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Effect of study partner on the conduct of Alzheimer disease clinical trials

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ABSTRACT

Objective: Alzheimer disease (AD) dementia clinical trials require 2 participants: a patient and a study partner. We assessed the prevalence of study partner types and how these types associate with patient-related outcome measures.

Methods: Retrospective analyses of 6 Alzheimer's Disease Cooperative Study (ADCS) randomized clinical trials were conducted. Study partners were categorized as spouse, adult child, or other. Prevalence of study partner type and associations between study partner type and trial outcomes including study completion and placebo decline on the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale–cognitive subscale, the Clinical Dementia Rating scale Sum of the Boxes score, and the ADCS–Activities of Daily Living were examined.

Results: More participants (67%) enrolled with spouses than adult children (26%) or other study partners (7%). Participants with spouse partners had a lower dropout rate (25%) than those with adult child (32%) or other study partners (34%); only the difference vs others was statistically significant. Participants with adult child and other partners randomized to placebo performed worse at baseline than those with spouse partners on the ADCS–Activities of Daily Living ($p = 0.04$), but were not different at 18 months. There were no differences at baseline for the Mini-Mental State Examination, Clinical Dementia Rating scale Sum of the Boxes score, or Alzheimer's Disease Assessment Scale–cognitive subscale. In multivariate models of the rates of change over time among placebo participants, no differences among study partner groups reached statistical significance.

Conclusions: Patients with nonspouse caregivers less frequently participate in AD dementia trials. Increased enrollment of AD patients with nonspouse caregivers may require additional recruitment and retention strategies. *Neurology*® 2013;80:282–288

GLOSSARY

AD = Alzheimer disease; **ADAS-cog** = Alzheimer's Disease Assessment Scale–cognitive subscale; **ADCS** = Alzheimer's Disease Cooperative Study; **ADCS-ADL** = Alzheimer's Disease Cooperative Study–Activities of Daily Living; **AE** = adverse event; **CDR-SB** = Clinical Dementia Rating scale Sum of the Boxes; **CI** = confidence interval; **DHA** = docosahexaenoic acid; **MMSE** = Mini-Mental State Examination; **NSAID** = nonsteroidal antiinflammatory drug; **OR** = odds ratio; **SAE** = serious adverse event.

Alzheimer disease (AD) dementia clinical trials face a number of unique recruitment challenges and often struggle to achieve enrollment goals.[1] One challenge is the requirement of enrolling 2 participants: a patient and a study partner.

The primary caregiver generally fulfills the role of study partner. Patients with AD receive care from a multitude of persons. According to the most recent Alzheimer's Association's *Facts & Figures*, the 5.4 million Americans who have AD receive care from nearly 15 million spouses, relatives, and friends.[2]

This study examined how the relationship between AD patient and caregiver affects trial participation. Based on previous preliminary examinations,[1] we hypothesized that significantly more AD dementia trial participants were coenrolled with a spouse than any other type of study partner.

Supplemental data at www.neurology.org

Supplemental Data

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Patients with AD who are cared for by adult children are older than those cared for by spouses. Unmarried patients with mild cognitive impairment had a higher rate of drop out in a previous large multicenter dementia prevention trial.[3] Given these observations, we also hypothesized that participants with nonspouse study partners would have a lower rate of trial completion than those with spouse study partners. Finally, we modeled placebo decline among the study partner groups to examine whether the finding that patients with AD who have adult child caregivers may experience a faster rate of disease progression[4] is seen in clinical trials.

METHODS

Included trials. We conducted a secondary data analysis of Alzheimer's Disease Cooperative Study (ADCS) treatment trials that collected demographic information for the study partner and used similar inclusion/exclusion criteria. Six studies meeting these criteria were identified: trials of the nonsteroidal antiinflammatory drugs (NSAIDs) rofecoxib and naproxen,[5] B vitamin supplementation,[6] valproate,[7] the ω-3 fatty acid docosahexaenoic acid (DHA),[8] simvastatin,[9] and the Chinese herb huperzine.[10] Trials had similar designs (table e-1 on the *Neurology*® Web site at www.neurology.org). The simvastatin trial delivered 20 mg of study drug to all participants for 6 weeks and then randomized participants to 40 mg or placebo (1:1 ratio) for the remainder of the trial. All other trials randomized to drug or placebo at study onset, although varying ratios of drug to placebo were incorporated (table e-1). The huperzine and NSAID studies used 6- and 12-month protocols, respectively. The remaining studies had at least 18-month protocols.

Participants. For each trial, participants were required to meet National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD. The valproate study accepted patients with possible or probable AD; all other trials enrolled only patients with probable AD. Mini-Mental State Examination (MMSE) criteria for entry for the trials are listed in table e-1. With the exception of the huperzine trial, which excluded patients taking anticholinesterase drugs, patients were permitted to take FDA-approved AD medications, provided they were on stable doses at baseline. Minimum age criteria of the trials ranged from 50 to 55 years. None of the trials used an upper age limit as exclusion criteria. Trials had exclusion criteria specific to study designs. For example, the valproate trial excluded patients with previous behavioral symptoms (the primary outcome was the prevention of onset of such symptoms); the simvastatin trial excluded patients taking lipid-lowering medications; and the DHA trial excluded patients who consumed too high of DHA levels in their diet or took it as a supplement. Otherwise, standard exclusion criteria were applied; specifically, participants could not have another potential contributor to cognitive impairment and could not take anticholinergic or psychoactive drugs with the exception of those to treat behavioral symptoms, if at stable doses. Participants were categorized as having a spouse, adult child, or other study partner.

Study outcomes. We examined descriptive measures of subject and study partner demographics, the rate of adverse events (AEs) and serious adverse events (SAEs), and the proportion of participants who completed trials. We also examined placebo decline, as assessed by 4 frequently used clinical trial outcome measures: the MMSE,[11] the 11-item Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog[12]), the Clinical Dementia Rating scale Sum of the Boxes (CDR-SB[13]) score, and the ADCS–Activities of Daily Living[14] (ADL) scale.

Statistical analyses. Initial examinations compared trials to ensure consistency and appropriate combination of trial data. Statistical comparisons were performed by Pearson χ^2 test for dichotomous variables and analysis of variance for continuous variables. Descriptive statistics for participant and study partner demographics and the rate of AEs and SAEs across trials were compared among study partner categories. We used a logistic regression model for categorical variables and a linear regression model for continuous outcomes, as appropriate. Data sets were combined across the trials and study was included in the model as a fixed effect. For all analyses, data from 42 participants who experienced a change in study partner were excluded. We observed no differences in demographic variables among these 42 participants and those included in the current analyses.

To examine the impact of study partner type on disease progression, we analyzed data from participants assigned to placebo in the 4 trials with at least 18-month follow-up for the ADAS-cog, ADCS-ADL, and MMSE. Placebo data for the CDR-SB were available for the DHA, B vitamin supplementation, and valproate studies. Descriptive statistics (mean ± SD) compared each outcome measure at selected time points (baseline, month 6, month 12, and month 18) and the change from baseline at those time points. Mixed-effects regression models explored associations between study partner type and change in outcome measure scores over time, adjusting for trial, participant age, participant education, screening MMSE, participant gender, participant race/ethnicity (Caucasian vs non-Caucasian), study partner education, study partner gender, and study partner and participant coresidence. Time (in months) was treated as a continuous variable and the interaction between time and study partner type was specifically examined. Similarly, we modeled trial completion using multivariable logistic regression analyses adjusting for trial, participant age, participant education, screening MMSE, participant gender, participant race/ethnicity (Caucasian vs non-Caucasian), study partner education, and study partner gender. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to examine the risk of dropout among the study partner types.

All statistical analyses were conducted using R version 2.14.0 (www.r-project.org).

RESULTS

Comparison of the 6 trials. Among the 6 trials, rates of the proportion of study partner types were comparable (table 1; χ^2, $p = 0.09$), and no differences existed in the mean age or level of education of participants, or in the proportion of participants who were African American, Hispanic, or married (data not shown). Trials were similar in the proportion of genders of study participants (percentage female participants: DHA = 52%, vitamin B = 56%, huperzine = 64%, simvastatin = 60%, NSAIDs = 52%, valproate = 57%; χ^2, $p = 0.08$), but the genders of study partners demonstrated a significant effect among the trials (percentage female study partners: DHA = 67%, vitamin B = 68%, huperzine = 54%, simvastatin = 59%, NSAIDs = 59%, valproate = 59%; χ^2, $p < 0.01$).

Characteristics of the AD participants and their study partners. Among 2,041 ADCS trial participants,

Table 1 Study partner types across trials[a]

Trial	Study partner		
	Spouse	Adult child	Other
DHA	272 (67.7)	104 (25.9)	26 (6.5)
Vitamin B	249 (62.3)	119 (29.8)	32 (8.0)
Huperzine	127 (62.3)	65 (31.9)	12 (5.9)
Simvastatin	258 (67.3)	100 (25.1)	30 (7.5)
NSAIDs	254 (74.1)	69 (20.1)	20 (5.8)
Valproate	200 (68.0)	72 (24.5)	22 (7.5)
Total	1370 (67.1)	529 (25.9)	142 (7.0)

Abbreviation: DHA = docosahexaenoic acid; NSAIDs = nonsteroidal antiinflammatory drugs.
[a] Data are no. (%).

more enrolled with spouse study partners (67%) than adult child (26%) or other study partners (7%). Table 2 provides demographic summaries of the trial participants. Participants with adult child study partners were older and less educated than those with spouse or other study partner types. Fewer participants with spouses than with adult child or other study partners were female. Across the trials, only 5% of participants were Hispanic; those with an adult child study partner were twice as likely as those with spouse partners to be Hispanic. Similarly, 6% of all participants were African American; those with adult child study partners were nearly 3 times as likely to be African American as those with spouse study partners.

Table 3 summarizes the demographics of the study partners. Adult child and other study partners were younger and more likely to be female than spouse study partners. They less frequently lived with the participant than did spouse study partners. Seventy-one percent of spouse study partners, but only 20% of adult child and 44% of other study partners, were retired.

AE and SAE rates across study partner groups. Across trials, 91% of participants experienced AEs, whereas 26% of participants experienced an SAE. Multivariable logistic regression analyses indicated statistically significant differences in rates of AEs ($p = 0.03$) and SAEs ($p = 0.04$) across the 3 study partner groups. Fewer participants with adult child study partners experienced AEs compared with the spouse group (89% vs 92%; OR = 0.55; CI: 0.35, 0.86; $p = 0.01$). More participants with a study partner who was neither a spouse nor an adult child experienced SAEs compared with those with spouse partners (34% vs 24%; OR = 1.59; CI: 1.05, 2.39; $p = 0.03$) or adult child partners (34% vs 27%; OR = 1.69; CI: 0.68, 1.10, 2.60; $p = 0.02$). No difference between spouse and adult child study partner groups was observed for the rate of SAEs (OR = 0.94; CI = 0.68, 1.28; $p = 0.68$).

Rates of placebo decline among the groups. In univariate analyses, participants with adult child and other partners performed worse at baseline than those with spouse partners on the ADCS-ADL (table 1). No other differences in trial outcomes were observed at baseline. At 18 months, participants with spouse study partners performed worse than those with nonspouse study partners for the ADAS-cog (spouse = 33.9 ± 15.7; adult child = 30.9 ± 12.3; other = 29.1 ± 13.0; $p = 0.04$). No significant differences were observed for the ADCS-ADL, MMSE, or CDR-SB score (data not shown).

A mixed-effects regression model examined placebo decline, relative to baseline, among the study partner groups. Controlling for trial, participant age,

Table 2 Demographic characteristics of ADCS trial participants

Characteristic	Total sample	Study partner type			Comparison of study partner types, overall *p* value
		Spouse	Adult child	Other	
No. (%)	2,041 (100)	1,370 (67.1)	529 (25.9)	142 (7.0)	NP
Age, y, mean ± SD	75.7 ± 8.4	74.1 ± 8.2	80.0 ± 7.0	75.1 ± 9.6	<0.0001
Female gender, n (%)	1,148 (56.3)	588 (42.9)	456 (86.2)	104 (73.2)	<0.0001
African American, n (%)	126 (6.2)	49 (3.58)	62 (11.7)	15 (10.6)	<0.0001
Hispanic, n (%)	98 (4.8)	49 (3.6)	42 (7.9)	7 (4.9)	0.0004
Education, y ± SD	14.0 ± 3.1	14.5 ± 2.9	12.5 ± 3.2	14.7 ± 3.3	<0.0001
Screening MMSE, mean ± SD[a]	19.8 ± 4.0	20.0 ± 4.0	19.4 ± 4.0	20.2 ± 3.8	0.21
Baseline ADAS-cog, mean ± SD[a]	25.1 ± 10.3	25.1 ± 10.8	25.3 ± 9.4	24.5 ± 9.1	0.91
Baseline CDR-SB score, mean ± SD[a]	6.3 ± 2.9	6.2 ± 3.0	6.7 ± 3.0	5.8 ± 2.5	0.15
Baseline ADCS-ADL, mean ± SD[a]	59.7 ± 12.5	60.6 ± 11.9	57.8 ± 13.7	58.3 ± 12.5	0.04

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR-SB = Clinical Dementia Rating scale Sum of the Boxes; NP = not performed.
[a] Placebo participants only.

Table 3 Demographic characteristics of ADCS trial study partners

Characteristic	Total sample	Study partner type			Comparison of study partner types, overall *p* value
		Spouse	Adult child	Other	
Age, y, mean ± SD	66.1 ± 13.2	72.7 ± 8.9	51.5 ± 8.1	61.4 ± 14.5	$F = 889.1$, $p < 0.0001$
Female gender, n (%)	1,262 (61.8)	782 (57.1)	369 (69.8)	111 (78.2)	$F = 2{,}669.2$, $p < 0.0001$
Coresident with participant, n (%)	1,347 (79.3)	1,114 (99.8)	177 (38.5)	56 (45.9)	$p < 0.0001$[a]
Education, y ± SD	14.9 ± 2.8	14.6 ± 2.8	15.6 ± 2.6	14.7 ± 3.0	$F = 27.1$; $p < 0.0001$
Retired, n (%)	717 (55.2)	606 (71.5)	71 (19.7)	40 (43.5)	$F = 1{,}497.6$, $p < 0.001$

Abbreviation: ADCS = Alzheimer's Disease Cooperative Study.
[a] Unadjusted *p* value because of sparse data.

participant and study partner education, participant and study partner gender, participant race/ethnicity, screening MMSE score, and coresidence status, we did not find an interaction between study partner type and time for the ADCS-ADL (F value = 1.02, p = 0.36) or the CDR-SB score (F value = 0.08, p = 0.93). A trend toward significant interaction was observed between study partner type and time for the MMSE (F value = 2.60, p = 0.07) and the ADAS-cog (F value = 2.50, p = 0.08). Participants with spouse study partners demonstrated a trend toward significantly greater mean decline over time on the MMSE than did the adult child or the other study partner groups. Similarly, the spouse group demonstrated a faster rate of decline than the adult child partner group for the ADAS-cog (table 4; figure).

Trial completion. Across trials, a greater proportion of participants with spouse study partners (75%) than adult child (68%) or other study partners (66%) completed trials. The rates of dropout differed among the included trials (range: 16%–45%; table e-2). In a multivariable logistic regression model, trial, participant age, screening MMSE, and study partner type all predicted dropout. With spouse study partner as reference group, results showed that participants with other study partners but not those with adult child study partners were at increased risk to discontinue study participation (other: OR = 1.70; CI: 1.13, 2.56; p = 0.01; adult child: OR = 1.30; CI: 0.96, 1.76; p = 0.09). In subanalyses that included only trials for which participant and study partner living status was available, separate residence was not a significant predictor of dropout (OR = 0.8; CI: 0.54, 1.16; p = 0.23). Similar results were observed when examining treatment discontinuations (data not shown). Eight percent of participants who discontinued therapy still completed the study, including 5% of those with adult child partners, 9% of those with other partners, and 9% of those with spouse study partners (p = 0.11).

DISCUSSION Half of all unpaid AD caregivers are younger than 50 years[15] and as many as 68% are the children, children-in-law, or grandchildren of patients with AD.[16] In striking contrast, in this sample of 2,041 patients with mild-to-moderate AD participating in 6 clinical trials, 67% of all AD patient participants had a spouse as their study partner.

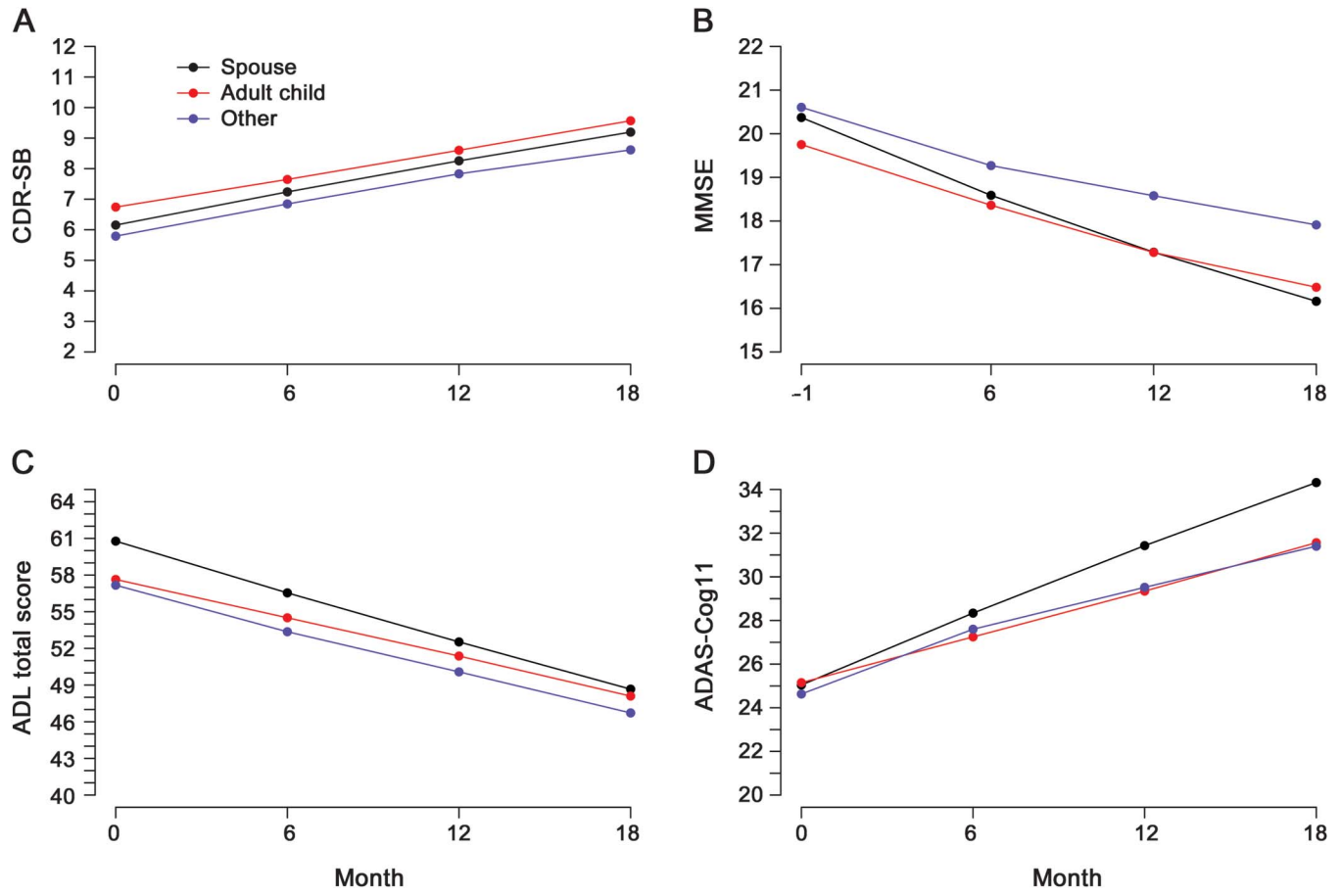
The current data do not explain why participants with nonspouse study partners were underrepresented. However, compared with spouses, adult child study partners were more likely to be working and living apart from the patient. This difference suggests

Table 4 Slope of mixed-effects model analysis (placebo patients only)[a]

Comparison	Estimate	Standard error	*p* Value
MMSE			
Adult child vs spouse	0.0426	0.0242	0.0789
Other vs spouse	0.0711	0.0409	0.0824
Other vs adult child	0.0284	0.0437	0.5156
ADCS-ADL			
Adult child vs spouse	0.0927	0.0669	0.1659
Other vs spouse	0.0658	0.1131	0.5609
Other vs adult child	−0.0270	0.1210	0.8238
CDR-SB			
Adult child vs spouse	−0.0070	0.0191	0.7135
Other vs spouse	−0.0060	0.0311	0.8469
Other vs adult child	0.0010	0.0335	0.9762
ADAS-cog			
Adult child vs spouse	−0.1030	0.0484	0.0336
Other vs spouse	−0.0864	0.0826	0.2953
Other vs adult child	0.0165	0.0882	0.8513

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR-SB = Clinical Dementia Rating scale Sum of the Boxes; MMSE = Mini-Mental State Examination.
[a] Estimates and *p* value obtained from a mixed-effects regression model including trial, participant age, participant education, screening MMSE, participant gender, participant race/ethnicity (Caucasian vs non-Caucasian), study partner education, study partner gender, and study partner and participant coresidence as covariates.

Figure Change in Alzheimer disease trial clinical and cognitive outcome measures



Change in the Clinical Dementia Rating scale–Sum of Boxes (CDR-SB) (A), Mini-Mental State Examination (MMSE) (B), Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADL) total scale (C), and Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog11) (D) scores over time for participants with spouse, adult child, and other study partners, using a linear mixed-effects regression model.

that patients with AD who have adult child caregivers face increased logistical challenges to research participation. Adult child caregivers also see their burden as greater[17] and patient quality of life as poorer[18,19] than do spouse caregivers. These differences in attitude may have a negative impact on the likelihood of research participation. Another possible reason is that trials typically require patients with mild severity and thus enroll young AD patients who, in turn, may be more likely to have spouses. Among patients with probable AD enrolled in the National Alzheimer's Coordinating Center Uniform Data Set, however, patients with a nonspouse study partner are less likely than those with spouse study partners to be eligible for typical AD trial entry criteria, even when controlling for age.[20] Although screen fail data were not available to examine this hypothesis in the current set of trials, it is possible that patients with adult child caregivers were less frequently eligible for these trials.

Between participants with spouse and adult child study partners, we observed several relevant differences that could affect trial conduct, results, and interpretations. Among the participants in this set of trials, 11% were of minority race or ethnicity. This low proportion is similar to previous observations in NIH-sponsored AD dementia trials,[21] and represents an important area of need in AD research. Minority patients with AD are more likely to receive care from nonspouse family members, relative to Caucasians.[22,23] For example, despite accounting for approximately a quarter of the total population in this set of trials, patients with adult child partners accounted for nearly half (46%) of all minority participants. Thus, increasing enrollment of patients with AD who have adult child caregivers may facilitate increased minority participation. To enhance enrollment of patients with AD who have nonspouse caregivers, investigators designing AD dementia trials may need to use inclusion criteria that allow for increased participation rates (e.g., no or high upper age limit and lower MMSE exclusion criteria[20]).

Our results suggest that enhanced enrollment of patients with AD who have nonspouse caregivers could present new challenges to investigators. Among participants with other study partners, the rates of SAEs were

slightly higher and they were more likely to drop out. Additional strategies toward participant retention may be necessary for these patients. Placebo decline on the ADAS-cog and the MMSE trended toward a difference among the study partner groups. To the extent that study partner type may affect trial data interpretation, investigators may need to consider adjusting designs to account for such differences. Interestingly, differences among the groups in placebo decline were observed for caregiver-independent, but not caregiver-dependent scales. It is unclear why some scales showed differences whereas others did not.

In this sample, observed differences among study partner groups suggest that trial participants with adult child study partners may have progressed slower on some outcome measures than did those with spousal study partners even after controlling for age. Nevertheless, participants with adult child study partners are older than those with spouse study partners, and a similar analysis of a smaller sample of ADCS trials recently demonstrated slower decline on the ADAS-cog and MMSE among older, relative to younger, AD trial participants.[24] Our observations are in contrast, however, to findings from the Cache County community-based study that suggested accelerated decline among patients with AD who have adult child caregivers.[4] The discrepancy between the current findings and those from the Cache County study may result from differences between research and community populations. Patients and caregivers who participate in AD dementia trials may differ from those who do not participate, and these differences may have benefits beyond participation.[25] Such differences may be magnified in the patients with AD who have adult child caregivers who overcome additional barriers to participate in trials.

This study has some limitations. The sample of AD dementia trials was limited to federally funded studies conducted largely by academic trial sites. It is unclear how the current results may relate to larger trials, including those supported by industry, which recruit to more diverse site types. The low number of minority participants made examination of effects of race or ethnicity on trial outcomes challenging. We examined only a subset of available AD trial clinical and cognitive outcome measures. Future studies should replicate these findings and should explore how differences between study partner groups may or may not relate to the type of outcome measure used to assess disease progression.

AUTHOR CONTRIBUTIONS

Dr. Grill: study concept and design, analysis and interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Raman: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Ms. Ernstrom: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Aisen and Dr. Karlawish: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

J. Grill has served as consultant to Avanir and Phloronol; and serves as site investigator for clinical trials sponsored by Elan, Genentech, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb, Medivation, Pfizer, and the Alzheimer's Disease Cooperative Study. R. Raman and K. Ernstrom report no disclosures relevant to the manuscript. P. Aisen serves on a scientific advisory board for NeuroPhage; serves as a consultant to Elan Corporation, Wyeth, Eisai Inc., Schering-Plough Corp., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co., Roche, Amgen, Genentech, Inc., Abbott, Pfizer Inc., Novartis, Bayer, Astellas, Dainippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, and Medivation, Inc.; and receives research support from Pfizer Inc., Eli Lilly and Company, and Baxter International Inc., and the NIH (NIA U01-AG10483 [PI], NIA U01-AG024904 [Coordinating Center Director], NIA R01-AG030048 [PI], and R01-AG16381 [Co-I]). J. Karlawish reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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