Background: Factors that affect the rate of progression of Alzheimer disease (AD) need to be considered in the clinical trial designs of potential disease-modifying therapies.

Objective: To determine the influence of age on AD course in a clinical trial setting.

Design: Pooled cohort study from 3 AD clinical trials of 18-month duration conducted by the Alzheimer Disease Cooperative Study group.

Setting: Alzheimer disease research centers from across the United States.

Patients: Four hundred seventy-one subjects with mild to moderate AD assigned to the placebo arm of 3 clinical trials.

Main Outcome Measures: The relationships between baseline age and rate of change in the Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-cog) 11, Mini-Mental State Examination, Clinical Dementia Rating scale Sum of Boxes score, Alzheimer Disease Cooperative Study–activities of daily living scale, and Neuropsychiatric Inventory were analyzed using a mixed-effect regression model. Sample size calculation for possible future AD clinical trials lasting 18 months using the results of the change in ADAS-cog 11 by tertiles of age groups.

Results: Older age at baseline was associated with a slower rate of decline in the ADAS-cog 11 and the Mini-Mental State Examination scores. Almost twice as many subjects aged 80 years and older compared with those aged younger than 70 years would be required to demonstrate a 30% treatment effect on the ADAS-cog 11 in an 18-month AD trial.

Conclusion: Subject age is an important factor to consider when defining the study population in and analyzing data from AD trials of potential disease-modifying therapies.
US Alzheimer Disease Cooperative Study (ADCS), we explored the influence of age on disease course in clinical trial settings. We hypothesized that older individuals decline at slower rates than younger patients with AD in clinical trials.

Studies included in this pooled analysis shared the following characteristics: conducted by the ADCS since 2000; lasted 18 months or longer; and had as outcome measures the ADAS-cog 11, Clinical Dementia Rating scale–Sum of Boxes (CDR-SB), Mini-Mental State Examination (MMSE), Alzheimer Disease Cooperative Study–activities of daily living (ADCS-ADL), or Neuropsychiatric Inventory (NPI) scores.

Three studies fulfilled these criteria and involved trials with simvastatin, B vitamins/homocysteine lowering, and docosahexaenoic acid (DHA). Four hundred seventy-one subjects who were enrolled in the placebo arms (and who completed at least 9 months of the trial) were included in the analysis.

The following participant characteristics among the 3 trials were compared using a Kruskal-Wallis test for continuous variables and a Fisher-Freeman-Halton test for categorical variables: age, sex, education level, apolipoprotein E ε4 status, baseline Hachinski Ischemic and MMSE scores, blood pressure, creatinine levels, and use of antihypertensive or antidiabetes medications. The more common outcome measures used in AD trials (ADAS-cog 11, CDR-SB, MMSE, ADCS-ADL, and NPI scores) were examined across trials, with a linear regression line fit for each individual and fitted slope summarized for descriptive analysis. Univariate correlation analyses using Spearman correlation were performed between the fitted intercept and slope of each outcome measure and the predictors to assess degree of association.

The relationship between baseline age and each of the outcome measures over time was analyzed using a mixed-effects regression model. This model included time (months since baseline), age, trial (simvastatin, B vitamins/homocysteine lowering, and DHA), time by age interaction as fixed effects, and a random intercept and slope using a compound symmetry variance-covariance structure. Individual predictors that were associated with the outcome (P < .10) in the univariate correlation analysis were also included in the model as fixed effects. The association of age on rate of change in outcome measures over time was determined by the time by age interaction.

The potential impact that a differential effect of age on rate of change would have on the sample size for future clinical trials in AD was examined using the ADAS-cog 11. Sample size calculations were based on an analysis of covariance model, calculated for tertiles of age groups to compare 18-month mean change from baseline in ADAS-cog 11 between 2 treatment groups. The calculations assumed a 30% effect size, a correlation between baseline and 18-month ADAS-cog 11 scores of 0.78, a type I error of 5%, 80% power and used estimates of the expected mean 18-month change, and standard deviation of 18-month change obtained from the mixed-effects model for the different age groups.

All statistical analyses were conducted using R version 2.9.2 (R Foundation for Statistical Computing; http://www.r-project.org).

The details of the 3 studies included in the analysis along with baseline participant characteristics are listed in the Table. There were no significant differences in baseline age, sex, education, apolipoprotein E status, MMSE score, blood pressure, ADAS-cog, CDR-SB, ADCS-ADL, or NPI scores.

### RESULTS
among the studies. Owing to the nature of the inclusion/exclusion requirements, subjects in the simvastatin trial were less likely to be on antihypertensive and antidiabetes medications and had a slightly lower Hachinski Ischemic Score. Fewer of the DHA trial subjects were on cholinesterase inhibitors, and they were more likely to be taking memantine.

Overall, data from 471 placebo subjects were available. The mean age of the group was 76 years (range, 51-94 years), with the cohort relatively well educated (mean, 14 years), more likely to be female (58%), and possessing an apolipoprotein E ε4 allele (63%). Most subjects were taking a cholinesterase inhibitor (92%), with a substantial number (62%) also taking memantine.

Among the outcome measures, mean MMSE score at study entrance was 21. The MMSE score dropped on average 3.5 points during 18 months. For the ADAS-cog, mean baseline scores were 23.6, which declined approximately 7.4 points by 18 months. The CDR-SB moved on average from 5.7 at baseline to 8.4 by month 18, and the mean ADCS-ADL declined 10 points from 60.9 to 50.9.

Older age at baseline was significantly associated with a slower rate of decline in ADAS-cog 11, ADAS-memory subscore, and MMSE scores in an adjusted mixed-effects regression model. There was no relationship between older age and rate of change in CDR (either Sum of Boxes or Memory Box), ADCS-ADL, or NPI scores (Figure 1).

The potential effect of age on sample size calculations for future 18-month clinical trials using the ADAS-cog score as a primary outcome are shown in Figure 2. There was an age dose effect in the number of subjects needed to demonstrate a 30% treatment effect, with 66 patients required for those aged younger than 70 years, 92 needed for those aged 71 to 80 years, and 112 for those aged 80 years and older.

**COMMENT**

In this cohort of subjects with mild to moderate AD pooled from the placebo arms of 3 well-conducted clinical trials,
older age was associated with a slower rate of decline during 18 months measured by the ADAS-cog 11 (total and memory score) and MMSE scores. Based on the observed mean difference in 18-month change score, it would take almost twice as many subjects aged older than 80 years compared with a sample of subjects aged younger than 70 years to demonstrate a 30% treatment effect on the ADAS-cog in a clinical trial. It is clearly important to consider the age of the population entering a trial when making power calculations and determining the sample size.

The influence that age had on measures of cognitive change is consistent with previous research of the natural history of AD. Several cohort studies have reported a relationship between younger age at onset and more rapid rate of cognitive decline in those with AD.10-13 The population studies that failed to show this link between age and cognitive course either did not include participants aged younger than 65 years or had an older cohort in general.14,15 Brain atrophy measured by serial magnetic resonance imaging volumetric measures have been correlated with AD clinical decline and reflect the progression of neurofibrillary tangle distribution.16-18 Magnetic resonance imaging–based whole brain and temporal lobe atrophy rates have been reported to be faster in younger subjects particularly those with disease onset before age 65 years.19-21 Thus, both clinical and biomarker outcomes in trials may be influenced by age, with less progression in the older cohorts.

The different disease trajectories related to age may reflect different biological subtypes of AD. Pathological studies have reported greater neuritic plaque burden and greater cholinergic, noradrenergic, and serotonergic deficits in early-onset compared with late-onset AD.22,23 In vivo β-amyloid burden as measured by the positron emission tomographic radioligand carbon 11–labeled Pittsburgh compound B has been reported to be greater in subjects with early- vs late-onset AD.24 When AD is subtyped based on the distribution of histopathologic lesions into hippocampal-sparing, typical, and limbic-predominant cases, those with limbic-predominant AD are significantly older than either of the other 2 groups at onset and death. Limbic-predominant AD had a longer clinical course; lower Braak stage; and greater abundance of TDP-43, Lewy body, and vascular pathology than the hippocampal-sparing form.25 Although most cases at any age have typical AD, younger trial populations are likely to have a greater proportion of the hippocampal-sparing type of AD, whereas older trial participants will have a disproportionate number from the limbic-predominant group. The latter group has a longer duration of the disease to death and will progress more slowly in trials. In addition to the challenge of demonstrating the effect of therapy when the placebo group declines at a slower rate, the different distribution of pathology types in older patients may cause them to respond differently or not at all to agents that may produce benefit in younger patients.

The ε4 allele of the apolipoprotein gene is associated with earlier onset of AD.26 Adjusting our analysis for ε4 carrier status did not affect the conclusions, and the ε4 allele does not appear to account for the age-related effect observed in these trials.

In this analysis, age affected the rate of decline in the ADAS-cog 11 and MMSE scores but not on the CSR-SB, NPI, or ADCS-ADL measures. There may be several reasons for these discrepancies. Both the CDR-SB and ADCS-ADL capture global clinical or functional change.27,28 The influence of age may be too small to have a measurable clinical effect on these measures during 18 months. Elderly persons may be more adept at compensating for functional changes compared with cognitive changes. Cognition may also reflect involvement of areas of the brain more prone to be affected by the more aggressive earlier-onset form of the disease. Alternatively, the CDR-SB and ADCS-ADL may not be sensitive enough instruments to detect more subtle age-related differences.

The major implication of our study findings relates to future clinical trial design. Demonstration of a disease-modifying effect requires detecting a difference in decline between the active treatment and placebo groups. Factors that may attenuate the rate of placebo group decline need to be anticipated when planning sample size and recruitment. If the ADAS-cog 11 is used as a primary outcome measure in a trial, then intentionally limiting the number of older subjects may enhance the likelihood of placebo group decline and improve the chance of identifying a modest drug effect. Moreover, the sample size needed to show a reasonable drug effect would be smaller, potentially accelerating recruitment and conduct of the study. Though age restriction will reduce the generalizability of the results, it may allow a promising agent to proceed in clinical development. If a wide age range is included, power estimates and analysis plans must consider the impact of age, and stratifying randomization by age to ensure balance should be considered.

The conclusions of this study should be tempered by several considerations. The strengths of our study include the fact that the study population is representative in demographic features and rate of change on outcome measures of other AD trials.2 Moreover, the 3 trials...
selected for analysis were all conducted through the ADCS at sites that were very experienced in AD research. On the other hand, the included trials were of agents that are available over the counter or Food and Drug Administration–approved for other indications, raising the possibility that these trials may have attracted participants that differ in some characteristics from trials that are testing investigational agents with more perceived risk. Finally, the relationship between age and rate of ADAS-cog change may have been owing to an unidentified age-related factor but not owing to age itself.

There is currently a recognized need to design trials for disease-modifying therapies in a way to maximize the chance of detecting a beneficial effect while minimizing sample size and recruitment time. Depending on the primary outcome measures chosen, subject age is an important factor to consider in defining the study population and analyzing trial data.

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Correspondence: Charles Bernick, MD, Cleveland Clinic, Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106 (bernicc@ccf.org).

Author Contributions: Study concept and design: Bernick, Cummings, Sun, and Aisen. Acquisition of data: Bernick, Cummings, Ryan, Sun, and Aisen. Drafting of the manuscript: Bernick, Cummings, and Raman. Critical revision of the manuscript for important intellectual content: Bernick, Cummings, Ryan, Sun, and Aisen. Statistical analysis: Raman and Sun. Administrative, technical, and material support: Bernick and Cummings. Study supervision: Bernick and Aisen.

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