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Effect of *APOE* Genotype Status on Targeted Clinical Trials Outcomes and Efficiency in Dementia and MCI due to AD

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Abstract

Background—Apolipoprotein ε4 genotype has been recommended as a potential inclusion or exclusion criterion in targeted clinical trials for Alzheimer disease and MCI due to AD, and implemented in trials of immunotherapeutic agents.

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

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Contributors

All authors participated in the writing and editing of the manuscript.

Conflict of interest statement

During the 36 month window before submission

Dr Schneider reports being an editor on the Cochrane Collaboration Dementia and Cognitive Improvement Group, which oversees systematic reviews of drugs for cognitive impairment and dementia; receiving a grant from the Alzheimer's Association for a registry for dementia and cognitive impairment trials; receiving grant or research support from Baxter, Eli Lilly, Genentech, Novartis, and Pfizer; and having served as a consultant for or receiving consulting fees from AC Immune, Accera, Allon, AstraZeneca, Baxter, Biogen Idec, Chiesi, Elan, Eli Lilly, En Vivo, GlaxoSmithKline, Ipsen, Johnson & Johnson, Lundbeck, Merck, Pfizer, Roche, Takeda, Toyama, and Zinfandel.

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

Interpretations—Although samples enriched for *APOE* ε4 carriers in AD or MCI clinical trials showed slightly more cognitive impairment and greater decline using 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. *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.

Keywords

Alzheimer disease; mild cognitive impairment; apolipoprotein ε4; clinical trials; clinical trials simulations; biomarkers; Alzheimer's Disease Neuroimaging Initiative (ADNI); Alzheimer's Disease Cooperative Study (ADCS); Alzheimer's Disease Assessment Scale

BACKGROUND

The apolipoprotein E ε4 (*APOE* ε4) genotype is the major genetic risk factor for Alzheimer's disease (AD), 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) due to 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 β (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. The clinical trials for tacrine, performed in 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, 6, 7, 8]. Two retrospective analyses of clinical trials of subjects with MCI due to 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 due to AD based on *APOE* ε4 status, in which 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 non-carriers would more likely benefit from bapineuzumab perhaps due to lower Aβ burden or to fewer cerebrovascular adverse effects.

We empirically tested the potential efficiency of these recommendations by statistically simulating clinical trials scenarios of MCI due to AD or 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].

METHODS

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, 8 had both relevant clinical ratings and *APOE* genotyping, 6 for AD (DHA, CE, HC, LL, PR, SL, and ADNI) and 2 for MCI (MIS, ADNI) (Table 1). The primary outcome measure was the 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 over the first 2 years.

All diagnoses of dementia due to AD were based on NINDS-ARDRA criteria [16], with the additional requirement of a minimal severity based on clinical ratings. These were a Clinical Dementia Rating (CDR) [17] score of 2 or greater for the SL trial and Mini-Mental State Examination (MMSE) [18] scores between 14 and 26 (DHA, HC), between 12 and 28 (CE), between 12 and 26 (LL), and between 13 and 26 (PR). Diagnosis of amnestic MCI or MCI due to AD required a CDR score of 0.5 with the memory box scored at 0.5 or greater, and delayed recall from the Logical Memory II subscale of the Wechsler Memory Scale–Revised [19] to be ≤ 8 for 16 years of education, ≤ 4 for 8–15 years, or ≤ 2 for 0–7 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 anti-dementia drugs if they had been on stable doses prior to entry.

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 due to AD with one treatment and placebo group, 1:1 allocation ratio, and parameters selected to be consistent with previously published trials (e.g., [10], [21]). While 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 randomly choosing from the meta-database with replacement, i.e., patients from the dataset 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 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 randomly generated from a chi-square distribution with a mean equal to the expected treatment effect. The individual treatment effect was shifted by subtracting 2 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 below. Dropout rates of 20% and 40% in both the treatment and placebo groups were incorporated into the scenarios.

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, i.e., having genotypes of ε2/ε4, ε3/ε4, or ε4/ε4; and *APOE* ε4 noncarriers if they had no copies of the *APOE* ε4 allele, i.e., 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 above. 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 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 MMSE ≥ 16, i.e., milder impairment to better represent recent phase 2 and 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 1 copy of the ε4 allele and a rate of 100% enrichment would correspond to a trial enrolling only *APOE* ε4 homozygote carriers with 2 copies of the ε4 allele. Finally, because having one *APOE* ε2 allele appears particularly protective against AD, an exploratory simulation was performed using only the *APOE* ε2 carriers (i.e., those with genotypes ε2/ε2, ε2/ε3, or ε2/ε4), even though such a trial would not be pragmatic as only 10% of a sample with dementia due to AD would satisfy inclusion criteria that required *APOE* ε2 carriers.

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 between the treatment and placebo groups. The mixed effects model was employed as it utilizes data from all participants (rather than just completers) and minimizes bias and better controls 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 $i = 1,2$, n at visit $j = 1,2$, n_i, the full model was

$$ADAS_{i,j} = age_i + education_i + group_i + time_{i,j} + group_i \cdot time_{i,j} + \varepsilon_{i,j}$$

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 chi-squared distribution with the appropriate degrees of freedom. Secondary analyses examined last observation carried forward (LOCF) samples to impute missing values using the nonparametric Wilcoxon test to detect any differences between treatment and placebo groups due to the skewed distributions of the resultant outcomes. For all analyses, the missing data pattern present in the meta-database was used to realistically simulate dropouts; observations were missing in simulated datasets 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 3 digits. Power was calculated as the proportion of 1000 simulated trials per trial scenario having an a error p-value ≤ 0.05. Analyses were performed using version 2.15.0 of the R programming environment [26]. Mixed model analyses were performed using version 3.1-89 of the *nlme* package for R [27].

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

RESULTS

Patient characteristics

For both AD dementia and MCI due to AD, the *APOE* ε4 carriers and noncarriers were similar on most demographic and clinical characteristics, being predominantly Caucasian, married and highly educated (Tables 2 and 3). Slightly more than half of the MCI participants were males, while slightly more than half of the AD participants were females. 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.

Outcomes

Power calculations for the mixed model analyses are shown across a range of effect and sample sizes providing for 40% dropouts and 18-month duration for AD and 24-month for MCI due to AD (Figures 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 2% increase in power (Tables 4 and 5; additional details 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 above also did not show a meaningful 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 between diagnostic groups. (Supplemental Tables 3 and 4 and Supplemental Figures 1 and 2). Analyses using only milder dementia participants with MMSE ≥ 16 did not differ from results using all dementia participants (Supplemental Table 5 and Supplemental Figure 3). Simulations using only ε2 carriers (8.5% and 6.8% of the MCI due to AD sample and AD sample, respectively) did show slower progression and decreased variability compared to simulations predominantly involving ε3 and ε4, leading to slightly greater power to detect treatment differences (Supplemental Tables 6 and 7 and Supplemental Figures 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 1 or with 2 copies of the ε4 allele, echoing the results when simply selecting based on presence or absence of the ε4 allele (Supplemental Tables 8 and 9 and Supplemental Figures 6 and 7).

By 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.

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 due to 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 to 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 to that of cholinesterase inhibitors, an un-enriched trial with only 60% *APOE* ε4

carriers would require approximately 432 participants to achieve 80% power. By comparison, note that this is about 15% lower 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 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 trials 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 here assuming 40% are noncarriers, 1075 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 CSF $A\beta_{1–42}$ and $A\beta_{1–42}$ /t-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]. As approximately 60% of clinical trial participants are *APOE* ε4 carriers and 40% are non-carriers [30], selecting for *APOE* ε4 status fails to satisfy the former. (Even selection of *APOE* ε4 non-carriers, 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 as no differential response based on *APOE* ε4 status has been convincingly demonstrated 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 non-carriers, based on reduction of amyloid 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, while others arguing for better response among *APOE* ε4 non-carriers 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 due to AD and mild AD who were *APOE* ε4 carriers, 88% and 98%, respectively, had a low CSF Aβ level less than 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 indirectly imply an assumption of differential response when this was not intended.

Thus, *APOE* ε4 carriers who are ultimately enrolled in clinical trials may be more likely to be positive on CSF and PET Aβ biomarkers [32, 33, 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, 36, 37,

38, 39, 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 adversely affect trial outcomes, as demonstrated by our simulations. Despite greater clinical worsening of about 0.5 ADAS-cog points 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 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 trial [10] -- may mainly identify 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 due to 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 sizes, 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 pre-planned 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 (as 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, which were not examined in this study, but may preclude further analyses of differential effect of *APOE* status within the trial if the number of noncarriers becomes sufficiently small.

Finally, 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 due to AD. Thus, further research is needed before conclusions can be reached about APOE ε4 enrichment in the former type of design. Particularly 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 – 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 trials simulations based on the ADNI dataset [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, as the design of the ADNI study 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 due to 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 6 possible genotypes. This was also consistent with the goal of evaluating enrichment strategies for clinical trials, where more extensive stratification is not likely to be feasible. Similarly, this study did not evaluate the effects of different statistical model parameterizations, but instead utilized a single model with age and education as covariates. The random slope model has been recommended for the analysis of clinical trial data in Alzheimer's disease 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 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 as none has been consistently shown 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 due to *APOE* carrier status may not be sufficient to justify such screening strategies. Finally, although resampling strategies incorporate the variability from sample to sample that is usually not adequately contained in parametric models, even resampling may not capture all of 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 due to AD for a clinical trial on the basis of *APOE* ε4 carrier status (which also predicts amyloid-beta biomarker positivity) will most likely not enhance the trials' statistical power. Results of these simulations likely will be confirmed in the near future in ongoing clinical trials that utilize *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 to not require *APOE* ε4 genotyping for trials entry, but to restrict their use as explanatory or stratification variables when there are reasons to do so.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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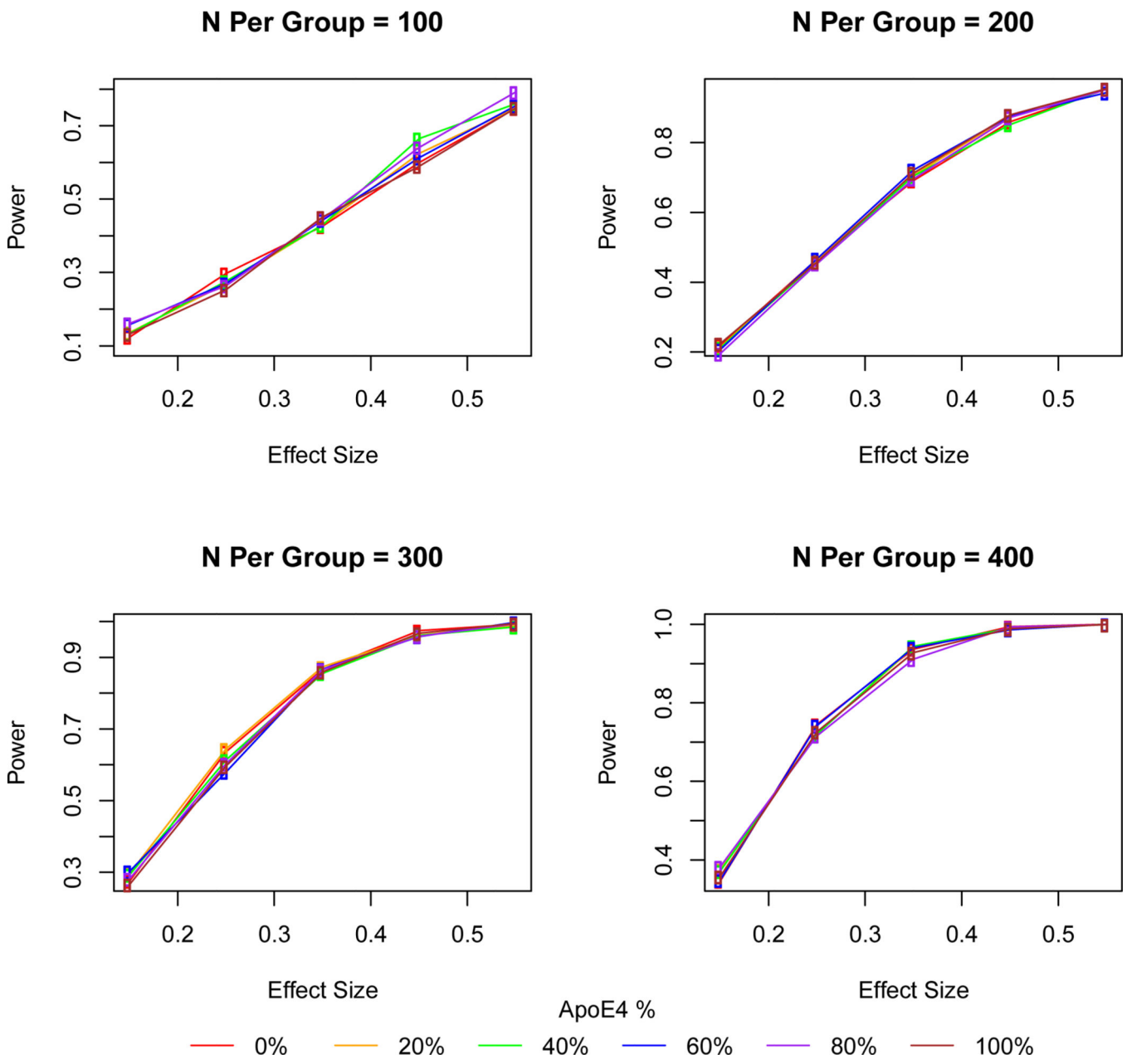

Figure 1. Power for ADAS-cog outcomes in 24 month long trials of participants with MCI due to AD

Power calculations for the ADAS-cog by effect size and sample size across with *APOE* ε4 carriers ranging from 0% to 100% of the sample. Enrichment based on *APOE* ε4 carrier status did not appreciably increase power under any of the scenarios. Simulation parameters included α=0.05, Chi-squared random errors, and 40% dropouts with mixed model analysis for participants with missing data.

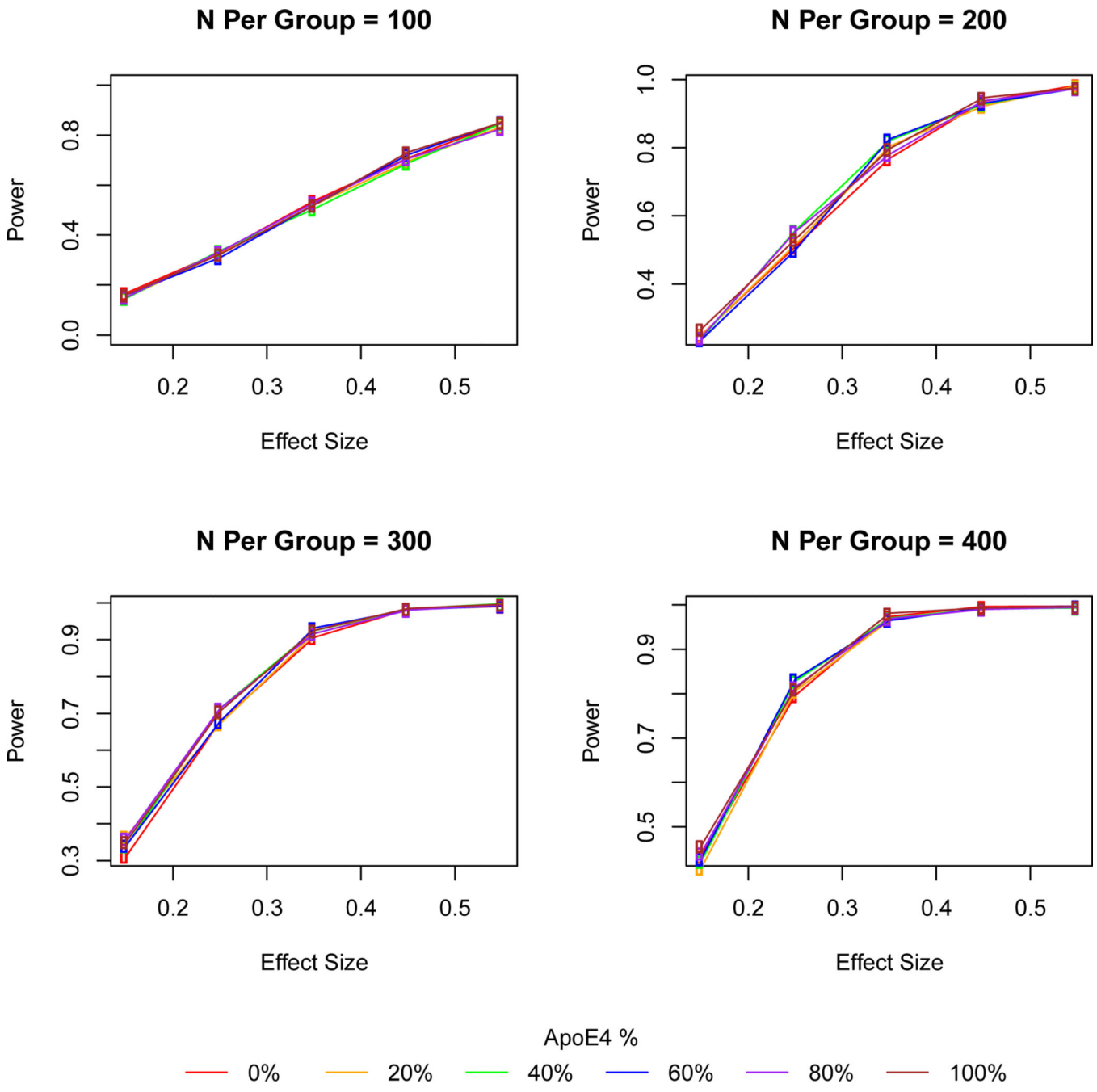

Figure 2. Power for ADAS-cog outcomes in 18 month long trials of participants with dementia due to AD

Power calculations for the ADAS-cog by effect size and sample size across with *APOE* ε4 carriers ranging from 0% to 100% of the sample. Enrichment based on *APOE* ε4 carrier status did not appreciably increase power under any of the scenarios. Simulation parameters included α=0.05, Chi-squared random errors, and 40% dropouts with mixed model analysis for participants with missing data.

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

Studies were drawn from the Alzheimer's Disease Cooperative Study (ADCS; http://www.adcs.org) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; http://adni.loni.ucla.edu) and included those with MCI or dementia due to AD and *APOE* genotyping.

Study (code), dates	Design	Intervention	N	Duration (months)
Selegiline, vitamin E, 1993–1996	RCT, moderate to severe AD	Vitamin E, selegiline	341	24
Prednisone 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)

Table 2

Clinical characteristics and ratings among participants with dementia due to AD based on *APOE* ε4 carrier status

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

Study Name		ADNI		DHA		ES		HC		LL		PR		Overall		
		ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	P-value
	N	(N=64)	(N=124)	(N=170)	(N=232)	(N=10)	(N=16)	(N=128)	(N=246)	(N=150)	(N=208)	(N=23)	(N=47)	(N=545)	(N=873)	
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)	<0.001
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)	0.9
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%)	0.077
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%)	0.001
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%)	0.85
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%)	0.19
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%)	<0.001
Baseline CDRsb	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)	0.65
Baseline MMSE	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)	0.06
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)	0.82
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)	0.18
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)	0.19
18 months	793	--	--	28 (13)	29 (12)			25 (12)	29 (12)	29 (12)	30 (12)	--	--	27 (12)	29 (12)	0.042
24 months	133	26.4 (9.9)	28.8 (12.6)	--	--	--	--	--	--	--	--	--	--	26.4 (9.9)	28.8 (12.6)	0.57

Table 3

Clinical characteristics and ratings among participants with MCI due to AD based on *APOE*4 carrier status

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

Study Name		ADNI		MIS trial		Overall		
		ε4−	ε4+	ε4−	ε4+	ε4−	ε4+	P-value
	N	(N=187)	(N=215)	(N=357)	(N=433)	(N=544)	(N=648)	
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)	0.054
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)	0.73
Ethnicity, Hispanic	1134	8 (4%)	6 (3%)	19 (6%)	9 (2%)	27 (5%)	15 (2%)	0.013
Marital status, married	1182	143 (78%)	172 (80%)	251 (71%)	353 (82%)	394 (73%)	525 (82%)	<0.001
Race, White	1134	165 (93%)	196 (94%)	303 (90%)	384 (94%)	468 (91%)	580 (94%)	0.046
Gender, Female	1134	60 (34%)	77 (37%)	146 (43%)	194 (47%)	206 (40%)	271 (44%)	0.18
APOE ε2 Carrier	1192	17 (9%)	11 (5%)	52 (15%)	21 (5%)	69 (13%)	32 (5%)	<0.001
Baseline CDRsb	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)	0.049
Baseline MMSE	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)	0.005
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)	<0.001
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)	<0.001
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)	<0.001
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)	<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)	<0.001

Table 4

Power for ADAS-cog outcomes in 24 month long trials of participants with MCI due to AD based on *APOE* ε4 carrier status

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 greater 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 α=0.05, effect sizes of 0.25 to 0.45 with Chi-squared random errors, and 40% dropouts with mixed model analysis for participants with missing data.

N per group	Effect Size	Apo 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

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Table 5

Power for ADAS-cog outcomes in 18 month long trials of participants with dementia due to AD based on *APOE* ε4 carrier status

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%, and for medium size effects of 0.45, somewhat greater than 100 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 α=0.05, effect sizes of 0.25 to 0.45 with Chisquared random errors, and 40% dropouts with mixed model analysis for participants with missing data.

N per group	Effect Size	Apo 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

N per group	Effect Size	Apo e4 %	Treatment group mean	Placebo group mean	Treatment group SD	Placebo group SD	Power mixed model
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

Table 6

Sample size calculations based on effect sizes and slope reductions. 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. 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.

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