Predictors of Improvement after Cognitive Training in Mild Cognitive Impairment: Insights from the Cognitive Training and Neuroplasticity in Mild Cognitive Impairment Trial

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Objective: Cognitive training may benefit older adults with mild cognitive impairment (MCI), but the prognostic factors are not well-established.

Methods: This study analyzed data from a 78-week trial with 107 participants with MCI, comparing computerized cognitive training (CCT) and computerized crossword puzzle training (CPT). Outcomes were changes in cognitive and functional measures from baseline. Linear mixed-effect models were used to identify prognostic factors for each intervention.

Results: Baseline neuropsychological composite z-score was positively associated with cognitive and functional improvements for both interventions in univariable models, retaining significance in the final multivariable model for functional outcome in CPT ($P < 0.001$). Apolipoprotein E e4 carriers had worse cognitive ($P = 0.023$) and functional ($P = 0.001$) outcomes than noncarriers for CPT but not CCT. African Americans showed greater functional improvements than non-African Americans in both CPT ($P = 0.001$) and CCT ($P = 0.010$). Better baseline odor identification was correlated with cognitive improvements in CPT ($P = 0.006$) and functional improvements in CCT ($P < 0.001$).

Conclusion: Baseline cognitive test performance, African American background, and odor identification ability are potential prognostic factors for improved outcomes with cognitive interventions in older adults with MCI. Apolipoprotein E e4 is associated with poor outcomes. Replication of these findings may improve the selection of cognitive interventions for individuals with MCI.

Key Words: mild cognitive impairment, computerized cognitive training, crosswords puzzle training, prognostic factors

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Mild cognitive impairment (MCI) is associated with a higher likelihood of progression to dementia, notably Alzheimer disease (AD).[1] Given the lack of efficacy of most medications in treating MCI, cognitive training interventions have emerged as approaches aimed at maintaining or even improving cognitive and functional abilities.[2]

Computerized cognitive training (CCT) involves computer-delivered standardized tasks or games designed to enhance specific cognitive domains.[3] Due to its safety, applicability, affordability, scalability, and convenience, CCT has received increasing attention in recent years.[4] In some studies, it has demonstrated potential benefits in improving cognitive abilities among older adults with MCI,[5] possibly through stimulating neuroplasticity.[6,7] In contrast, cognitively stimulating leisure activities, such as reading, crossword puzzles, and board games, are aimed at improving cognitive and social functioning.[8] A community-based study showed that engaging in crossword puzzles delayed the onset of memory decline during the preclinical phases of dementia, possibly by enhancing cognitive reserve.[9]

Older adults with MCI exhibit a wide range of demographic, clinical, and biomarker features that are associated with progression to dementia.[10–12] In a recent systematic review, Roheger et al[13] investigated prognostic factors for changes in cognitive test performance in healthy older adults after multidomain cognitive training and concluded that results were inconsistent in different studies. In the Cognitive Training and Neuroplasticity in Mild Cognitive Impairment (COG-IT) trial, participants with MCI were randomized to either CCT or computerized crossword puzzle training (CPT) for 12 weeks of intensive

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sessions, followed by booster sessions, for a total of 78 weeks.[14] The previously published primary analysis showed that, on average, patients randomized to CPT demonstrated superior efficacy compared with CCT on the 11-item Alzheimer Disease Assessment Scale–Cognitive (ADAS-Cog11) and the Functional Activities Questionnaire (FAQ).[15] Using data collected from the COG-IT trial, we also showed that African American participants had better functional outcomes after cognitive training interventions as compared with white participants,[16] and that therapeutic expectancy was not associated with any of the outcomes.[17] In this manuscript, we conducted a comprehensive analysis to explore baseline factors that were predictive of clinical outcomes in the COG-IT study sample. We examined multiple baseline factors, both individually and in combination, as potential predictors because many of these factors are closely interrelated and cannot be considered in isolation.

METHODS

Trial Design and Participants

In the randomized trial, participants were enrolled at 2 sites, Columbia University and Duke University, between November 2017 and November 2021 through clinical referrals supplemented by advertising. The study was approved by the Institutional Review Boards of both sites, and all participants provided informed consent. Participants were aged 55 to 95 years, English-speaking, and met the criteria for MCI that included early MCI and late MCI as defined in the Alzheimer Disease Neuroimaging Initiative studies.[18] Additional inclusion criteria included a Folstein Mini-Mental State Examination score ≥ 23 out of 30 and the availability of an informant to provide information about the participant's functioning. Participants were required to have a home computer with an internet connection to access the study website. Key exclusion criteria encompassed current major psychiatric or neurological disorders, dementia, contraindication to magnetic resonance imaging, and the use of online cognitive games or crossword puzzles twice per week or more in the past year. The trial duration was 78 weeks, with intensive training for the first 12 weeks, followed by booster sessions at specified time points during the remainder of the 78-week trial. The full protocol of the study design, consort diagram, and results of the primary efficacy analysis have been published.[14,15]

Cognitive and Functional Outcomes

We considered 2 outcomes from the published efficacy paper.[15] The cognitive outcome, which was primary, was a change in ADAS-Cog11 total score. ADAS-Cog11 scores range from 0 to 70, with higher scores indicating greater cognitive impairment.[19] ADAS-Cog11 was evaluated at weeks 0, 12, 52, and 78. The functional outcome was the change in the FAQ score as reported by informants. FAQ scores range from 0 to 30, with higher scores indicating greater impairment in instrumental activities of daily living.[20] These activities include paying bills, shopping, remembering appointments, and taking medications. The FAQ assessments were administered at weeks 0, 12, 20, 32, 52, and 78. The primary and secondary endpoints were 78 and 12 weeks, respectively.

Statistical Analyses

De-identified participant data were analyzed. We selected 10 baseline variables known to impact, or likely to impact, participant outcomes with cognitive training intervention. These included sociodemographic variables (age, sex, race, and education), family history of dementia or AD, apolipoprotein E (apoE) e4 genotype, brain imaging measures (magnetic resonance imaging mean cortical thickness and mean hippocampal volume assessed by Freesurfer 6.0[21,22]), baseline test score in the University of Pennsylvania Smell Identification Test (UPSIT[23,24]), and baseline neuropsychological composite z-score. The neuropsychological composite z-score is a standardized composite of 11 tests in the diagnostic neuropsychological assessment, with higher scores indicating better cognitive performance. For the race variable, we differentiated between African American and non-African American participants (white and Asian combined because only 2 participants were identified as Asian). All the assessments were conducted in English. Descriptive statistics for baseline variables were summarized by intervention arms.

We employed a 2-stage approach to identify prognostic factors for changes in ADAS-Cog11 and FAQ scores. Linear mixed-effect (random intercept) models were used to account for the within-subject correlation of the longitudinal measures. For each outcome, the change in measure (baseline minus the study time point) was the dependent variable. Initially, we developed ten individual linear mixed-effect models, each assessing the impact of a single candidate variable on the outcome. This assessment was performed independently of other candidate variables. Each model incorporated the candidate variable, study time point (as a categorical variable), and their interaction as predictors. Subsequently, we used a forward stepwise selection procedure to construct a multivariable model that identified prognostic factors for the outcome while accounting for the impact of all other selected variables. All the candidate variables were eligible for selection. We initiated the process using a linear mixed-effect model, with the study time point as a categorical predictor. This corresponds to a time point-specific intercept model. We then selected a candidate variable and its interaction with the study time point for inclusion in the model if their incorporation resulted in the most improved fit among all candidate variables, based on the Akaike information criterion.[25] This process was iterated to produce a series of models, ranging from a model with only the study time point as a predictor to a full model encompassing all variables and their interactions with the study time point. The model with the smallest Akaike information criterion value was selected as the final model.

As prognostic factors may be different for patients undergoing different interventions, the previous analysis was conducted separately for each intervention arm. No adjustments for multiple testing were made because the analyses were exploratory. Only a few instances of missingness were present in some baseline continuous variables, and missing values were imputed using the intervention-specific sample mean. All statistical analyses were performed using SAS 9.4 and R.

RESULTS

A total of 109 participants met the criteria and were enrolled in the trial. Two participants were excluded because

TABLE 1. Baseline Characteristics of Participants With MCI

covariate	Overall (n = 107)	CCT (n = 51)	CPT (n = 56)
Age (y)	71.2 ± 8.80	71.1 ± 8.54	71.3 ± 9.12
Sex (M)	45/107 (42.1)	17/51 (33.3)	28/56 (50.0)
African American	24/107 (22.4)	11/51 (21.6)	13/56 (23.2)
Education (y)	16.7 ± 3.14	16.6 ± 3.04	16.8 ± 3.25
Family history of dementia or Alzheimer	49/105 (46.7)	28/51 (54.9)	21/54 (38.9)
apoE e4 positive	47/107 (43.9)	26/51 (51.0)	21/56 (37.5)
baseline cortical thickness (mm)	2.35 ± 0.09	2.35 ± 0.1	2.35 ± 0.09
baseline hippo volume (cm^3)	3.04 ± 0.40	2.99 ± 0.42	3.08 ± 0.39
baseline neuropsych composite z-score	0.00 ± 1.00	−0.13 ± 1.00	0.11 ± 0.99
baseline UPSIT score	28.2 ± 7.57	27.9 ± 8.05	28.5 ± 7.18

Mean ± SD was reported for continuous variables, and number/total number (%) was reported for categorical variables.
apoE indicates apolipoprotein E; CCT, computerized cognitive training; CPT, crossword puzzle training; MCI, mild cognitive impairment; UPSIT, University of Pennsylvania Smell Identification Test.

they had not completed any training sessions. A total of 107 participants were included in the final analytical sample, with 56 and 51 participants in the CPT and CCT arms, respectively. The mean and SD for continuous variables and frequencies (%) for categorical variables for the overall sample and each treatment arm are summarized in Table 1. The average age was 71.2 years (SD: 8.8), with 42.1% of the sample being males and 22.4% African American. There were no differences in the distribution of baseline variables between the two intervention arms.

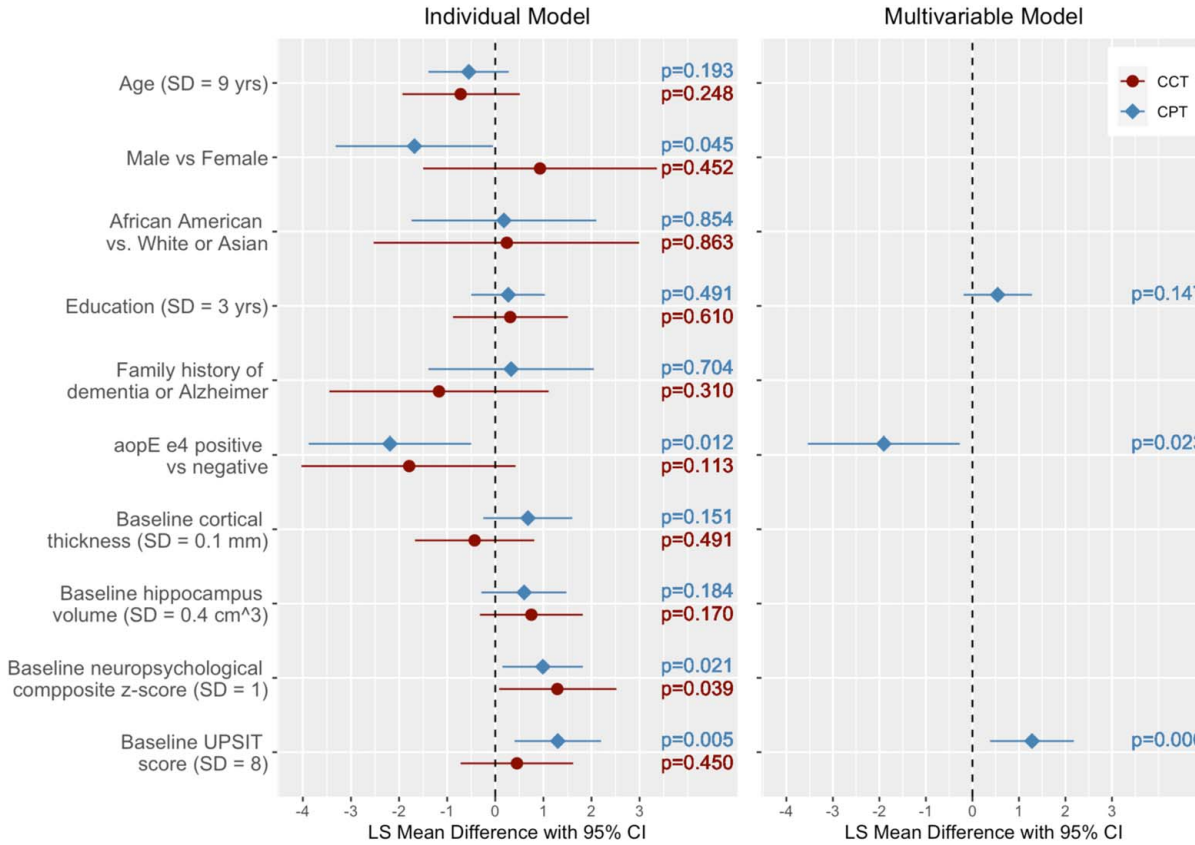

FIGURE 1. Forest plot for change in ADAS-Cog11 at 78 weeks from linear mixed-effect models. Changes in ADAS-Cog11 scores were analyzed as baseline minus the study time point, with positive values indicating improvement. Each individual linear mixed-effect model included the baseline variable, study time point (weeks 12, 52, and 78), and their interaction. A multivariable linear mixed-effect model was constructed using forward stepwise selection. No variables were included in the final multivariate model of the CCT arm. For each categorical variable, the difference in LS mean change in ADAS-Cog11 at 78 weeks between subgroups of the variable is presented. For each continuous variable, the difference in LS means that a one SD increase in the variable was presented. ADAS-Cog11 indicates 11-item Alzheimer Disease Assessment Scale–Cognitive; CCT, computerized cognitive training; LS, least-square. full color online

Change in 11-item Alzheimer Disease Assessment Scale–Cognitive

The least-square (LS) mean differences from the individual and multivariable linear mixed-effect models for changes in ADAS-Cog11 at 78 weeks are depicted in Figure 1. For each categorical variable, the LS mean difference represents the difference in LS mean change in ADAS-Cog11 between the variable subgroups. For each continuous variable, the LS mean difference represents the change in LS mean with a one SD increase in the variable. Larger values of LS mean represent improved cognitive outcomes. Detailed regression coefficient information at 78 weeks and 12 weeks are presented in Supplementary Table S1 (Supplemental Digital Content 1, http://links.lww.com/WAD/A499).

For the CPT arm, in the individual model analysis, males did not improve (LS mean: −0.22, SE: 0.58), whereas females improved (LS mean: 1.46, SE: 0.61) in ADAS-Cog11 at 78 weeks (LS mean difference: −1.68, 95% CI: −3.32 to −0.05, $P = 0.045$). apoE e4 carriers worsened (LS mean: −0.85, SE: 0.70), whereas apoE e4 noncarriers improved (LS mean: 1.34, SE: 0.52) in ADAS-Cog11 at 78 weeks (LS mean difference: −2.19, 95% CI: −3.88 to −0.50, $P = 0.012$). A higher baseline neuropsychological composite z-score (LS mean difference: 0.99, 95% CI: 0.15 to 1.82, $P = 0.021$) and a higher baseline UPSIT score (LS mean difference: 1.3, 95% CI: 0.4 to 2.2, $P = 0.005$) were positively associated with improvement in ADAS-Cog11 at 78 weeks. After the model selection procedure, education, apoE e4 status, and baseline UPSIT score entered the final multivariable model in which apoE e4 carriers remained negatively associated (LS mean difference: −1.9, 95% CI: −3.54 to −0.27, $P = 0.023$) and baseline UPSIT score remained positively associated (LS mean difference: 1.28, 95% CI: 0.38 to 2.18, $P = 0.006$) with improvements in ADAS-Cog11 at 78 weeks. None of the variables was significantly associated with improvement in ADAS-Cog11 at 12 weeks, a secondary endpoint.

For the CCT arm, a higher baseline neuropsychological composite z-score was positively associated with improvement in ADAS-Cog11 at 78 weeks in the individual model analysis (LS mean difference: 1.29, 95% CI: 0.08 to 2.52, $P = 0.039$). Nonetheless, it did not enter the final multivariable model after forward stepwise selection, indicating that the neuropsychological composite z-score itself did not contribute to model improvement compared with a time-specific intercept model. None of the variables were significantly associated with improvement in ADAS-Cog11 at 12 weeks.

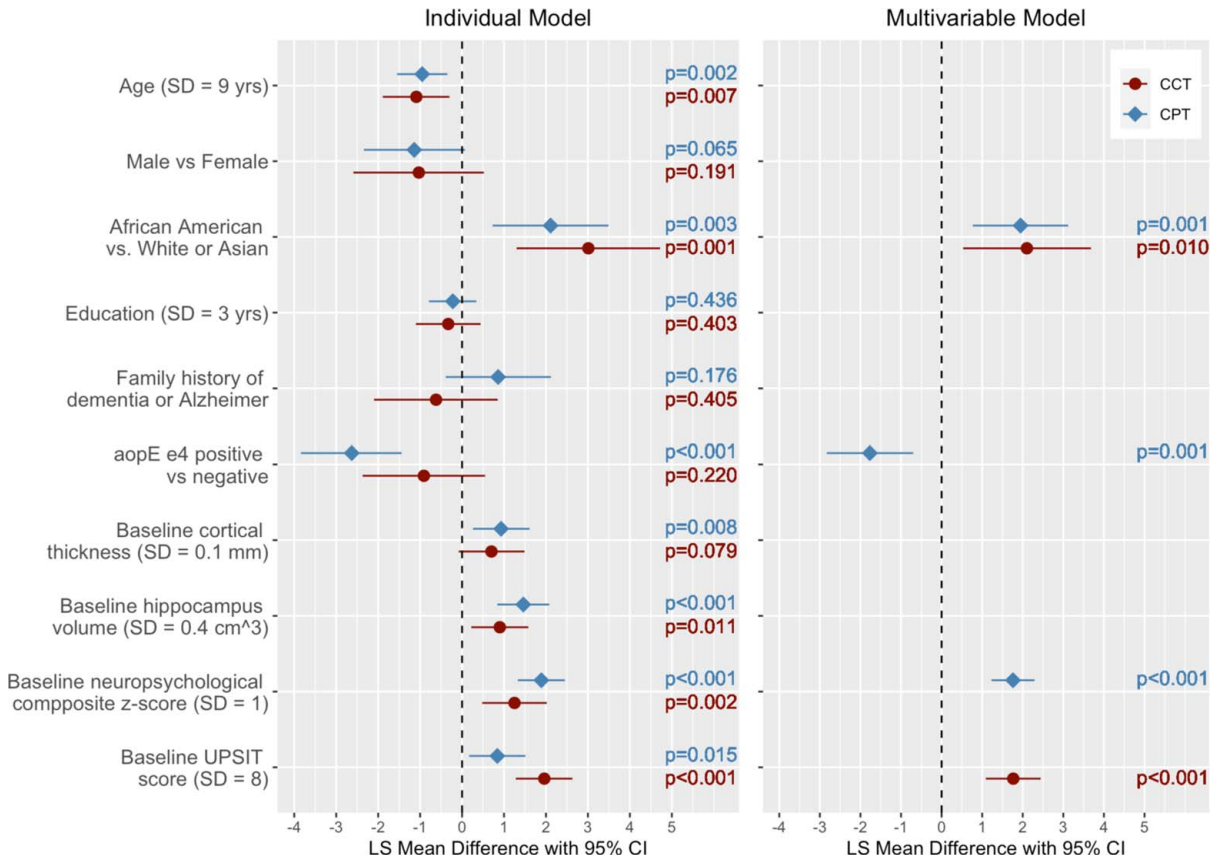

FIGURE 2. Forest plot for change in FAQ at 78 weeks from linear mixed-effect models. Changes in the FAQ were analyzed as baseline minus the study time point, with positive values indicating improvement. Each individual linear mixed-effect model included the baseline variable, study time point (weeks 12, 20, 32, 52, and 78), and their interaction. A multivariable linear mixed-effect model was constructed using forward stepwise selection. For each categorical variable, the difference in the LS mean change in FAQ at 78 weeks between subgroups of the variable is presented. For each continuous variable, the difference in LS means that a one SD increase in the variable was presented. FAQ indicates Functional Activities Questionnaire; LS, least-square. full color online

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Change in Functional Activities Questionnaire

The LS mean differences from individual and multivariable linear mixed-effect models for changes in FAQ at 78 weeks are shown in Figure 2. Larger values of LS mean represent improved functional outcomes. Detailed regression coefficient information for changes in FAQ at 78 weeks and 12 weeks are presented in Supplementary Table S2 (Supplemental Digital Content 1, http://links.lww.com/WAD/A499).

In the individual model analysis of the CPT arm, older age was negatively associated with improvement in FAQ at 78 weeks (LS mean difference: −0.95; 95% CI: −1.55 to −0.35; $P = 0.002$). apoE e4 carriers worsened (LS mean: −2.66, SE: 0.49) more than apoE e4 noncarriers (LS mean: −0.03, SE: 0.37) in FAQ at 78 weeks (LS mean difference: −2.63, 95% CI: −3.84 to −1.44, $P < 0.001$). African Americans (LS mean: 0.62, SE: 0.62) improved, whereas white and Asian Americans worsened (LS mean: −1.50, SE: 0.35) in FAQ at 78 weeks (LS mean difference: 2.11, 95% CI: 0.73 to 3.49, $P = 0.003$). Greater cortical thickness (LS mean difference: 0.93, 95% CI: 0.26 to 1.61, $P = 0.008$), larger hippocampal volume (LS mean difference: 1.46, 95% CI: 0.84 to 2.08, $P < 0.001$), higher baseline neuropsychological composite z-score (LS mean difference: 1.89, 95% CI: 1.33 to 2.45, $P < 0.001$), and higher baseline UPSIT score (LS mean difference: 0.84, 95% CI: 0.17 to 1.51, $P = 0.015$) were positively associated with improvement in FAQ at 78 weeks. After the forward stepwise selection, being African American (LS mean difference: 1.95, 95% CI: 0.77 to 3.12, $P = 0.001$), being apoE e4 positive (LS mean difference: −1.77, 95% CI: −2.83 to −0.70, $P = 0.001$), and having a higher baseline neuropsychological composite z-score (LS mean difference: 1.76, 95% CI: 1.23 to 2.29, $P < 0.001$) were selected into the final model and remained significant. None of the variables were significantly associated with improvements in FAQ scores at 12 weeks.

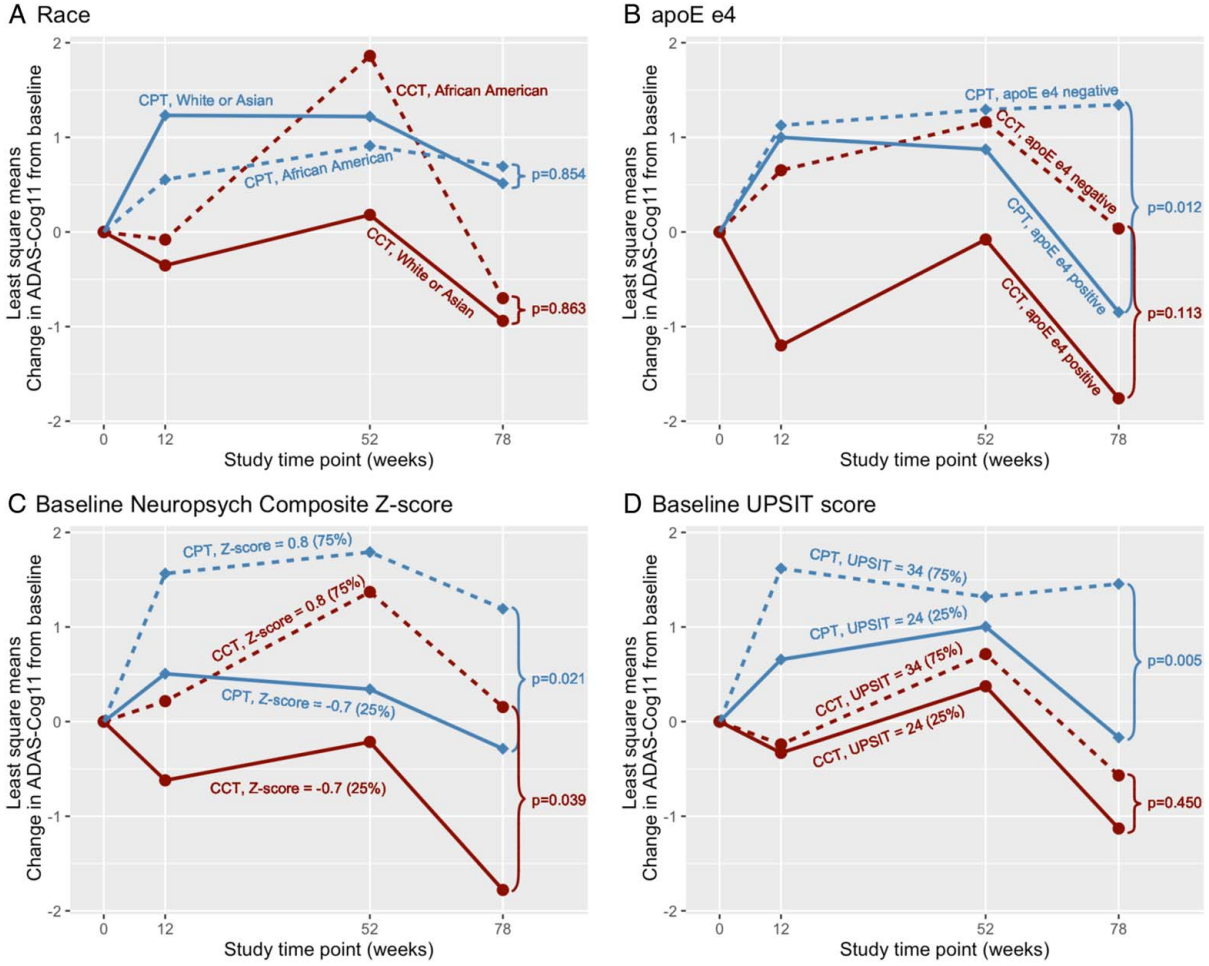

FIGURE 3. Effect of selected predictors on cognitive outcome (change in ADAS-Cog11) by Intervention arms. A, The change in ADAS-Cog11 scores from baseline to week 78 by race. B, The change in ADAS-Cog11 for apoE e4 positive and negative patients. C, The change in ADAS-Cog11 scores at the 25th and 75th percentiles of baseline neuropsychological composite z-scores. D, The change in ADAS-Cog11 scores at the 25th and 75th percentiles of the baseline UPSIT scores. The 25th and 75th percentiles, representing the mid-points of the lower and upper 50% of the data, respectively, were selected to depict subgroups with differing levels of continuous variables. LS means from individual linear mixed-effect model analysis are represented on the *y*-axis, with positive values indicating improvement. ADAS-Cog11 indicates 11-item Alzheimer Disease Assessment Scale–Cognitive; apoE, apolipoprotein E; LS, least-square; UPSIT, University of Pennsylvania Smell Identification Test. full color online

In the individual model analysis of the CCT arm, older age (LS mean difference: −1.09, 95% CI: −1.89 to −0.3, P = 0.007) was negatively associated with improvement in FAQ at 78 weeks. African Americans (LS mean: 0.32, SE: 0.78) improved, whereas white and Asian Americans worsened (LS mean: −2.69, SE: 0.41) in FAQ at 78 weeks (LS mean difference: 3.01, 95% CI: 1.3 to 4.72, P = 0.001). A larger hippocampal volume (LS mean difference: 0.9, 95% CI: 0.22 to 1.58, P = 0.011), higher baseline neuropsychological composite z-score (LS mean difference: 1.25, 95% CI: 0.48 to 2.02, P = 0.002), and higher baseline UPSIT score (LS mean difference: 1.96, 95% CI: 1.28 to 2.63, P < 0.001) were positively associated with FAQ improvement at 78 weeks. After the forward stepwise selection, being African American (LS mean difference: 2.1, 95% CI: 0.53 to 3.68, P = 0.010) and having a higher baseline UPSIT score (LS mean difference: 1.77, 95% CI: 1.09 to 2.44, P < 0.001) entered the final multivariable model and remained significantly positively associated with improvements in FAQ at 78 weeks. None of the variables were significantly associated with improvements in FAQ scores at 12 weeks.

DISCUSSION

The aim of the present study was to identify factors predicting changes in cognitive and functional outcomes after CPT or CCT in older participants with MCI. In summary, we found four potentially significant prognostic factors in our final statistical model. To better visualize the findings, the effects of these four predictors on cognitive and functional outcomes over time are summarized in Figures 3 and 4, respectively.

Our findings revealed that better cognitive function at baseline, as measured by the neuropsychological composite z-score, was positively linked to improvements in both cognitive and functional outcomes in each intervention arm. This association retained its significance in the final multivariable model for functional outcomes (FAQ) in the CPT

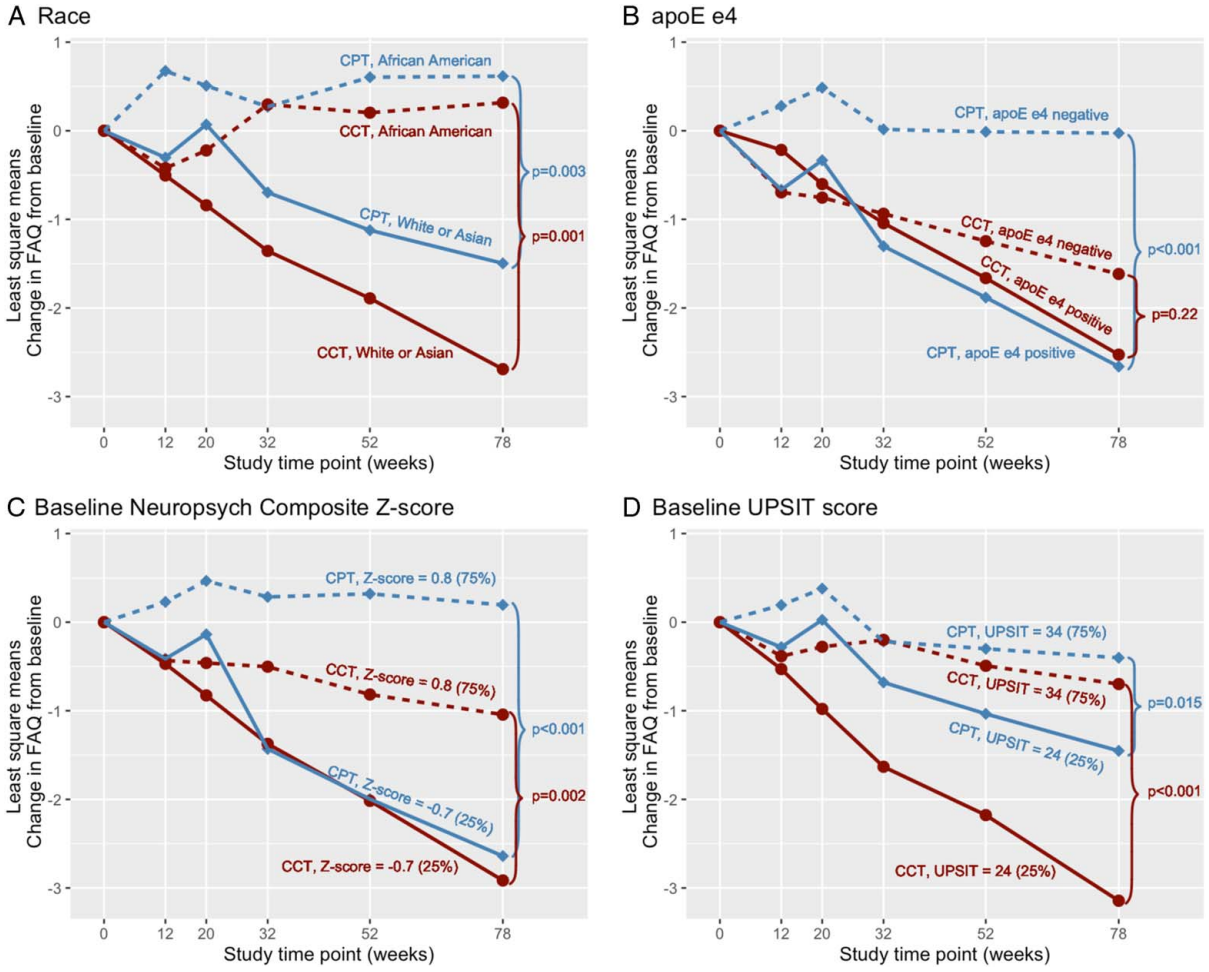

FIGURE 4. Effect of selected predictors on functional outcome (change in FAQ) by Intervention arms. A, The change in FAQ from baseline to week 78 by race subgroup. B, The change in FAQ by apoE e4 subgroup. C, The change in FAQ scores at the 25th and 75th percentiles of baseline neuropsychological composite z-scores. D, The change in the FAQ at the 25th and 75th percentiles of the baseline UPSIT scores. The 25th and 75th percentiles, representing the mid-points of the lower and upper 50% of the data, respectively, were selected to depict subgroups with differing levels of continuous variables. LS means from individual linear mixed-effect model analysis are represented on the *y*-axis, with positive values indicating improvement. apoE indicates apolipoprotein E; FAQ, Functional Activities Questionnaire; LS, least-square; UPSIT, University of Pennsylvania Smell Identification Test. full color online

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arm. This implies that early intervention with CPT in patients with MCI with relatively better cognitive abilities may yield more favorable outcomes. Notably, this result aligns with a previous randomized controlled trial that compared an early cognitive intervention (ie, memory rehabilitation) with a waitlist approach for participants with amnestic MCI.[26] Our findings are consistent with that report and suggest that early cognitive interventions at the MCI stage may contribute to improved cognitive outcomes in individuals with this disorder.

ApoE e4 carriers had worse cognitive and functional outcomes than apoE e4 noncarriers among patients with MCI receiving CPT. This association, although still evident, did not reach statistical significance in the CCT arm. The apoE e4 genotype has been widely recognized as the most consistent genetic risk factor for AD.[27,28] A previous study demonstrated that apoE e4 noncarriers exhibited better outcomes in certain cognitive domains compared with apoE e4 carriers after cognitive training among healthy older adults.[29] This underscores the relevance of genetic factors in influencing the response to cognitive interventions and suggests the need for personalized approaches that consider individual genetic profiles in the design and implementation of cognitive training interventions.

The observed greater benefit in functional outcome (on the FAQ) among African American participants in both the CPT and CCT arms, as opposed to non-African American participants, is a noteworthy finding in our study. Although in our sample, African American participants were, on average, seven years younger than their White and Asian counterparts (mean ± SD = 65.7 ± 5.6 vs 72.8 ± 9.0, $P < 0.001$), indicating a potential confounding effect of age, the significance of race persisted even after accounting for age differences. As race was selected into the final multivariable model, but age was not, following a forward stepwise selection procedure, the differential functional benefit among African American participants may indeed be genuine. Our findings align with a substantial pooled population cohort study, which highlighted that African American individuals exhibited significantly slower declines in executive function compared with white participants.[30] Another possible reason is that African American informants tend to rate participant FAQ lower compared with other racial/ethnic groups. A detailed discussion of this issue is provided in our previously published paper.[16]

Our study also demonstrated that better odor identification at baseline, measured by the UPSIT score, was positively correlated with cognitive outcomes in the CPT arm and functional outcomes in the CCT arm. This association was significant for functional outcomes in the CPT arm when UPSIT was considered individually, but UPSIT was not selected for the final multivariable model. Notably, clinical and community-based studies have shown that impaired odor identification, which is a consequence of neurodegeneration in olfactory brain pathways, predicts faster cognitive decline among dementia-free older adults.[31–33] For patients with MCI, research has shown that odor identification deficits predict the transition from MCI to AD.[34] Conversely, better cognitive test performance and odor identification performance, both of which are indicators of better brain functioning and resilience, increased the likelihood of improvement with cognitive training interventions in COG-IT.

CONCLUSION

In summary, our preliminary findings suggest that baseline cognitive test performance, apoE e4 genotype, race, and baseline odor identification ability are potential prognostic factors for improved cognitive and functional ability with cognitive training interventions in older adults with MCI, with more consistent effects in CPT than CCT. The findings were drawn from a rigorously conducted clinical trial with a long study duration and a relatively low attrition rate. However, there are also some limitations, including a relatively small sample size, an average high level of education that restricts generalizability, and the lack of a control arm in the trial. Therefore, our findings should be interpreted with caution. Investigations in other clinical trials of cognitive training interventions are required to replicate these findings.

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