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Effect of *APOE* genotype status on targeted clinical trials outcomes and efficiency in dementia and mild cognitive impairment resulting from Alzheimer's disease

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Abstract

Background: The apolipoprotein E (*APOE*) ε4 genotype has been recommended as a potential inclusion or exclusion criterion in targeted clinical trials for Alzheimer's disease (AD) and mild cognitive impairment (MCI) resulting from AD, and has been implemented in trials of immunotherapeutic agents.

Methods: We tested this recommendation with clinical trial simulations using participants from a meta-database of 19 studies to create trial samples with *APOE* ε4 proportions ranging from 0% (all noncarriers) to 100% (all carriers). For each percentage of *APOE* ε4 carriers, we resampled the database randomly for 1000 trials for each trial scenario, planning for 18- or 24-month trials with samples from 50 to 400 patients per treatment or placebo group, up to 40% dropouts, and outcomes on the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) with effect sizes from 0.15 to 0.75, and calculated statistical power.

Results: Enrichment of clinical trial participants based on *APOE* ε4 carrier status resulted in minimal increases in power compared with enrolling participants with the *APOE* ε3 genotype only or enrolling patients without regard to *APOE* genotype. Increased screening requirements to enhance the sample would offset gains in power.

Conclusions: Although samples enriched for *APOE* ε4 carriers in AD or MCI clinical trials showed slightly more cognitive impairment and greater decline using the number *APOE* ε4 alleles as an inclusion criterion most likely would not result in more efficient trials, and trials would take longer because fewer patients would be available. The *APOE* ε4/εX (where X = 2, 3 or 4) genotype could be useful, however, as an explanatory variable or covariate if warranted by a drug's action.

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Keywords: Alzheimer disease; Mild cognitive impairment; Apolipoprotein E ε4; Clinical trials; Clinical trial simulations; Biomarkers; Alzheimer's Disease Neuroimaging Initiative; Alzheimer's Disease Cooperative Study; Alzheimer's Disease Assessment Scale

1. Introduction

The apolipoprotein E ε4 (*APOE* ε4) genotype is the major genetic risk factor for Alzheimer's disease (AD), and is associated with both increased risk for developing AD and earlier age of onset [1]. It is also associated with increased risk for developing mild cognitive impairment (MCI) resulting from AD, and progression from MCI to dementia [2]. *APOE* has a primary role as a lipid transport protein in the central nervous system and as a cholesterol transport protein in the periphery [3]. In addition, *APOE* is a major transporter for the amyloid beta (Aβ) proteins that compose the plaques of AD, and thus may play a direct role in the neuropathogenesis of this disorder [4].

Because of its central role as a risk factor for AD, many clinical trials include post hoc analyses of the effect of *APOE* ε4 on trial outcomes, but results have been mixed.

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Table 1
Placebo-controlled and observational studies included in the analyses

Study (code), dates	Design	Intervention	n	Duration, months
Selegiline, vitamin E (SL), 1993–1996	RCT, moderate to severe AD	Vitamin E, selegiline	341	24
Prednisone (PR), 1995–1998	RCT, mild to moderate AD	Prednisone	138	16
Conjugated estrogens (CE), 1995–1999	RCT, mild to moderate AD	Conjugated estrogens	120	15
Memory impairment study (MIS), donepezil, vitamin E, 1999–2004	RCT, MCI	Donepezil, vitamin E	769	36
Simvastatin (LL), 2003–2008	RCT, mild to moderate AD	Simvastatin	406	18
Vitamins B (HC), 2003–2007	RCT, mild to moderate AD	B vitamins	409	18
DHA (DHA), 2006–2009	RCT, mild to moderate AD	DHA	402	18
ADNI (ADNI), 2005–2010	Observational, AD, MCI, normal	None	800	36 (AD) 48 (MCI) 48 (NL)

Abbreviations: RCT, randomized clinical trial; AD, Alzheimer's disease; MCI, mild cognitive impairment; LL, lipid lowering; HC, homocysteine; DHA, Docosahexaenoic Acid; ADNI, Alzheimer's Disease Neuroimaging Initiative; NL, normal.

NOTE. Studies were drawn from the Alzheimer's Disease Cooperative Study (http://www.adcs.org) and the ADNI (http://adni.loni.ucla.edu), and included those with MCI or dementia resulting from AD and apolipoprotein E genotyping.

The clinical trials for tacrine, performed during the late 1980s, suggested that subjects with an *APOE* ε4 allele were more likely to respond, but similar studies with newer cholinesterase inhibitors did not show a differential *APOE* genotype effect [5–8]. Two retrospective analyses of clinical trials of subjects with MCI resulting from AD suggested lower rates of progression to dementia for patients receiving active therapy with rivastigmine or donepezil occurred selectively among *APOE* ε4 carriers [9,10]. More recently, experts have considered enrichment of clinical trials in AD dementia and MCI resulting from AD based on *APOE* ε4 status, in which the number of *APOE* ε4 alleles (or lack thereof) would be an entry criterion for the study [11]. Such enrichment is expected to lead to reduced sample sizes and greater efficiency for clinical trials by directing therapies more specifically to the underlying neuropathological changes. This recommendation was implemented in the industry-sponsored trial of bapineuzumab, in which subjects are enrolled in one of two parallel trials, depending on their *APOE* genotype [12], with the hypothesis that *APOE* ε4 noncarriers would more likely benefit from bapineuzumab perhaps because of lower Aβ burden or fewer cerebrovascular adverse effects.

We tested the potential efficiency of these recommendations empirically by statistically simulating clinical trial scenarios of MCI resulting from AD or of AD patients across a broad percentage of *APOE* ε4 carriers enrolled using a recently developed meta-database of studies from the Alzheimer's Disease Cooperative Study (ADCS) [13] and the Alzheimer's Disease Neuroimaging Initiative (ADNI) [14].

2. Methods

2.1. Study overview and participants

Participants for the simulations were drawn from a meta-database consisting of 18 ADCS studies and ADNI, representing both clinical trials and observational studies in AD, MCI, and normal individuals (National Institutes of Health grant R01 AG037561; details available from the authors). Of the available studies, eight had both relevant clinical ratings and *APOE* genotyping, six for AD (docosahexaenoic acid [DHA], conjugated estrogens [CE], homocysteine [HC], lipid lowering [LL], prednisone [PR], selegiline [SL], and ADNI) and two for MCI (Memory Impairment Study [MIS] and ADNI) (Table 1). The primary outcome measure was the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) [15], which evaluates memory, reasoning, orientation, praxis, language, and word finding difficulty, and is scored from 0 to 70 errors. Clinical assessments were done at 6-month intervals for the first 2 years.

All diagnoses of dementia resulting from AD were based on National Institute of Neurological Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria [16], with the additional requirement of a minimal severity based on clinical ratings, including a Clinical Dementia Rating (CDR) [17] score of 2 points or more for the SL trial, and a Mini-Mental State Examination (MMSE) [18] score between 14 points and 26 points (DHA and HC), between 12 points and 28 points (CE), between 12 points and 26 points (LL), and between 13 points and 26 points (PR). Diagnosis of amnestic MCI or MCI resulting from AD required a CDR score of 0.5 point, with the memory box scored at 0.5 point or more, and delayed recall from the Logical Memory II subscale of the Wechsler Memory Scale–Revised [19] to be $\leq$8 points for 16 years of education, $\leq$4 points for 8 to 15 years, or $\leq$2 points for 0 to 7 years [10,14]. Patients had to be largely intact with regard to general cognition and functional performance, and could not qualify for a dementia diagnosis. Participants with AD or MCI, as in most of the trials analyzed, could continue using marketed antidementia drugs if they had been on stable doses prior to entry.

2.2. Simulation methods

Simulations were conducted under a detailed protocol [20], as described in this section, to reflect typical clinical

trials of an experimental drug for amnestic MCI or dementia resulting from AD with one treatment and placebo group, 1:1 allocation ratio, and parameters selected to be consistent with previously published trials (e.g., [10] and [21]). Although use of standard formulae for sample size or power can be used, this simulation approach allows for relaxation of those assumptions, giving a slightly more realistic assessment of power. For each trial scenario, a separate set of patients was constructed by choosing randomly from the meta-database with replacement (i.e., patients from the data set could be present in the simulated groups more than once in the same or different treatment arm). Sample sizes of 50, 100, 200, and 400 per group were used; 12-, 18-, and 24-month-long trials were considered; and the ADAS-cog score was the primary outcome. The placebo group outcome was the score for the patient at the specified time point in the meta-database. For the treatment group, a range of effect sizes from 0.15 to 0.75 in 0.10 increments were used to compute an expected treatment effect (or slowing of decline) reflecting very small to moderately large effect sizes [22]. For each patient, an individual treatment effect was generated randomly from a χ^2 distribution with a mean equal to the expected treatment effect. The individual treatment effect was shifted by subtracting two times the expected treatment effect, then adding to the patient's score at the specified time point in the database. Thus, even when a patient was reused in the analysis, the actual value used would be modified by this randomly selected amount in the treatment arm. In the placebo arm use of the same patient would lead to a slight underestimate of the variance, slightly improving the statistical power to be examined. Dropout rates of 20% and 40% in both the treatment and placebo groups, respectively, were incorporated into the scenarios.

2.3. Selection criteria

Patients were selected for the samples as though they were applying for clinical trials using differing levels of *APOE* ε4 enrichment, ranging from 0% to 100% in 20% increments. Patients were classified as *APOE* ε4 carriers if they had one or more copies of the *APOE* ε4 allele (having genotypes of ε2/ε4, ε3/ε4, or ε4/ε4) and *APOE* ε4 noncarriers if they had no copies of the *APOE* ε4 allele (having genotypes of ε2/ε2, ε2/ε3, or ε3/ε3). Thus, a rate of 0% enrichment would correspond to a trial enrolling only *APOE* ε4 noncarriers, and a rate of 100% enrichment would correspond to a trial enrolling only *APOE* ε4 carriers, as defined. Intermediate percentages would correspond to the typical clinical trial with 60% *APOE* ε4 carriers, with lesser percentages representing enrichment for *APOE* ε4 noncarriers and greater percentages indicating enrichment for *APOE* ε4 carriers. Secondary analyses were performed excluding individuals with an *APOE* ε2 genotype so that *APOE* ε4 carriers would have genotypes of ε3/ε4 or ε4/ε4 and *APOE* ε4 noncarriers would have a genotype of ε3/ε3; as well as restricting AD dementia samples to those having an MMSE scored ≥16 points (i.e., milder impairment to represent more completely recent phase 2 and phase 3 AD trials). Simulations were also performed using only *APOE* ε4 carriers, with enrichment based on the number of ε4 alleles, to evaluate dosage effects. In this set of simulations, a rate of 0% enrichment would correspond to a trial enrolling only *APOE* ε4 heterozygote carriers with one copy of the ε4 allele; a rate of 100% enrichment would correspond to a trial enrolling only *APOE* ε4 homozygote carriers with two copies of the ε4 allele. Last, because having one *APOE* ε2 allele appears particularly protective against AD, an exploratory simulation was performed using the *APOE* ε2 carriers only (i.e., those with genotypes ε2/ε2, ε2/ε3, or ε2/ε4), even though such a trial would not be pragmatic because only 10% of a sample with dementia resulting from AD would satisfy inclusion criteria that required *APOE* ε2 carriers.

2.4. Statistical analysis

The primary analyses were conducted using a mixed-effects linear model (random coefficients model) [23], which adjusts for missing data to test for differences in the slopes (rate of change) of the ADAS-cog score between the treatment and placebo groups. The mixed-effects model was chosen because it uses data from all participants (rather than just completers), and minimizes bias and controls better for Type I error in the presence of missing data [24]. For each simulated trial, a full model was constructed with group effect, visit effect, and group-by-visit interactions, with age and gender as covariates, and a reduced model with visit, age, and gender effects. Thus, for participant $i = 1, 2, \rightleftharpoons, n$ at visit $j = 1, 2, \rightleftharpoons, n_i$, the full model was

$$ADAS_{i,j} = Age_i + Education_i + Group_i + Time_{i,j} + Group_i \times Time_{i,j} + \varepsilon_{i,j}$$

and the reduced model was

$$ADAS_{i,j} = Age_i + Education_i + Group_i + Time_{i,j} + \varepsilon_{i,j},$$

where the model includes both fixed effects of time at the group level and random effects of time at the individual level. An unstructured covariance matrix was used to model the independence of the slope and intercept parameters. Parameters were estimated using maximum likelihood. *P* values for the group (treatment) effect were found using −2 times the difference in the log likelihood of the full and reduced model, which follows a χ^2 distribution with the appropriate degrees of freedom. Secondary analyses examined last-observation-carried-forward samples to impute missing values using the nonparametric Wilcoxon test to detect any differences between treatment and placebo groups resulting from the skewed distributions of the resultant outcomes. For all analyses, the missing data pattern present in the meta-database was used to simulate dropouts realistically; observations were missing in simulated data sets if they were originally missing in the meta-database.

This approach would minimize bias arising from differential dropout among groups [25].

One thousand simulations were done for each scenario so that estimates of power could be obtained to three digits. Power was calculated as the proportion of 1000 simulated trials per trial scenario having an α error P value $\leq .05$. Analyses were performed using version 2.15.0 of the R programming environment (Vienna, Austria) [26]. Mixed-model analyses were performed using version 3.1-89 of the *nlme* package for R [27].

Last, we compared the results from simulations using standardized effect sizes to compute the change in ADAS-cog scores over time with the results using a percentage in slope reduction. The former assumes that the magnitude of the change, relative to the variability, is constant whereas the latter assumes that the rate of change is constant.

3. Results

3.1. Patient characteristics

For both AD dementia and MCI resulting from AD, the *APOE* ε4 carriers and noncarriers were similar on most demographic and clinical characteristics, being predominantly white, married, and highly educated (Tables 2 and 3). Slightly more than half the MCI participants were male, whereas slightly more than half of the AD participants were female. The *APOE* ε4 noncarriers were older than the carriers, although this only reached statistical significance in the AD group.

For the MCI group, *APOE* ε4 carriers had worse performance on the ADAS-cog, which occurred at baseline and all subsequent time points. For the AD dementia group, *APOE* ε4 carriers also showed worse performance on the ADAS-cog, although these differences were statistically significant only at 18 months.

3.2. Outcomes

Power calculations for the mixed-model analyses are shown across a range of effect and sample sizes providing for 40% dropouts and an 18-month duration for AD and 24 months for MCI resulting from AD (Figs. 1 and 2). Power increased with increasing effect size and sample size but there was generally little difference in power across the range of *APOE* ε4 carrier percentages—typically less than a 2% increase in power (Tables 4 and 5; additional details are shown in Supplemental Tables 1 and 2). Patients showed considerable heterogeneity in their clinical course and within each diagnostic group. Although there were greater mean differences between placebo and treatment groups among *APOE* ε4 carriers, there were also greater increases in variability that tended to offset these differences in computing power and sample size.

Analyses of other trial durations using the scenarios mentioned earlier also did not show a meaningful

Table 2
Clinical characteristics and ratings among participants with dementia resulting from Alzheimer's disease based on *APOE* ε4 carrier status

		Study name																	
		ADNI		DHA		ES		HC		LL		PR		Overall					
Characteristic	n	ε4− (n = 64)	ε4+ (n = 124)	ε4− (n = 170)	ε4+ (n = 232)	ε4− (n = 10)	ε4+ (n = 16)	ε4− (n = 128)	ε4+ (n = 246)	ε4− (n = 150)	ε4+ (n = 208)	ε4− (n = 23)	ε4+ (n = 47)	ε4− (n = 545)	ε4+ (n = 873)	*P* value			
Age, years	1368	76.7 (8.5)	74.4 (6.9)	76.5 (9.3)	75.5 (7.9)	78.6 (4.1)	76.6 (5.2)	77.2 (8.6)	75.4 (7.2)	74.2 (10.4)	73.4 (8.5)	69.3 (8.9)	72.4 (7.0)	75.8 (9.5)	74.7 (7.7)	<.001			
Education, years	1374	14.8 (3.3)	14.6 (3.0)	14.4 (3.0)	14.2 (2.7)	11.9 (2.5)	11.9 (1.9)	14.0 (3.3)	13.9 (2.9)	14.0 (3.5)	14.6 (2.9)	14.3 (4.1)	14.1 (2.9)	14.2 (3.3)	14.2 (2.9)	.9			
Ethnicity, Hispanic	1374	0 (0%)	4 (3%)	6 (4%)	8 (3%)	0 (0%)	2 (12%)	10 (8%)	10 (4%)	15 (10%)	7 (3%)	0 (0%)	1 (2%)	31 (6%)	32 (4%)	.077			
Marital status, married	1411	45 (70%)	108 (88%)	121 (71%)	165 (71%)	3 (30%)	10 (62%)	80 (62%)	171 (70%)	99 (66%)	156 (75%)	19 (83%)	44 (94%)	367 (67%)	654 (75%)	.001			
Race, white	1374	59 (94%)	111 (93%)	158 (93%)	210 (91%)	9 (90%)	13 (81%)	103 (85%)	201 (87%)	130 (90%)	188 (93%)	23 (100%)	46 (98%)	482 (91%)	769 (91%)	.85			
Gender, female	1374	35 (56%)	51 (43%)	88 (52%)	122 (53%)	10 (100%)	16 (100%)	67 (55%)	127 (55%)	92 (63%)	113 (56%)	11 (48%)	22 (47%)	303 (57%)	451 (53%)	.19			
APOE ε2 carrier	1418	5 (8%)	4 (3%)	23 (14%)	10 (4%)	1 (10%)	0 (0%)	16 (12%)	8 (3%)	22 (15%)	6 (3%)	2 (9%)	0 (0%)	69 (13%)	28 (3%)	<.001			
Baseline CDRsb score	1057	4.4 (1.7)	4.3 (1.6)	5.6 (2.6)	5.8 (2.6)	6.0 (1.9)	6.2 (2.8)	5.6 (2.7)	5.7 (2.7)	—	—	5.3 (1.8)	5.6 (2.7)	5.4 (2.5)	5.5 (2.6)	.65			
Baseline MMSE score	1418	23.2 (2.1)	23.3 (2.0)	21.0 (3.7)	20.4 (3.5)	21.4 (3.3)	20.4 (3.9)	21.4 (3.4)	20.8 (3.5)	20.5 (4.7)	20.2 (4.7)	22.1 (4.1)	21.1 (4.8)	21.3 (3.9)	20.9 (3.9)	.06			
ADAS-cog scores																			
Baseline	1392	18.9 (7.1)	18.6 (5.9)	23.3 (9.2)	23.8 (8.3)	12.9 (4.9)	15.3 (6.6)	21.9 (8.2)	22.7 (8.9)	24.2 (10.3)	24.1 (9.3)	17.8 (8.2)	16.0 (7.7)	22.3 (9.2)	22.2 (8.7)	.82			
6 months	1252	21.1 (8.4)	20.7 (7.5)	25.1 (10.3)	26.4 (10.2)	15.5 (6.9)	18.4 (8.6)	22.9 (9.5)	24.5 (9.2)	25.4 (11.1)	26.2 (10.3)	20.5 (8.4)	17.6 (9.8)	23.7 (10.1)	24.3 (9.9)	.18			
12 months	1129	22.2 (9.1)	22.5 (8.8)	26.0 (11.1)	27.4 (11.5)	18.0 (10.9)	17.7 (7.3)	24.3 (9.6)	26.9 (10.2)	27.4 (12.3)	28.4 (11.2)	27.3 (12.0)	19.8 (10.8)	25 (11)	27 (11)	.19			
18 months	793	—	—	28 (13)	29 (12)			25 (12)	29 (12)	29 (12)	30 (12)	—	—	27 (12)	29 (12)	.042			
24 months	133	26.4 (9.9)	28.8 (12.6)	—	—	—	—	—	—	—	—	—	—	26.4 (9.9)	28.8 (12.6)	.57			

Abbreviations: APOE, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; DHA, docosahexaenoic acid; CE, conjugated estrogens; HC, homocysteine; LL, lipid lowering; PR, prednisone; CDRsb, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale.

NOTE. Clinical characteristics are shown for individual studies, but are pooled for calculating statistical significance of between-group differences.

Table 3
Clinical characteristics and ratings among participants with mild cognitive impairment resulting from Alzheimer's disease based on *APOE* ε4 carrier status

		Study name						
		ADNI		MIS trial		Overall		
Characteristic	n	ε4− (n = 187)	ε4+ (n = 215)	ε4− (n = 357)	ε4+ (n = 433)	ε4− (n = 544)	ε4+ (n = 648)	*P* value
Age, years	1134	75.7 (8.1)	73.8 (6.7)	72.2 (8.0)	72.4 (6.5)	73.4 (8.2)	72.9 (6.6)	.054
Education, years	1134	15.7 (3.1)	15.7 (3.0)	14.6 (3.2)	14.7 (3.0)	15.0 (3.2)	15.0 (3.1)	.73
Ethnicity, Hispanic	1134	8 (4%)	6 (3%)	19 (6%)	9 (2%)	27 (5%)	15 (2%)	.013
Marital status, married	1182	143 (78%)	172 (80%)	251 (71%)	353 (82%)	394 (73%)	525 (82%)	<.001
Race, white	1134	165 (93%)	196 (94%)	303 (90%)	384 (94%)	468 (91%)	580 (94%)	.046
Gender, female	1134	60 (34%)	77 (37%)	146 (43%)	194 (47%)	206 (40%)	271 (44%)	.18
APOE ε2 carrier	1192	17 (9%)	11 (5%)	52 (15%)	21 (5%)	69 (13%)	32 (5%)	<.001
Baseline CDRsb score	402	1.52 (0.85)	1.68 (0.89)	1.70 (0.77)	1.90 (0.78)	1.52 (0.85)	1.68 (0.89)	.049
Baseline MMSE score	1192	27.1 (1.8)	26.9 (1.8)	27.5 (1.9)	27.1 (1.8)	27.3 (1.8)	27.1 (1.8)	.005
ADAS-cog scores								
Baseline	402	10.5 (4.4)	12.4 (4.3)	10.4 (4.1)	12.0 (4.5)	10.4 (4.2)	12.1 (4.4)	<.001
6 months	1038	11.5 (5.5)	13.0 (5.4)	9.3 (4.8)	11.8 (5.1)	10.2 (5.2)	12.2 (5.2)	<.001
12 months	972	11.6 (6.2)	13.5 (6.1)	9.9 (5.1)	12.8 (5.8)	10.6 (5.6)	13.0 (5.9)	<.001
18 months	872	12.1 (6.7)	14.8 (7.7)	10.0 (5.1)	13.6 (6.6)	10.8 (5.8)	14.0 (7.0)	<.001
24 months	814	12.6 (7.4)	15.3 (7.3)	9.6 (5.6)	14.4 (7.3)	10.7 (6.5)	14.7 (7.3)	<.001

Abbreviations: *APOE*, apolipoprotein E; ADNI, Alzheimer's Disease Neuroimaging Initiative; MIS, Memory Impairment Study; CDRsb, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale.

NOTE. Clinical characteristics are shown for individual studies, but are pooled for calculating statistical significance of between-group differences.

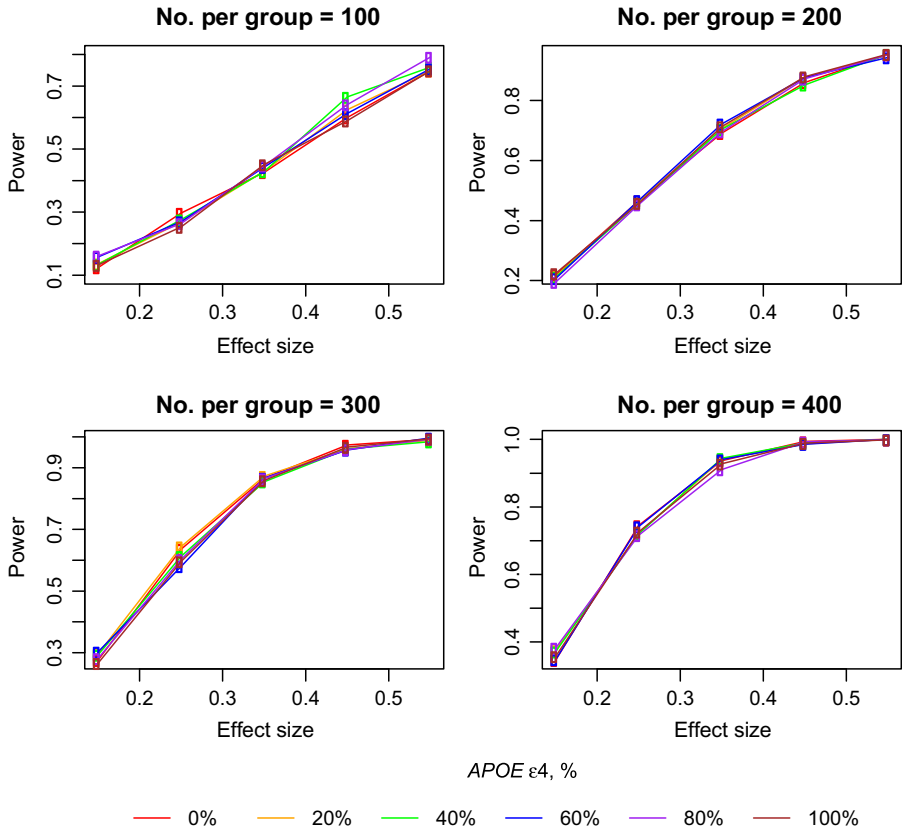

Fig. 1. Power for Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog), outcomes in 24-month-long trials of participants with mild cognitive impairment resulting from Alzheimer's disease. Power calculations are for the ADAS-cog by effect size and sample size with apolipoprotein E (APOE) ε4 carriers ranging from 0% to 100% of the sample. Enrichment based on *APOE* ε4 carrier status did not increase power appreciably under any of the scenarios. Simulation parameters included $\alpha = 0.05$, χ^2 random errors, and 40% dropouts, with mixed-model analysis for participants with missing data.

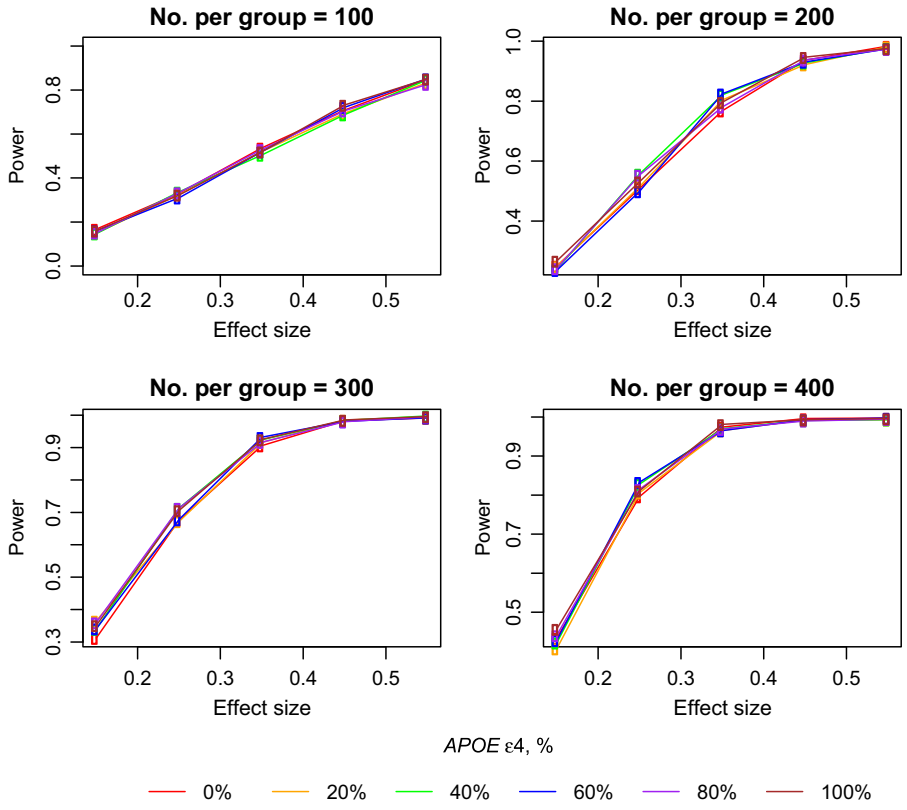

Fig. 2. Power for Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) outcomes in 18-month-long trials of participants with dementia resulting from Alzheimer's disease. Power calculations are for the ADAS-cog by effect size and sample size with apolipoprotein E (*APOE*) ε4 carriers ranging from 0% to 100% of the sample. Enrichment based on *APOE* ε4 carrier status did not increase power appreciably under any of the scenarios. Simulation parameters included $\alpha = 0.05$, χ^2 random errors, and 40% dropouts, with mixed-model analysis for participants with missing data.

difference in power for the outcomes across *APOE* ε4 carrier percentages (data not shown). Secondary analyses using samples excluding individuals with the ε2 genotype showed similar, very small differences among diagnostic groups (Supplemental Tables 3 and 4 and Supplemental Figs. 1 and 2). Analyses using only milder dementia participants with MMSE scores $\geq$ 16 points did not differ from results using all dementia participants (Supplemental Table 5, Supplemental Fig. 3). Simulations using only ε2 carriers (8.5% and 6.8% of the MCI resulting from AD sample and AD sample, respectively) did show slower progression and decreased variability compared with simulations predominantly involving ε3 and ε4, leading to slightly greater power to detect treatment differences (Supplemental Tables 6 and 7, Supplemental Figs. 4 and 5). Simulations of trials with enrichment based on the number of *APOE* ε4 alleles showed little difference in power when selecting those with one or two copies of the ε4 allele, echoing the results when selecting simply based on presence or absence of the ε4 allele (Supplemental Tables 8 and 9, Supplemental Figs. 6 and 7).

In contrast, power calculations using a fixed reduction in slope showed an increase in power as the percentage of *APOE* ε4 carriers increased (Table 6). However, increases in the mean and, to a lesser extent, the variance in ADAS-cog scores also meant that the effect size was large among *APOE* ε4 carriers.

4. Discussion

This study provides an empirical evaluation through the use of simulations of recent recommendations for the incorporation of biomarkers, specifically *APOE* ε4, in clinical trials of AD dementia and MCI resulting from AD [20]. Enrichment of the clinical trial population based on *APOE* ε4 carrier status did not result in meaningful increases in the efficiency of the trials compared with the typical approach of enrolling AD or MCI participants regardless of *APOE* ε4 status. For example, for an MCI trial with an expected small effect size of 0.25, typical of that for cholinesterase inhibitors, an unenriched trial with only 60% *APOE* ε4 carriers would require approximately 432 participants to achieve 80% power. In comparison, note that this is about 15% less than the 506 participants that would be required based on a *t* test of differences, and illustrates the advantages of using simulations with longitudinal data. Furthermore, the simulations can be adapted to model more complex trials while avoiding the assumptions needed for fixed formulas

Table 4
Power for ADAS-cog outcomes in 24-month-long trials of participants with mild cognitive impairment resulting from Alzheimer's disease based on *APOE* ε4 carrier status

No. per group	Effect size	APOE ε4, %	Treatment group mean	Placebo group mean	Treatment group SD	Placebo group SD	Power mixed model
50	0.45	0	−1.15	0.96	5.22	4.85	0.363
50	0.45	0.6	−0.55	1.71	5.89	5.48	0.367
50	0.45	1	−0.12	2.24	6.16	5.75	0.376
100	0.45	0	−1.14	0.96	5.36	4.96	0.600
100	0.45	0.6	−0.57	1.76	6.02	5.60	0.613
100	0.45	1	−0.10	2.29	6.24	5.86	0.590
200	0.35	0	−0.71	0.91	5.36	5.00	0.691
200	0.35	0.6	−0.07	1.75	5.95	5.59	0.722
200	0.35	1	0.35	2.26	6.25	5.95	0.713
200	0.45	0	−1.17	0.94	5.44	5.00	0.860
200	0.45	0.6	−0.60	1.77	6.00	5.63	0.876
200	0.45	1	−0.16	2.26	6.31	5.97	0.879
300	0.35	0	−0.72	0.96	5.40	5.07	0.866
300	0.35	0.6	−0.07	1.79	5.98	5.66	0.867
300	0.35	1	0.35	2.28	6.26	6.00	0.859
400	0.25	0	−0.24	0.96	5.28	5.05	0.745
400	0.25	0.6	0.44	1.78	5.87	5.66	0.742
400	0.25	1	0.89	2.29	6.22	6.03	0.726
400	0.35	0	−0.73	0.94	5.37	5.07	0.937
400	0.35	0.6	−0.10	1.75	5.95	5.68	0.940
400	0.35	1	0.37	2.25	6.27	5.99	0.928

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; *APOE*, apolipoprotein E; SD, standard deviation.

NOTE. To ensure an approximate power of 80% to 90% for the mixed model analysis in a trial of 100% *APOE* ε4 carriers, simulations show that for small effects of 0.25, typical to that of cholinesterase inhibitors, somewhat more than 400 patients per group are needed with a dropout rate of 40%. Enrichment based on *APOE* ε4 carrier status resulted in very small increases in statistical power across most scenarios. Simulation parameters included $\alpha = .05$, effect sizes of 0.25 to 0.45 with χ^2 random errors, and 40% dropouts with mixed model analysis for participants with missing data.

Table 5
Power for ADAS-cog outcomes in 18-month-long trials of participants with dementia resulting from Alzheimer's disease based on *APOE* ε4 carrier status

No. per group	Effect size	APOE ε4, %	Treatment group mean	Placebo group mean	Treatment group SD	Placebo group SD	Power mixed model
50	0.45	0.0	2.43	5.63	8.03	7.61	0.437
50	0.45	0.6	3.02	6.35	7.99	7.63	0.474
50	0.45	1.0	3.55	6.82	7.91	7.54	0.454
100	0.45	0.0	2.29	5.69	8.18	7.83	0.709
100	0.45	0.6	2.96	6.32	8.04	7.69	0.722
100	0.45	1.0	3.37	6.66	7.95	7.60	0.732
200	0.35	0.0	3.06	5.69	8.20	7.87	0.768
200	0.35	0.6	3.68	6.31	8.03	7.74	0.825
200	0.35	1.0	4.11	6.66	7.95	7.65	0.797
200	0.45	0.0	2.27	5.67	8.23	7.82	0.937
200	0.45	0.6	2.90	6.29	8.11	7.71	0.931
200	0.45	1.0	3.36	6.65	8.03	7.64	0.947
300	0.25	0.0	3.81	5.68	8.09	7.86	0.676
300	0.25	0.6	4.44	6.29	7.98	7.75	0.678
300	0.25	1.0	4.83	6.66	7.88	7.65	0.706
300	0.35	0.0	3.03	5.68	8.19	7.88	0.906
300	0.35	0.6	3.68	6.32	8.09	7.79	0.932
300	0.35	1.0	4.13	6.69	7.95	7.65	0.925
400	0.25	0.0	3.77	5.68	8.14	7.90	0.796
400	0.25	0.6	4.41	6.30	7.98	7.77	0.833
400	0.25	1.0	4.85	6.69	7.89	7.68	0.811
400	0.35	0.0	3.04	5.72	8.20	7.91	0.974
400	0.35	0.6	3.71	6.32	8.06	7.75	0.965
400	0.35	1.0	4.08	6.68	7.96	7.68	0.981

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; *APOE*, apolipoprotein E; SD, standard deviation.

NOTE. To ensure an approximate power of 80% to 90% for the mixed model analysis, simulations show that for small effects of 0.25, typical to that of cholinesterase inhibitors, somewhat fewer than 400 patients per group are needed with a dropout rate of 40%; for medium-size effects of 0.45, somewhat more than 100 patients per group are needed with a dropout rate of 40%. Enrichment based on *APOE* ε4 carrier status resulted in very small increases in statistical power. Simulation parameters included $\alpha = .05$, effect sizes of 0.25 to 0.45 with χ^2 random errors, and 40% dropouts with mixed model analysis for participants with missing data.

using repeated measures. An enriched trial of 100% *APOE* ε4 carriers would require essentially the same number of participants, approximately 440 patients, to achieve 80% power. However, assuming 60% of otherwise eligible clinical trial applicants are *APOE* ε4 carriers, approximately 734 subjects would need to be screened to reach this goal of 440. Similar results would apply for enrichment based on *APOE* ε4 noncarrier status; but, in this situation, assuming 40% are noncarriers, 1075 subjects would have to be screened. Thus, the small gains in power based on *APOE* ε4 enrichment are almost certain to be offset by the time and effort required in screening.

As with our previous evaluation of cerebrospinal fluid (CSF) amyloid beta $(A\beta)_{1–42}$ and $A\beta_{1–42}$/total tau biomarkers in simulated clinical trials [28], *APOE* ε4 carrier status has several drawbacks that limit its usefulness as an inclusion criterion for the selection of participants. The utility of biomarkers in clinical trials depends on the effectiveness of the drug in both the biomarker-positive and -negative groups, the proportion of biomarker-positive patients in the sample, and the accuracy of the assay [29]. Enrichment strategies are generally effective when less than 50% of applicants are biomarker positive, and the drug has little benefit for biomarker-negative patients [29]. Because approximately 60% of clinical trial participants are *APOE* ε4 carriers and 40% are noncarriers [30], selecting for *APOE* ε4 status fails to satisfy the former. (Even selection of *APOE* ε4 noncarriers, the minority of patients who enter trials, may not screen out a sufficient number of subjects to make it an effective biomarker.) Furthermore, the latter criterion is not satisfied because no differential response based on *APOE* ε4 status has been demonstrated convincingly to date, although it has sometimes been argued so based on theoretical grounds or post hoc analyses of completed trials. (For example, rosiglitazone has been postulated to have preferential effects in *APOE* ε4 noncarriers, based on reduction of amyloid

Table 6
Sample size calculations based on effect sizes and slope reductions

Effect size		0.25					0.35					0.45				
APOE ε4, %	Baseline ADAS-cog	Placebo change	Treatment change	Drug-placebo difference	Slope reduction, %	Effect size	Power	Placebo change	Treatment change	Drug-placebo difference	Slope reduction, %	Effect size	Power	Placebo change	Treatment change	Drug-placebo difference	Slope reduction, %	Effect size	Power
0	10.4 (4.2)	0.97 (5.04)	−0.22 (5.24)	1.19	123	0.08	0.466	0.97 (5.04)	−0.71 (5.36)	1.62	167	0.10	0.691	0.94 (5.00)	−1.17 (5.44)	2.11	224	0.11	0.860
60	11.3 (4.3)	1.77 (5.66)	0.45 (5.88)	1.32	75	0.13	0.467	1.77 (5.66)	−0.07 (5.95)	1.82	103	0.16	0.722	1.77 (5.66)	−0.6 (6.00)	2.37	134	0.19	0.876
100	12.1 (4.4)	2.29 (5.95)	0.93 (6.14)	1.36	59	0.15	0.458	2.29 (5.95)	0.35 (6.25)	1.91	83	0.19	0.713	2.26 (5.97)	−0.16 (6.31)	2.10	107	0.23	0.879
Slope reduction		40%					50%					60%							
APOE ε4, %	Baseline ADAS-cog	Placebo change	Treatment change	Drug–placebo difference	Slope reduction, %	Effect size	Power	Placebo change	Treatment change	Drug–placebo difference	Slope reduction, %	Effect size	Power	Placebo change	Treatment change	Drug–placebo difference	Slope reduction, %	Effect size	Power
0	10.4 (4.2)	0.97 (5.04)	0.582 (5.04)	0.388	123	0.08	0.117	0.97 (5.04)	0.485 (5.04)	0.485	167	0.10	0.159	0.94 (5.00)	0.376 (5.00)	0.564	224	0.11	0.202
60	11.3 (4.3)	1.77 (5.66)	1.062 (5.66)	0.708	75	0.13	0.236	1.77 (5.66)	0.885 (5.66)	0.885	103	0.16	0.345	1.77 (5.66)	0.708 (5.66)	1.062	134	0.19	0.465
100	12.1 (4.4)	2.29 (5.95)	1.374 (5.95)	0.916	59	0.15	0.336	2.29 (5.95)	1.145 (5.95)	1.145	83	0.19	0.484	2.26 (5.97)	0.904 (5.97)	1.356	107	0.23	0.620

Abbreviations: *APOE*, apolipoprotein E; ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale.

NOTE. All scenarios are based on a sample size of 200 per group and 40% dropouts. For each effect size, simulations were used to compute the corresponding slope reduction, which was calculated as (Placebo - Treatment change)/Placebo change × 100, and power, which was calculated as the fraction of simulations with $P < .05$. For each slope reduction, effect sizes were calculated as (Treatment – Placebo change)/(Standard deviation of placebo), and power was calculated using a two-sample *t* test. Although power did increase with *APOE* ε4 enrichment in the slope reduction approach, this also corresponds to a greater differential effect in the *APOE* ε4 group.

plaque burden and amyloid-associated inflammation in animal models [31].) Indeed, even the theoretical basis for differential response has been conflicted, with some arguing for better response among *APOE* ε4 carriers based on more rapid rate of progression, and others arguing for better response among *APOE* ε4 noncarriers based on different metabolism and the lower accumulation of Aβ plaques in the brain [11]. *APOE* ε4 carriage is strongly predictive of positive Aβ biomarker status. For example, in ADNI, among participants with MCI resulting from AD and mild AD who were *APOE* ε4 carriers, 88% and 98%, respectively, had a low CSF Aβ level (<192 pg/mL). The issue of differential response must also be borne in mind when estimating sample sizes for the planning of clinical trials. For example, basing sample sizes on expected percentage of slope reduction may imply indirectly an assumption of differential response when this is not intended.

Thus, *APOE* ε4 carriers who are ultimately enrolled in clinical trials may be more likely to be positive on CSF and positron emission tomography Aβ biomarkers [32–34]. This may, however, reflect past Aβ accumulation and not be a further predictor of clinical response [12]. Another potential explanation for the minimal increase in power with *APOE* ε4 in clinical trial selection is the considerable heterogeneity among *APOE* ε4 carriers. Although multiple studies [35–40], including ADNI [41,42], have demonstrated more rapid progression of cognitive impairment in MCI and AD among *APOE* ε4 carriers, and increased risk of conversion from MCI to dementia, such studies have also demonstrated substantial variability among the participants within a group [43,44]. Such variation is likely to carry over into clinical trials and to affect trial outcomes adversely, as demonstrated by our simulations. Despite greater clinical worsening of about 0.5 ADAS-cog point in the *APOE* ε4 carriers, the standard deviations for the outcomes were larger, decreasing the power to detect drug–placebo differences (i.e., the within-group effect sizes were about the same).

A third consideration in the utility of *APOE* ε4 carrier status in the design of clinical trials is that, although carrier status is associated with more rapid decline, it is also associated with greater impairment at baseline assessment. This observation is consistent with previous studies showing that *APOE* ε4 primarily exerts its effect in AD by influencing age of onset [45]. Thus, it appears that *APOE* ε4 carrier status—when determined after a diagnosis of MCI has been made, as in ADNI and the MIS [10]—may identify primarily more advanced disease or more impaired cognitive scores at baseline, so that cognitive severity is the more pragmatic predictor of decline [46,47]. Under these circumstances, *APOE* ε4 status would have utility in the diagnosis of MCI resulting from AD or AD at a single time point, but this does not necessarily translate into utility in treatment trials that focus on rates of change over time. In a similar

vein, it must be recognized that participants in clinical trials and ADNI are samples of convenience, with their own prevailing characteristics, so that trends observed in population studies (such as the effect of genotype on disease progression or as a prognostic biomarker) may differ from trends observed in clinical trials. Particularly for trials with small sample size, trends contradictory to population studies may be seen [48].

Based on these considerations, *APOE* ε4 status may have greater utility as an explanatory covariate or stratification variable than as an inclusion criteria for clinical trials, especially in preplanned subanalyses incorporated into the trial design, and when warranted by the hypothesized actions of the drug treatment. In this context, *APOE* ε4 may serve as a proxy for disease severity (because it is associated with earlier age of onset, a measure of disease severity that can often only be approximated) or for unmeasured biological processes targeted by an intervention (such as fibrillar Aβ deposition). In addition, stratification could be useful with agents that show a strong differential response or adverse effect profile based on *APOE* ε4 status. Enrichment based on *APOE* ε4 status may also show benefits in such circumstances that were not examined in this study but that may preclude further analyses of differential effect of *APOE* status within the trial if the number of noncarriers becomes sufficiently small.

Last, it is important to note that this study did not address the utility of enrichment for *APOE* ε4 carrier status in prevention trials among participants who have not yet manifested illness, but only the utility of enrichment in therapeutic trials among individuals with a diagnosis of MCI or dementia resulting from AD. Thus, further research is needed before conclusions can be reached about *APOE* ε4 enrichment in the former type of design. In particular, if *APOE* ε4 affects age of onset rather than rate of decline, selecting *APOE* ε4 carriers for intervention prior to symptom onset may lead to very different results. It is also likely that the prevalence of *APOE* ε4 carriers in prevention trials would be lower—approaching the population rate of 25% rather than the 50% to 60% observed in the samples of convenience used in therapeutic clinical trials—and thus the utility of screening would be greater.

A particular strength of this study is that it expands previous clinical trial simulations based on the ADNI data set [28] by using a meta-database of several clinical trials and observational studies across a population of more than 5500 individuals. The inclusion of a large number of participants across several studies greatly increases generalizability, because the design of ADNI may limit the conclusions that can be drawn. Meta-databases may be rich resources not only for simulation studies, but also for meta-analyses and other investigations into the design and analysis of clinical trials in dementia and MCI resulting from AD.

One limitation to these results is that the utility of the *APOE* ε4 biomarker was assessed in isolation, and its usefulness in conjunction with other biomarkers was not evaluated. However, the primary goal of this study was to evaluate enrichment strategies for clinical trials, and *APOE* ε4 status is an inexpensive and readily available marker for such purposes. Another limitation is that the primary analyses only stratified based on the presence or absence of the *APOE* ε4 allele, and did not investigate the specific effects of each of the six possible genotypes. This was also consistent with the goal of evaluating enrichment strategies for clinical trials, in which more extensive stratification is not likely to be feasible. Similarly, this study did not evaluate the effects of different statistical model parameterizations, but instead used a single model, with age and education as covariates. The random slope model has been recommended for the analysis of clinical trial data in AD and MCI, and has flexibility and merits. Although the model selection is a key aspect of trial design that can influence the overall results, it should also be noted that the goal of this study was not to investigate the absolute power attained under a specific modeling strategy, but to look at the relative power (or difference in power) afforded by enrichment strategies.

A third limitation is this study assumed equal response between *APOE* ε4 carriers and noncarriers, and did not investigate potential gains or losses in power if *APOE* ε4 carrier status (or not) is associated with a preferential response to treatment. Such an approach could be interpreted as artificially inducing a lack of difference between groups, but it is also reflective of current clinical trial design and analysis, which in general have not included a differential response based on genotype because none has been shown consistently to date. However, if a therapy that is preferentially effective by *APOE* ε4 carrier status becomes available in the future, then enrichment of clinical trials based on *APOE* status may be more attractive. Previous simulation studies, however, have indicated that biomarker-positive status must be associated with a marked difference in response between groups for biomarker selection to be effective [29]. Therefore, even a moderate degree of preferential response resulting from *APOE* carrier status may not be sufficient to justify such screening strategies. Last, although resampling strategies incorporate the variability from sample to sample that is usually not contained adequately in parametric models, even resampling may not capture all the relevant characteristics of clinical trial participants. The use of a meta-database rather than a single study for the simulations tends to mitigate this problem by including a larger sample likely to be representative of clinical trial participants in general.

In sum, selecting patients with MCI or dementia resulting from AD for a clinical trial on the basis of *APOE* ε4 carrier status (which also predicts Aβ biomarker positivity) will most likely not enhance the trial's statistical

power. Results of these simulations likely will be confirmed in the near future in ongoing clinical trials that use *APOE* ε4 status as an inclusion criterion. In the absence of a strong scientific rationale positing a relationship between *APOE* ε4 status and therapeutic drug actions, it may be more practical and clinically relevant not to require *APOE* ε4 genotyping for trial entry, but to restrict its use as an explanatory or stratification variable when there are reasons to do so.

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RESEARCH IN CONTEXT

1. Systematic review: We identified relevant articles through PubMed related to the effect of the apolipoprotein E (*APOE*) ε4 genotype on the progression of Alzheimer's disease. Particular emphasis was placed on the effect of *APOE* εε4 on clinical trial entry criteria and design. Previous studies have suggested that enriching samples for individuals with the *APOE* ε4 genotype may improve clinical trial efficiency, but results are conflicting.
2. Interpretation: We used clinical trial simulations to evaluate the effect of *APOE* ε4 enrichment on trials for mild cognitive impairment and Alzheimer's disease under a variety of scenarios. Our results indicate that, in general, enrichment based on *APOE* ε4 status does not improve clinical trial efficiency.
3. Future directions: Although *APOE* ε4 enrichment does not improve clinical trial efficiency in general, additional work is indicated to delineate specific circumstances (such as in combination with other biomarkers) in which *APOE* ε4 status can affect trial design.

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