, Jessica Vazquez, Sergio Corrales –Guerrero, and Keimya Sadeghi. The first draft of the manuscript was written by Tim Ahles and all authors commented on previous versions. All authors read and approved the final manuscript.

Data Availability: Data will be made available upon reasonable request to the first author in accordance with the guidelines of the National Cancer Institute.

Ethics Approval: All methods and procedures were approved by the institutional review boards of Memorial Sloan Kettering Cancer Center and City of Hope Comprehensive Cancer Center.

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

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Figures

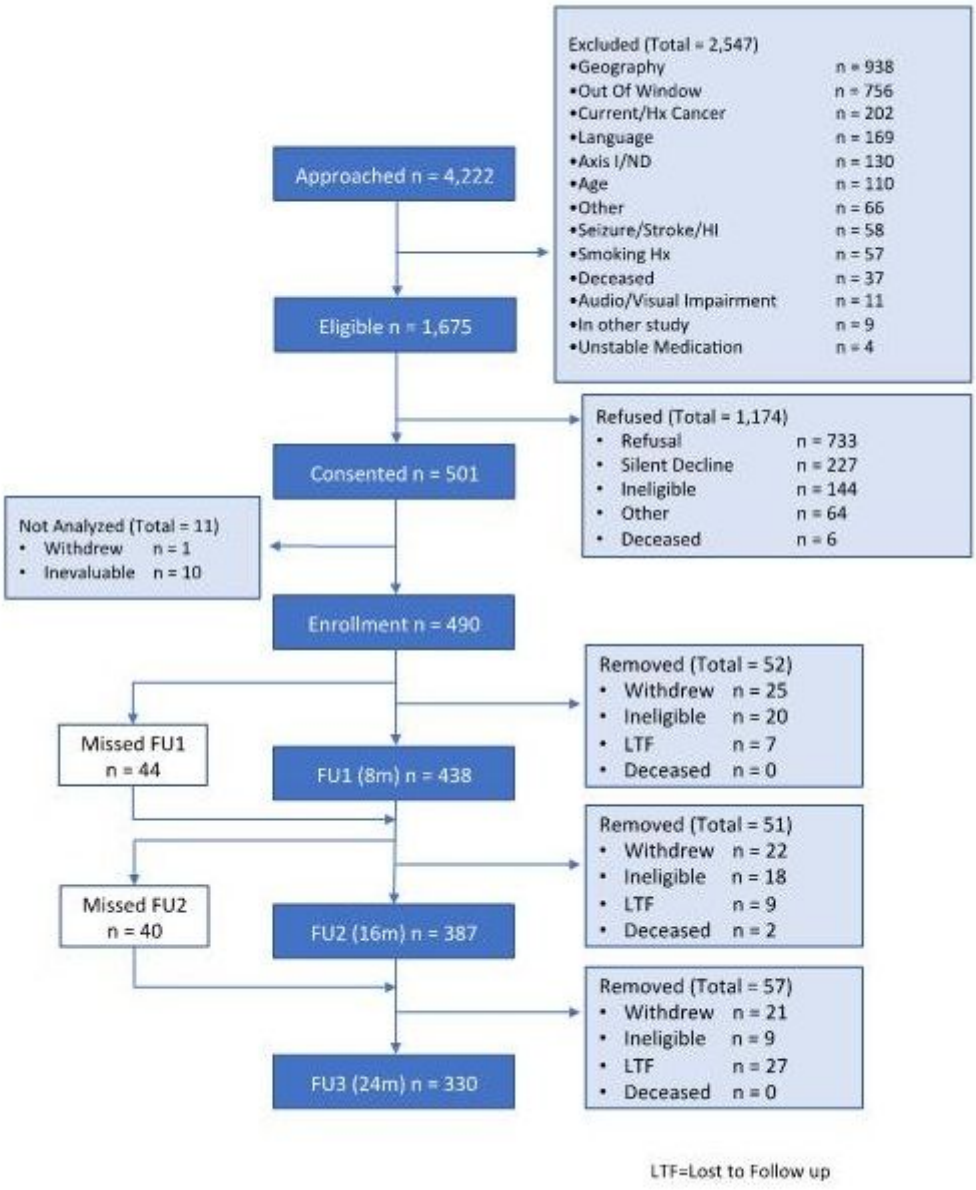

Figure 1

Longitudinal flow diagram

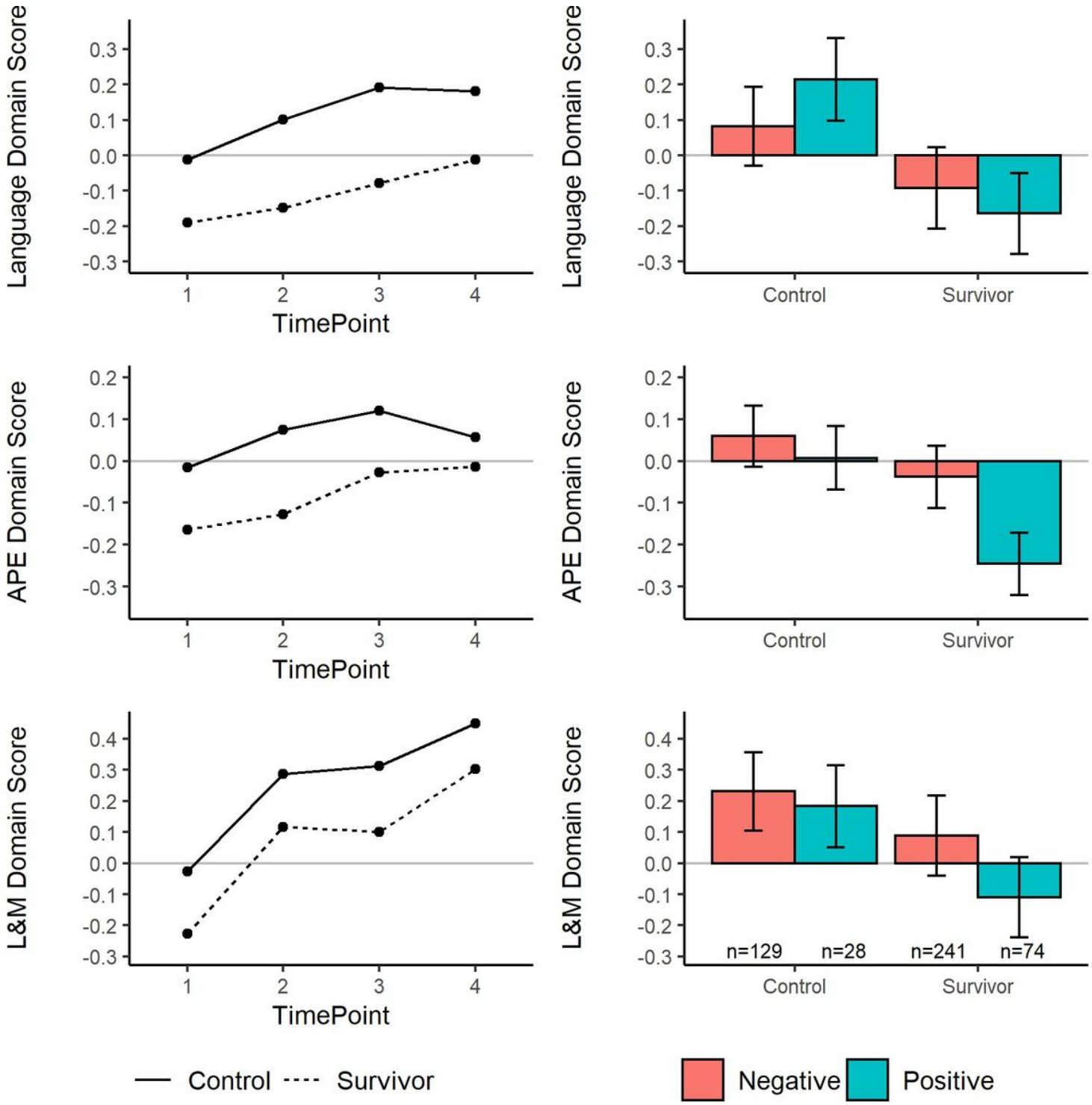

Figure 2

Left Panel. Longitudinal domain scores – survivors vs controls

Right Panel. Median estimated domain scores (50% HDR) by survivorship and e4 status, adjusting for age, WRAT, and CESD sum.

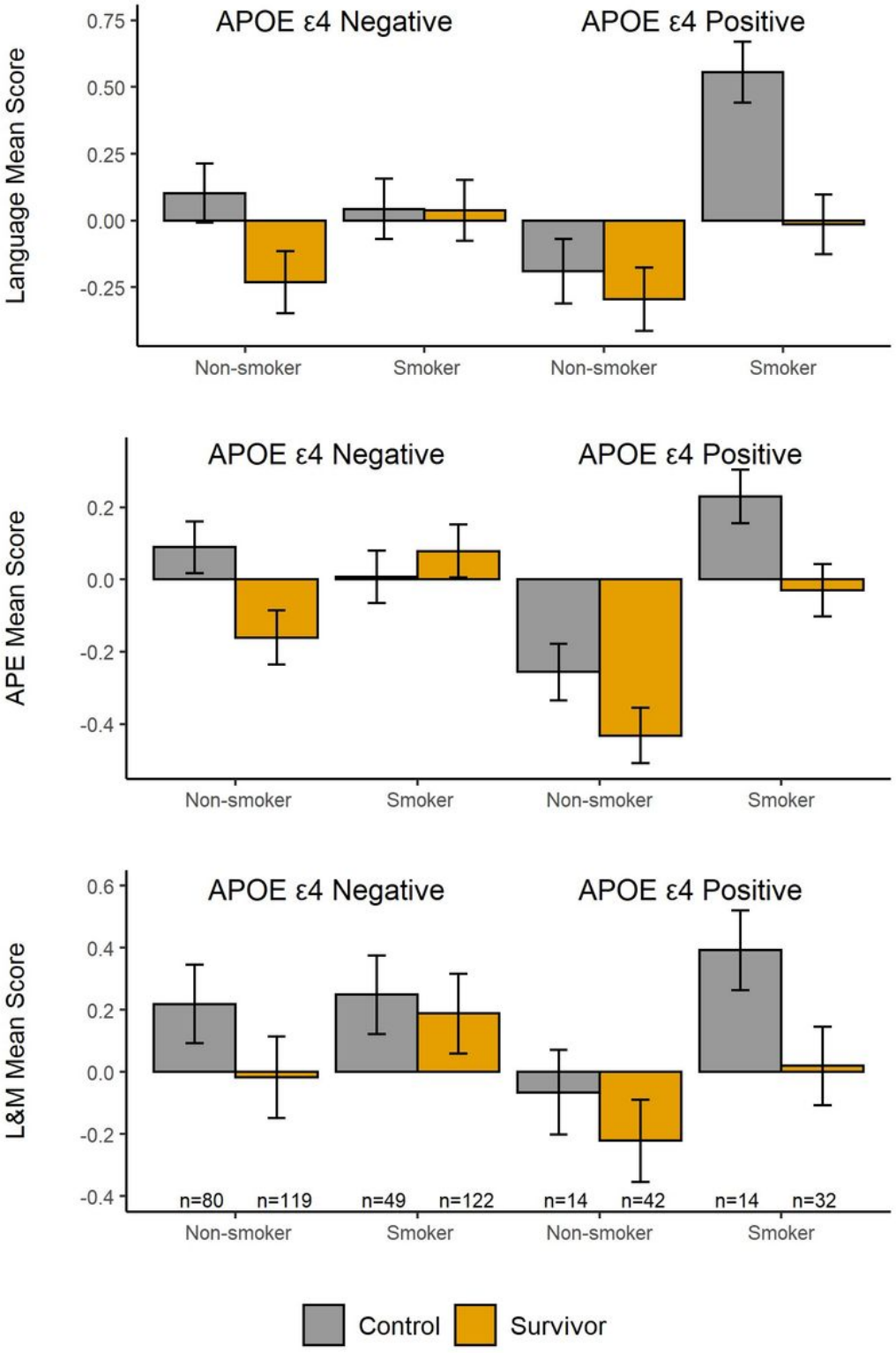

Figure 3

Median estimated domain scores (50% HDR) by smoking history, survivorship, and e4 status, adjusting for age, WRAT, and CESD sum.

Supplementary Files

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- AhlesSupplementaryInformation.docx