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APOE ε4, an Alzheimer's disease susceptibility allele, and smoking cessation

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Abstract

Possessing an *APOE* ε4 allele, advanced age, and smoking are risk factors for Alzheimer's disease and cognitive decline. Deficits in cognitive function also increase risk for smoking relapse. Data from 917 adult smokers of European ancestry were pooled across three randomized trials of smoking cessation. We examined whether smokers who carry at least one ε4 allele (n=252) have more difficulty quitting smoking compared to noncarriers (n=665), and whether age moderated this association. The genotype by age interaction was significant for 7-day point-prevalence abstinence rates (p=0.04) and time to 7-day failure (p=0.03). Among smokers over age 60, ε4 carriers were less likely to quit (OR=0.27, p=0.018) and relapsed more quickly (HR=3.38, p=0.001) compared to noncarriers. The genotype association with relapse was non-significant among younger smokers. An increased understanding of the underlying pathophysiological mechanisms of this association could facilitate the development of targeted therapies for smokers with increased risk for cognitive decline.

Keywords

smoking; smoking cessation; relapse; nicotine; cognition; *APOE*

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CONFLICTS OF INTEREST

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Chronic nicotine exposure produces neuroadaptive changes that make quitting smoking difficult.[1, 2] Persistent smoking is motivated in part by the positive rewarding effects of acute nicotine delivery, including cognitive enhancing effects.[2, 3] In contrast, quitting smoking produces deficits in executive cognitive function.[4] These deficits encompass a broad range of cognitive processes in both animals and humans, including deficits in attention,[5, 6] learning,[7, 8] memory,[9-12] and behavioral control.[13, 14] Importantly, deficits in executive cognitive function play an important role in smoking relapse in the general population of smokers[15, 16] as well as clinical populations.[17, 18]

Evidence linking cognitive function and smoking relapse risk suggests that smokers who are susceptible to cognitive impairment may have greater difficulty quitting smoking.[19] While not yet studied as a smoking relapse susceptibility gene, a relatively common variant in the Apolipoprotein E (*APOE*) gene, widely studied for its role in cognitive aging, would be a plausible risk marker. The functional *APOE* ε4 allele is associated with increased risk of developing Alzheimer's disease, with a two to three-fold increase for ε4 heterozygotes and 12 to 14-fold increase for ε4 homozygotes.[20] Prior to the emergence of clinical symptoms of Alzheimer's disease, healthy ε4 carriers exhibit deficits in executive cognitive function, memory, and perceptual speed that are qualitatively similar to those experienced by abstinent smokers.[21-23] Compared to noncarriers, healthy ε4 carriers also exhibit changes in brain structure[24-26] and function[27-29] that may reduce cognitive control over behaviors such as smoking. Thus, it is plausible that otherwise healthy ε4 carriers may be prone to "self-medicate" cognitive symptoms by smoking.[30]

Converging lines of evidence for nicotine's pro-cognitive effects, the role of cognitive deficits in smoking relapse, and the presence of cognitive deficits in healthy *APOE* ε4 allele carriers suggest the hypothesis that the *APOE* genotype may influence the ability to quit smoking. We tested this hypothesis in a sample of 917 smokers who participated in three independent smoking cessation clinical trials: a randomized placebo-controlled trial of bupropion, a randomized open-label trial of nicotine patch vs. nicotine spray, and an open-label trial of nicotine patch.[31, 32] We predicted that smokers with at least one ε4 allele would have reduced abstinence rates and shorter time to relapse. Based on evidence that the deleterious effects of the ε4 allele on cognition in healthy carriers tend to become more pronounced with advancing age,[33] age was tested as a moderator of genetic associations. Thus, we predicted that older ε4 carriers would be at the greatest risk for relapse. An understanding of the relationship of the *APOE* ε4 allele to smoking relapse could advance our understanding of underlying neurobiological mechanisms and point to novel therapeutic targets for medications development.

METHODS AND MATERIALS

Data from participants (n=917) across the independent clinical trials were pooled for analysis. The three trials were comparable with respect to the ascertainment methods, eligibility criteria, and study procedures. The analyses were limited to smokers of European ancestry; prior analyses of ancestry informative markers in these trials revealed no evidence for significant ethnic admixture that could bias genetic association analyses.[32, 34, 35]

Participants and Procedures (Study 1; Bupropion Placebo Controlled Trial)

Treatment-seeking smokers responding to advertisements were screened for eligibility from April 1999 to October 2001 at Georgetown University (Washington, DC) and SUNY Buffalo (New York). Inclusion criteria were: ages 18-65 and a smoking rate of >10 cigarettes a day for the previous 12 months. As is often the convention in phase III pharmacotherapy trials in nicotine dependence, individuals with comorbid diagnoses were excluded due to safety concerns and interacting psychoactive medications. Specifically, we excluded for a history of DSM-IV Axis I psychiatric disorders (except nicotine dependence), seizure disorder, current use of psychotropic medications, and pregnancy or lactation. There were 555 participants included in the intent-to-treat analysis, including 436 of self-reported European ancestry. Of the 404 participants for which DNA was available, *APOE* genotyping was completed for 383 participants (failed SNP assays and DNA samples with low call rates were removed from the data set after confirming replicate concordance). Of the 383 eligible participants, 55% were female, 47% were college graduates, the average age was 44.5 (SD=11.6) years, and baseline depression scores were 12.3 (SD=8.5). On average, participants smoked 22 cigarettes per day (SD=9.3) and were moderately nicotine dependent (mean FTND=5.2 [SD=2.1]). There were 180 (47%) participants randomized to the placebo condition, and 203 (53%) to the bupropion condition (Supplement 1A).

The study was approved by the institutional review boards from both universities (Clinicaltrials.gov registration number NCT00322205). Participants at both sites received identical assessments of demographics, smoking rate, and nicotine dependence (FTND),[36] and provided a 40-ml blood sample for genotyping. In this double-blind placebo controlled study, participants were randomized to receive 10 weeks of bupropion or matched placebo. Bupropion was administered according to the standard dosing regimen (150 mg/day for the first three days, followed by 300 mg/day). Participants were instructed to quit on a target quit date two weeks after initiating treatment. All participants received seven sessions of standardized cessation counseling during the medication phase. Self-reported smoking was assessed using the timeline follow-back procedure.[37] The primary outcome was biochemically verified (saliva cotinine ≤15 ng/ml) 7-day point-prevalence abstinence at the end of treatment (EOT) and 6-months post-TQD.

Participants and Procedures (Study 2; Transdermal Nicotine Therapy Open-Label Trial)

Treatment-seeking smokers were screened at the University of Pennsylvania (Philadelphia, PA) from 2004 to 2008, using methods and inclusion criteria similar to those described above. In the full cohort of 568 trial participants, there were 478 smokers of self-reported European ancestry. Of these, DNA was available for 443 participants and *APOE* genotyping was completed for 418 (failed SNP assays and DNA samples with low call rates were removed from the data set after confirming replicate concordance). Of the 418 eligible participants, 42% were female, 35% were college graduates, the average age was 45.2 (SD=10.5) years, and baseline depression scores were 8.5 (SD=6.6). On average, participants smoked 22 cigarettes per day (SD=8.9) and were moderately nicotine dependent (mean FTND=5.3 [SD=2.2]). In total, 204 (49%) participants were randomized to the extended nicotine patch condition, and 214 (51%) to the standard nicotine patch condition (Supplement 1B).

The study protocol was approved by the University of Pennsylvania institutional review board (Clinicaltrials.gov registration number NCT00364156). Participants completed pretreatment assessments identical to those described above. After a pre-quit counseling session, transdermal nicotine-patch therapy was initiated on the target quit date and continued for eight weeks. For the following 16 weeks, those in the extended treatment condition continued using nicotine patches while those in the standard treatment condition were given placebo patches. All participants received three sessions of behavioral counseling during the treatment period. The primary outcome was 7-day point-prevalence abstinence at the end of eight-week treatment (EOT) and at 6-month follow-up. Self-reported smoking for the seven days prior to each follow-up survey was biochemically verified using exhaled breath carbon monoxide (CO).

Participants and Procedures (Study 3; Nicotine Replacement Therapy Open-Label Trial [Patch vs. Spray])

Treatment-seeking smokers were recruited at Georgetown University and the University of Pennsylvania (Philadelphia, PA), from February 2000 to August 2003, using methods and inclusion criteria similar to those described above. In the full cohort of 600 participants, there were 397 smokers of self-reported European ancestry. Of these, DNA was available for 191 participants and *APOE* genotyping was completed for 116 participants (failed SNP assays and DNA samples with low call rates were removed from the data set after confirming replicate concordance). Of the 116 eligible participants, 43% were female, 61% were college graduates, the average age was 46.8 (SD=11.6) years, and baseline depression scores were 12 (SD=8.4). On average, participants smoked 24 cigarettes per day (SD=8.8) and were moderately nicotine dependent (mean FTND=5.5 [SD=2.2]). In total, 54 (47%) participants were randomized to the nicotine patch condition, and 62 (53%) to the nicotine spray condition (Supplement 1C).

The study was approved by the institutional review boards from both universities (Clinicaltrials.gov registration number NCT00326781). The procedures and outcome assessments were identical to those described above, except that participants were randomized to nicotine patch or nicotine nasal spray. Abstinence criteria were identical to those described above.

Measures

Genotyping—*APOE* ε2, ε3, and ε4 alleles were determined from allelic variants of two single nucleotide polymorphisms (SNPs; NCBI SNPs rs429358 and rs7412) which are differentiated on the basis of an amino acid substitution at positions 112 and 158. The ε2 allele is characterized based on the presence of cysteine at both sites, the ε3 allele has cysteine at site 112 and arginine at site 158, and the ε4 allele has arginine at both sites.[38] Genotyping was completed using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). PCR was performed with 2.25 ng of DNA, 2.5 μl of ABI Taqman Universal Mastermix, 0.125 μl of water, and 0.125 μl of 40X Assay on Demand SNP Assay for the *APOE* variant (ABI, Foster City, CA). The 5-μl reactions were performed in a 384-well plate (ABI). The plates were scanned utilizing the Allelic Discrimination End-Point Analysis on the ABI Prism 7900HT Sequence Detection System.

The allelic discrimination data were analyzed by the AutoCall algorithm of the SDS v2.1 Software (ABI).

Covariates—Sex, education, age, and nicotine dependence (FTND)[36] were assessed at baseline. The Center for Epidemiological Studies Depression (CES-D) measure[39] was used to assess baseline depression symptoms.

Outcomes—In accordance with the guidelines of the Society for Research on Nicotine and Tobacco,[40] we examined 7-day point-prevalence abstinence (EOT and 6-months), defined as self-reported abstinence (not even a puff) for each of the seven days immediately prior to the follow-up point and biochemically verified by a cotinine reading of ≤15 ng/ml (Study 1) or a CO reading of ≤10 ppm (Studies 2 and 3). Consistent with these recommendations, participants who failed to provide a sample for biochemical verification, or those exceeding the detection threshold, were coded as non-abstinent. Time to 7-day failure censored at six months was also examined. Relapse was defined as seven or more consecutive days of smoking, and considered to have occurred on the first day of the smoking interval.[40] Participants lost to follow-up were considered to be smokers, and time of relapse was recorded as the time of last contact.

Exploratory outcome—Self-reported inattention symptoms[41] were assessed at baseline in all three trials, and on the target quit date in the bupropion trial and the NRT (patch vs. spray) trial. This measure was used as a proxy for cognitive deficits, based on evidence that smokers with inattention symptoms are more likely to "self-medicate" with nicotine.[42]

Statistical analysis—Preliminary analyses were conducted to examine differences between ε4 carriers and noncarriers on baseline demographic and smoking characteristics using chi-square or one-way ANOVA. Because data were pooled across studies, treatment arm was controlled for in all models. The primary outcome, point-prevalence abstinence, was analyzed by longitudinal logistic regression, estimated using generalized estimating equation methods. *APOE* ε4 carrier status was dichotomized as at least one ε4 allele (ε4 carrier) versus no ε4 alleles (ε4 noncarrier). Because advanced age is a risk factor for cognitive decline, models were constructed that examine its effects independently and combined with *APOE* on the primary and secondary outcomes. Thus, the model included *APOE* ε4 carrier status (ε4 noncarrier = 0, ε4 carrier = 1), age, treatment arm, timepoint, and the genotype × age interaction. The treatment arm × timepoint and genotype × treatment arm interactions were not included because they were not significant and did not alter the genotype by age interaction. Sex, nicotine dependence, education, and baseline depression were included as covariates. Cox regression models were used to analyze time to 7-day failure. To illustrate the genotype by age interaction, the data were stratified into five age groups and the genotype effect was tested within each age group. To test whether ε4 carriers and noncarriers differed at baseline in terms of cognitive deficits, linear regression models were used to test for the presence of a genotype by age interaction on baseline inattention symptoms in the pooled sample. A similar regression model tested age by genotype effects on inattention symptoms reported on the target quit date in the bupropion trial and the NRT open-label trial, controlling for baseline inattention symptoms. Both models included the

covariates described above. An adjusted p-value of 0.038 was used to account for testing two outcomes with a correlation of r=0.61. All analyses were conducted using STATA 12.0 (Stata Corporation, College Station, TX).

RESULTS

Participant characteristics

In the pooled sample (N=917), there were 9 (1%) ε2/ε2, 100 (11%) ε2/ε3, 24 (2.6%) ε2/ε4, 556 (60.6%) ε3/ε3, 214 (23.3%) ε3/ε4, and 14 (1.5%) ε4/ε4. *APOE* genotypes were in Hardy-Weinberg equilibrium for the pooled sample (p=0.14), and for the three individual clinical trials (all p values >0.10). Across the three trials, ε4 carrier status did not differ between those who received placebo compared to active treatment (p=0.65). Table 1 depicts the descriptive data by *APOE* ε4 carrier status (ε4-[n=665] vs ε4+ [n=252]) for the pooled sample. There were no genotype differences within each of the five age categories for tobacco use characteristics or demographics (ps>0.09).

Abstinence

Overall, 275 (30%) participants met criteria for 7-day point prevalence abstinence at EOT and 223 (24.3%) were abstinent at six months. Using an adjusted p-value (p=0.038), there was a marginal genotype by age interaction, independent of treatment arm and follow-up time point, for quit rates (OR=0.972, 95% CI= 0.946-0.999, p=0.04) and a significant interaction for time to 7-day failure (HR=1.02, 95% CI= 1.002-1.04, p=0.029). To illustrate the interacting effects of genotype and age on quit rates, the data were stratified into five age categories (18-30 years, 31-40 years, 41-50 years, 51-60 years, and over 60 years) and the genotype effect was tested within each age group. In the oldest age group, ε4 carriers were significantly less likely to quit (OR=0.27, 95% CI= 0.092-0.798, p=0.018; Figure 1) and have shorter time to relapse (HR=3.38, 95% CI= 1.62-7.05, p=0.001; Figure 2) compared to ε4 noncarriers. There were no significant genotype effects in other age groups (ps>0.05). Education was not significantly related to either outcome (ps>0.33). The pattern of results in the NRT trials and the bupropion trial were very similar (Figure 3).

Inattention symptoms

Genotype groups were comparable at baseline with respect to inattention symptoms (ps>0.4). However, a significant genotype by age interaction was observed on the target quit date in the placebo group (p=0.046). Controlling for baseline symptoms, older ε4 carriers reported significantly more inattention symptoms at target quit date compared to older ε4 noncarriers (p=0.044). In contrast, younger ε4 carriers did not differ from younger ε4 noncarriers (p=0.29). There were no genotype effects in the groups receiving active treatment with bupropion or NRT (ps>0.25).

DISCUSSION

In this sample of treatment seeking smokers, *APOE* gene variation was associated with the ability to quit smoking and time to relapse in an age dependent manner. Among older smokers, *APOE* ε4 carriers had a significantly increased risk of relapse and relapsed more

quickly. To our knowledge, this is the first study to examine the relationship of *APOE* genotype with smoking relapse.

There are a number of plausible neurobehavioral mechanisms that may explain these findings. Binding to neuronal nicotinic acetylcholine receptors (nAChRs), nicotine enhances cholinergic signaling and synaptic plasticity, effects thought to contribute to its cognitive enhancing effects.[1, 43] Effects of acute nicotine delivery may be particularly rewarding for older *APOE* ε4 carriers given their susceptibility to cognitive deficits.[22, 23, 44, 45] Supporting this hypothesis, data from a recent placebo-controlled trial show that a low dose of transdermal nicotine improves executive cognitive function in non-smoking individuals with mild cognitive impairment, an effect that appears more pronounced among ε4 carriers.[46] It should be noted, however, that we did not observe genotype differences in cognitive symptoms of inattention at baseline, although this may be attributable to the fact that all participants were smoking at that assessment. Alternatively, it is possible that older *APOE* ε4 carriers experience more profound withdrawal-related cognitive deficits than noncarriers, an effect that could increase smoking relapse risk.[15, 18, 42] Although the clinical trials reported here did not include objective cognitive assessments, we conducted exploratory analyses of self-reported cognitive symptoms of inattention[41] on the target quit date within the bupropion and open-label NRT trials for which target quit date measures were available. Among smokers receiving placebo within the bupropion trial, there was a genotype by age interaction suggesting that older (unmediated) ε4 carriers reported more inattention symptoms on the target quit date compared to older ε4 noncarriers, controlling for baseline symptoms. No such interactions were observed among smokers receiving active treatment in these trials.

It is also possible that smokers carrying an *APOE* ε4 allele have limitations in cognitive resources that are essential to exert behavioral control over cravings and impulses to smoke. For example, relative to noncarriers, healthy ε4 carriers exhibit alterations in neural activation in the prefrontal cortices while performing cognitive tasks,[21, 47] as well as decreases in functional connectivity.[48] Age-related cortical thinning observed among ε4 carriers[26] may also contribute to a reduction in cognitive control resources required to maintain smoking abstinence. Interestingly, these alterations in cognition and brain function are qualitatively similar to those observed in abstaining smokers.[49-52]

Although these findings were observed in a large sample of treatment-seeking smokers, there are some limitations of this work. Although we controlled for education level, we did not screen for dementia, which may be important factors to consider. Using inattention symptoms as a proxy for cognitive impairment, we did not observe differences between ε4 carriers ε4 noncarriers at baseline, but it is possible that smoking masked these differences. In addition, although our sample ranged in age from 19 to 82 years old, the majority of participants were between the ages of 40 and 60. Thus, more work needs to be done to examine smoking cessation rates in younger and older ε4 carriers. Further, we included only smokers of European ancestry, and prior analyses of trial participants provide no evidence for ethnic admixture using ancestry informative markers.[32, 34, 35] A strength of our study is the relatively large sample size, but the generalizability of these findings to smokers with different ethnic backgrounds should be examined in future studies. Although the three

clinical trials reported here were designed as pharmacogenomic trials and DNA was collected from all participants, the present analyses were post-hoc. Independent validation in prospective clinical trials will be key to establish the translational significance of the current findings.

Conclusions and directions for future research

While the neurobiological mechanisms of this association remain to be elucidated, these findings may have implications for preventive neurology. For example, smokers known to carry an ε4 allele may be aided in their quitting attempts with cholinergic medications such as cholinesterase inhibitors (ACHEIs),[53, 54] and/or with nonpharmacological approaches such as cognitive exercise training.[55] Given the detrimental effects of continued smoking on risk for tobacco-related illness as well as risk of cognitive decline, such efforts could have substantial clinical significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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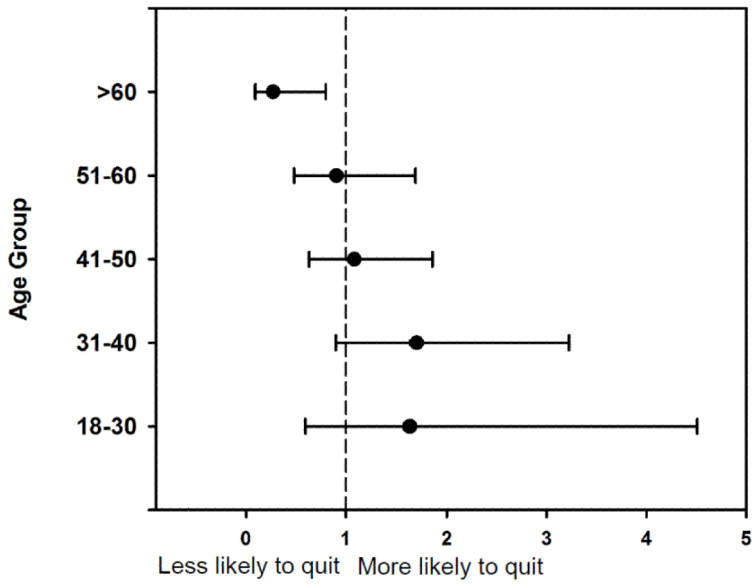

Figure 1.

Forest plot of odds ratios and 95% confidence intervals for ε4 carriers vs. noncarriers in GEE models of point prevalence abstinence. To illustrate the significant overall age by genotype interaction (OR=0.972, 95% CI= 0.946-0.999, p=0.04), the sample was stratified into five age categories. Odds ratios are adjusted for sex, education, nicotine dependence, and baseline depression. Ns=92 (18-30), 194 (31-40), 295 (41-50), 246 (51-60), and 90 (>60).

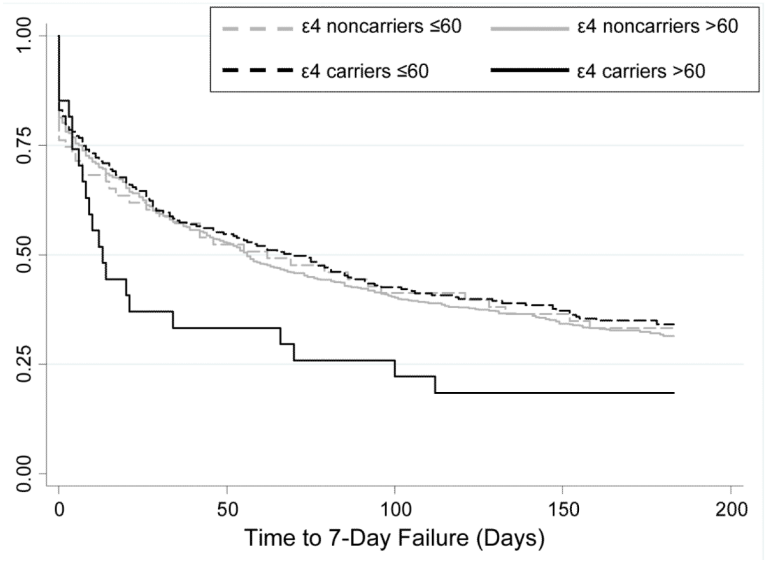

Figure 2.

Results of Cox proportional hazards model. The age by genotype interaction is significant (HR=1.02, 95% CI= 1.002-1.04, *p*=0.029) and is illustrated by genotype and age (>60 vs. ≤60). In the >60 age group, ε4 carriers had a significantly shorter time to relapse compared to noncarriers (HR=3.38, 95% CI= 1.62-7.05, *p*=0.001). For illustration purposes only, individuals who failed on the target quit day (day 0) are included in the figure.

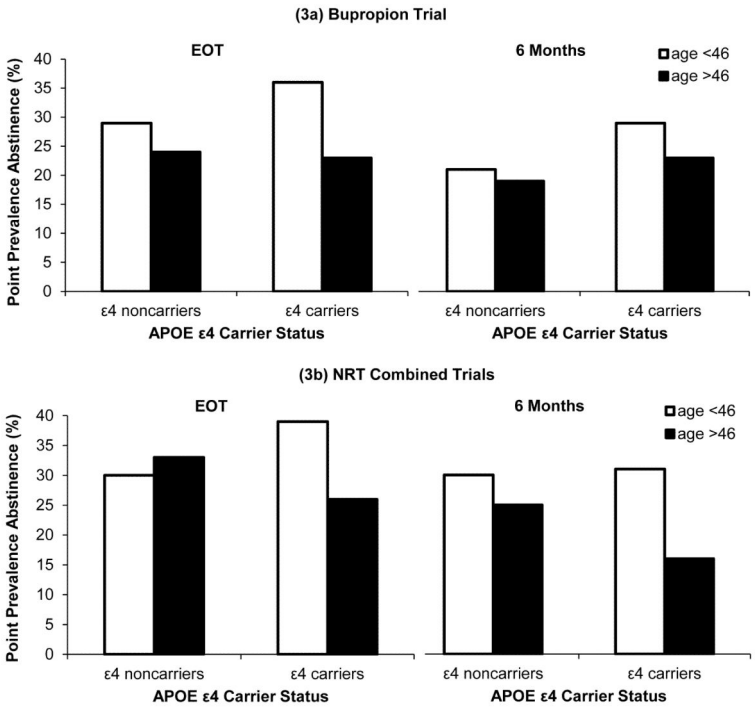

Figure 3.

Point-prevalence abstinence rates by *APOE* carrier status, age, and treatment trial. N=383 for bupropion trial (Figure 3a) and 534 for combined NRT trials (Figure 3b). Interaction effects: for the bupropion treatment trial (p=0.07) and for the NRT trials (p=0.17).

Table 1

APOE ε4 alleles, demographic and tobacco use characteristics by APOE ε4 carrier status (N=917)

	APOE ε4 Carrier		
	ε4 noncarrier n=665	**ε4 carrier n=252**	
Sex (n, % female)	332, 50%	107, 42%	p=0.04
Age (years)	45.1 (11.1)	45.3 (11.1)	p=0.81
Age group (n, %)			p=0.86
18-30	63, 9.5%	29, 11.5%	
31-40	142, 21.4%	52, 20.6%	
41-50	216, 32.5%	79, 31.4%	
51-60	181, 27.2%	65, 25.8%	
>**60**	63, 9.5%	27, 10.7%	
Baseline CPD	22.1 (9.2)	22.2 (8.8)	p=0.44
FTND [1]	5.29 (2.2)	5.19 (2.2)	p=0.56
Age smoking initiation	16.4 (3.7)	16.2 (4.3)	p=0.47
Treatment Arm (n, %)			p=0.03
Placebo	133, 20%	47, 19%	
Bupropion	153, 23%	50, 19%	
Transdermal Nicotine	326, 49%	146, 58%	
Nicotine Nasal Spray	53, 8%	9, 4%	
Baseline Depression	10.9 (8.3)	9.7 (6.7)	p=0.04
Education (n, % college graduate)	292, 44%	105, 42%	p=0.54

Note: Except where indicated, all the values represent mean and standard deviation (SD). FTND=Fagerstrom Test for Nicotine Dependence; CPD=cigarettes per day;

[1] Sex $p<0.05$