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Authors
Hakhu, Navneet R
Gillen, Daniel L
Grill, Joshua D
et al.

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Dyadic enrollment in a phase 3 mild cognitive impairment clinical trial

Navneet R. Hakhu, MS,
Department of Statistics, University of California, Irvine, Irvine, CA, USA

Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA

Daniel L. Gillen, PhD,
Department of Statistics, University of California, Irvine, Irvine, CA, USA

Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA

Alzheimer's Disease Research Center, University of California, Irvine, Irvine, CA, USA

Joshua D. Grill, PhD,
Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA

Alzheimer's Disease Research Center, University of California, Irvine, Irvine, CA, USA

Department of Psychiatry & Human Behavior, University of California, Irvine, Irvine, CA, USA

Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA, USA

Alzheimer's Disease Cooperative Study

Abstract

Background: Dyadic enrollment of a participant and study partner is required in mild cognitive impairment (MCI) clinical trials, despite participants being functionally independent. Research examining how the study partner requirement impacts MCI trials remains limited.

Methods: Using the Alzheimer's Disease Cooperative Study donepezil and vitamin E MCI trial data, we quantified the proportions of enrolled spouse, adult child, and other dyads. We used multinomial regression to identify which baseline participant characteristics (age, sex, race and ethnicity, apolipoprotein E (APOE) ε4 status, education, residence type) were associated with dyad type.

Results: Among 769 randomized dyads, 73% were spousal, 14% adult child, and 13% other dyads. Adjusting for multiple comparisons, underrepresented racial and ethnic background (e.g.,

Corresponding author (including address for reprints): Navneet R. Hakhu, Department of Statistics, Bren Hall 2019, University of California, Irvine, Irvine, CA, 92697-1250, USA, Phone: (408) 348-4175, nhakhu@uci.edu.
Daniel L. Gillen and Joshua D. Grill are co-senior authors.

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comparing Hispanic to non-Hispanic White participants: adult child vs. spouse odds ratio, OR=5.9; 95% CI: 2.09, 16.5; other vs. spouse OR=5.0; 95% CI: 1.83, 13.4), female sex, age, non-house residence, and APOE ε4 non-carriage were each associated with a higher odds of having an adult child, as well as an other, study partner at enrollment.

Discussion: Increasing participation among non-spousal dyads may facilitate more inclusive and representative MCI trial samples.

Background

Clinical trials enrolling people living with Alzheimer's disease (AD) dementia universally require dyadic enrollment of a participant and study partner. Study partners are vital to trial success.[1] They provide transportation, report medical history and adverse events, ensure compliance with medications and study visits, and serve as informants for trial outcome measures.[1–3] Additionally, study partners may serve as surrogate providers of informed consent and play a critical role in the decision to participate in trials.[4] Previous examinations of AD dementia trials reveal consistent patterns of enrollment by dyad type in which spousal dyads outnumber non-spousal dyads by a ratio of 2:1,[5] despite a predominance of non-spousal caregivers, including over 50% adult children,[6] in the United States.

In an effort to intervene earlier in disease, AD trials now include patients with mild cognitive impairment (MCI). MCI is defined as performance on cognitive tests that is below that expected based on age and education norms, but does not result in functional impairment or fulfill criteria for dementia.[7] Though individuals with MCI are functionally independent, MCI trials still require participants to enroll with a study partner, given that several key trial outcome measures were adopted from AD dementia trials and require an informant.

The impact of the study partner requirement in MCI trials is less understood than it is for AD dementia trials. We examined potential relationships between dyad type and baseline participant characteristics. Such findings may better inform future trials including designs, recruitment efforts, and generalizability of results. To this end, we had three aims in this study: (1) to quantify enrollment in an MCI trial by dyad type; (2) to identify participant-level characteristics associated with study partner type at baseline; and (3) to compare baseline participant-level characteristics across dyad types. To achieve these objectives, we performed retrospective analyses using data from the phase 3 Alzheimer's Disease Cooperative Study (ADCS) trial of donepezil and vitamin E as potential disease-slowing treatments for MCI.[8]

Study Methods

Data source

The ADCS donepezil and vitamin E MCI trial began in 1999 and was completed in 2004. Eligible participants were 55 to 90 years old, had baseline Mini-Mental State Examination (MMSE) scores from 24 to 30, Clinical Dementia Rating (CDR) global scores of 0.5, and had a study partner at baseline who spent at least 10 hours per week with the participant and agreed to ensure the participant's compliance with study drug, report adverse events, and attend all study visits. In total, 790 participants were randomized at one of 72 sites

in Canada or USA to one of three arms: Donepezil, Vitamin E, or Placebo. The primary outcome of the trial was time from randomization to clinical diagnosis of possible or probable AD (dementia) based on the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association criteria.[9] Participants were followed for a maximum of 3 years post-randomization with visits scheduled at baseline, month 3, and every six months from month 6 to month 36. All 769 randomized participants who had a baseline assessment were included in this study to form the full analysis set population. Baseline refers to participant or study partner information recorded at the screening or baseline study visits, although data were available only for those participants randomized in the study. Data used in the preparation of this manuscript were obtained from the University of California, San Diego ADCS Legacy database.

Data analysis/statistical methods

The primary outcome of this study was dyad type. We classified dyad types based on the relationship of the study partner to the participant with MCI: spouse, adult child, or other study partner. Based on previous analyses in dementia, we classified daughters, daughters-in-law, sons, and sons-in-law as adult child study partners, and anyone who was neither a spouse nor an adult child (e.g., sibling, friend, paid caregiver) as other study partners. Secondary outcomes were baseline participant characteristics, namely participant age (years), sex as a biological variable (female vs. male), race and ethnicity, apolipoprotein E (APOE) ε4 carrier status, education (years), and residence type. Due to sparsity for combinations of race and ethnicity and study partner type, we collapsed race and ethnicity from six to five categories: American Indian or Alaskan Native (AIAN), other, or unknown; Asian or Pacific Islander; Hispanic; non-Hispanic Black; and non-Hispanic White. Due to a similar sparsity issue, we collapsed residence type from seven to three categories that reflect similar living situations: house; condominium/apartment/trailer; and retirement community/assisted living/other.

For descriptive analyses, we reported the mean ± standard deviation (SD) for continuous characteristics, including study partner age and education, and counts with column percentages for categorical characteristics (ordered by descending frequency based on total counts), including marital status. We produced violin plots to compare the distributions of baseline study partner time spent with participant (hours per week) by dyad type.

For the primary analysis, we used multinomial regression to simultaneously model the relative odds of having an adult child vs. spouse study partner and the relative odds of having an other vs. spouse study partner. The predictors of interest included the baseline participant characteristics previously mentioned except for marital status. The category with the largest observed proportion for a multicategory variable served as the reference group in inferential analyses (e.g., non-Hispanic White for race and ethnicity; and house for residence type). We reported the estimated odds ratios (OR) and corresponding 95% confidence intervals (CI) from unadjusted analyses and adjusted analyses for pre-specified potential confounding factors and independent risk factors for study partner type (i.e., *a priori* believed to be casually associated with study partner type and not causally associated with the predictor of interest). These adjustment factors included participant age, female sex,

racial and ethnic background, APOE ε4 carrier status, education level, and residence type. Baseline study partner characteristics were *a priori* conjectured to be neither confounding factors nor independent risk factors of the outcomes, and hence were not included as covariates in the inferential model. To test whether the relative odds of adult child vs. spousal dyads was the same as the relative odds of other vs. spousal dyads, we computed a global *p* value based on a multivariate Wald test. For the primary analysis, we fit a multinomial regression model including all six predictors of interest described above and performed a multivariate Wald test for each predictor (six pre-specified analyses in total). To account for multiple comparisons, instead of the typical Bonferroni correction,[10] which tends to yield conservative inference (i.e., the type 1 error rate is lower than the pre-specified statistical significance level α), we used a Holm-Bonferroni correction[11] because it is less conservative while still maintaining the family-wise type 1 error rate of α and has more statistical power. To this end, instead of the typical two-sided statistical significance threshold of $\alpha = 0.05$ (when not adjusting for multiple comparisons) or the Bonferroni correction (a single common statistical significance threshold of 0.05/6 = 0.008 would have been used to compare each of the six *p* values), the Holm-Bonferroni threshold depended on the rank (*k*) of the *p* value after ordering the six *p* values from smallest to largest, $0.05/(6 - k + 1)$, corresponding to thresholds of 0.008, 0.01, 0.013, 0.017, 0.025, 0.05, respectively.

In secondary analyses, we compared baseline participant characteristics across dyad types. For continuous outcomes, we used linear regression with robust standard errors[12] to model the difference in means. For categorical outcomes, we used either logistic regression (for binary outcomes) or multinomial regression (for outcomes with at least three categories) to simultaneously model the relative odds of each non-reference category versus the reference category. We pre-specified potential confounding factors and independent risk factors for each outcome. For participant age as the outcome, we adjusted for participant sex, APOE ε4 carrier status, and racial and ethnic background. Since *a priori* we did not believe that any of the available data are independently causally associated with sex or race and ethnicity, no adjusted analyses were performed when these were outcome variables. For APOE ε4 carrier status as the outcome, we adjusted for participant sex and racial and ethnic background. For participant education level as the outcome, we adjusted for participant age, sex, and racial and ethnic background.[13] For participant residence type as the outcome, we adjusted for participant age, sex, racial and ethnic background, and marital status. Unadjusted and adjusted analyses were reported, as indicated above, along with a corresponding point estimate (e.g., difference in means or odds ratio) and 95% CI. As these secondary analyses served to support the primary analysis findings, no formal statistical significance tests were conducted, and hence the secondary analyses did not factor into the multiple comparisons correction noted above.

There were no missing data for study partner type or baseline participant characteristics. Two participants had missing baseline study partner characteristics: one spouse study partner had missing age; and one adult child study partner had missing age and years of education. This had no impact on the inferential analyses performed. Also, we assessed potential influential observations using delta betas and Cook's distance.[14] We found no qualitative differences in the effect sizes based on sensitivity analyses in which we removed potentially

influential observations. Hence, no participants were removed in the reported analyses. All analyses were performed using R version 4.0.3 for Mac OS.[15]

Results

Among 769 randomized participants included in this study, 560 (73%) enrolled with a spouse study partner, 109 (14%) enrolled with an adult child study partner, and 100 (13%) enrolled with an other study partner. Table 1 summarizes baseline participant and study partner characteristics. Overall, the mean age of participants was 73.0 ± 7.3 years; 45.8% were female; 92.1% were non-Hispanic White; 55.1% were APOE ε4 carriers; 73.6% lived in a house; and 77.6% were married. Participants with spouse study partners were 72.4 years old. Most were male, non-Hispanic White, APOE ε4 carriers, and lived in a house. Participants with adult child study partners were 75.6 years old on average. Most were female, non-Hispanic White, lived in a house, and were widowed. Fewer than half were APOE ε4 carriers. Participants with other study partners were 73.9 years old on average. Most were female, non-Hispanic White, lived in a house, and were either widowed or divorced. Forty-two percent were APOE ε4 carriers. On average, spouse study partners were older (69.5 years) than adult children (45.9 years) and other (64.4 years) study partners. Figure 1 summarizes baseline study partner time spent with participants by dyad type. On average, spouses spent 94.3 hours per week with the participant compared to 23.4 hours per week for adult children and 35.1 hours per week for other study partners.

Table 2 summarizes unadjusted and adjusted multinomial regression analyses with dyad type as the primary outcome. In unadjusted analyses, each of the six baseline participant characteristics was associated with dyad type. In analyses adjusting for potential confounding factors and independent risk factors, we found that participant age, female sex, underrepresented racial and ethnic background, APOE ε4 non-carrier status, and non-house residence type were each associated with a higher odds of having an adult child as well as an other study partner, respectively (spouse study partner as the reference group in each case). For example, comparing Hispanic to non-Hispanic White participants, we estimated the odds of having an adult child study partner to be 5.9-fold higher (OR=5.9; 95% CI: 2.1, 16.5) and the odds of having an other study partner to be 5.0-fold higher (OR=5.0; 95% CI: 1.8, 13.4), compared to having a spouse study partner, respectively.

Regression analyses for each of the secondary outcomes are summarized in Table 3. We found that dyad type was associated with several secondary outcomes including participant age, female sex, racial and ethnic background, and APOE ε4 carrier status. For example, we estimated the odds of a participant identifying as Hispanic to be 4.4-fold higher for adult child dyads (OR=4.4; 95% CI: 1.8, 10.7) and 5.1-fold higher for other dyads (OR=5.1; 95% CI: 2.1, 12.5), compared to spousal dyads. For brevity and ease of exposition, we omitted residence type from the table. No statistically significant difference was observed between dyad type and residence type.

Discussion

To our knowledge, this is among the first reports to examine the characteristics of participant dyads in MCI clinical trials. In the donepezil and vitamin E MCI trial, nearly three-quarters of participants enrolled with a spouse study partner. The proportion of non-spouse study partners was evenly split between adult child and other study partners. We found that underrepresented racial and ethnic backgrounds (i.e., being of non-White race or Hispanic ethnicity), age, and APOE ε4 non-carrier status were associated with a higher odds of having a non-spouse study partner. These findings may have implications to MCI trial recruitment strategies and inclusion/exclusion criteria, as well as study statistical power and generalizability of results.

That the majority of participants enrolled with a spouse study partner is consistent with AD dementia trials[5,16] and other MCI research.[17–20] The current data do not explain the apparent recruitment bias. It is possible that MCI participants lacking a spouse may have been differentially excluded.[21]. Unfortunately, screening data were not available to examine this possibility. Alternatively, the seemingly skewed rates of spousal dyad participation may be related to differential decision-making among dyad types.[4] In AD dementia trials, Cary and colleagues[22] found that spousal caregivers were associated with a higher willingness to participate in trials. Similarly, in another MCI study, spousal dyads tended to make a decision about enrolling in a trial in partnership, but non-spousal dyads tended to have relatively lower agreement and availability.[23] These findings may indicate that, as in AD dementia trials, the study partner requirement is a barrier to recruitment in MCI trials for at least some dyads.

Unfortunately, enrolled samples in AD trials[24,25] and in clinical trials in general suffer from gross underrepresentation of several racial and ethnic groups. Based on the 2021 Alzheimer's Disease Facts and Figures Special Report Race, Ethnicity and Alzheimer's in America[6] and the 2020 Profile of Older Americans,[26] among the estimated 6.2 million individuals aged 65 years or older with AD dementia in the US, 66% identify as White, 19% identify as Black, and 10% identify as Hispanic. The donepezil and vitamin E trial, in contrast, enrolled predominantly non-Hispanic White participants (92%)—with only 4% Hispanic and 2% non-Hispanic Black participants—a sample unlikely to be representative of the true MCI population.[27] More recently, the aducanumab clinical trials of individuals with MCI due to AD or mild AD had 97% (Study 103, proof-of-concept), 75% (Study 301, phase 3), and 78% (Study 302, phase 3) White participants randomized.[28] Nearly thirty years ago, the National Institutes of Health (NIH) Revitalization Act of 1993 led to the NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research.[29] Yet, underrepresentation still plagues clinical research. The US Food and Drug Administration's guidance documents on the collection of racial and ethnic background information[30] and enhancing diversity[31] in clinical trials are recent efforts to address underrepresentation. Increasing enrollment of diverse racial and ethnic groups in MCI trials is imperative to identify whether benefit-to-risk ratios may differ according to racial and ethnic background (i.e., differential safety or efficacy profiles due to effect modification by race and ethnicity).[32] We observed that participants from each underrepresented racial and ethnic background (four distinct groups: AIAN, other, or unknown; Asian or Pacific

Islander; Hispanic; non-Hispanic Black) were associated with a higher odds of having a non-spouse study partner. Additionally, we found that having a non-spouse study partner was associated with a higher odds of being from a specific underrepresented racial and ethnic background. These associations are consistent with observations in AD dementia trials[5] and may suggest that one way to address the lack of representativeness of racial and ethnic backgrounds in enrolled samples is to implement recruitment strategies to increase enrollment of non-spousal dyads. We also found that participants with an adult child or other study partner were associated with less frequently living in a house. This may indicate that these participants were of lower socioeconomic status than their counterparts with spouse partners. If their study partners were similarly of relatively lower socioeconomic status, this could have had implications to their ability to take time off from work or to travel to the study site for participation in visits. Implementing methods that make it easier for non-spouse study partners to participate, such as remote consenting and data capture through telephone or online approaches may therefore be key to increasing representation of these groups. Another interesting possibility is that these individuals may less frequently qualify to serve as study partners based on protocol-defined requirements (e.g., spending at least 10 hours per week with the participant for the donepezil and vitamin E trial). This possibility, and the potential implications of reducing the requirements to be an eligible study partner to trial data integrity warrant further study.

Other associations observed here may impact trial outcomes. For example, we found that having a non-spouse study partner was associated with older participant age. In dementia trials, older age is associated with slower rates of cognitive decline, potentially reducing trial power.[33,34] Alternatively, older age may be associated with slightly increased risk of progression from MCI to dementia,[35] so inclusion of older participants may increase power in trials with a design similar to the ADCS donepezil and vitamin E trial. In any case, lessening the restrictions on age may improve generalizability of results since older age is the most essential risk factor for MCI and AD dementia and constitutes the overwhelming majority of cases (now and in the future).[6,36–38]

Having a non-spouse study partner was also associated with a lower odds of being an APOE ε4 carrier. APOE ε4 carriers have a higher risk than do non-carriers of developing AD dementia.[35] Yet, the literature on APOE prevalence and risk among underrepresented racial and ethnic groups is mixed and remains limited. While larger studies consistently find higher risk for AD among APOE ε4 carriers,[6,39–41] the prevalence of APOE ε4 carriage varies among and within racial and ethnic groups[6,39] and the relationships with MCI[42,43] and AD biomarkers are complex.[44] Thus, it is not entirely clear what the implications of increasing enrollment of non-spousal dyads, especially those from underrepresented racial and ethnic groups, would be to study power in MCI trials.

Our study had several limitations. First, the trial data source is approximately two decades old. Yet, the observed rates of participation and associations with participant characteristics are unique contributions to the MCI trials literature not previously reported. Current MCI trials typically enrich for AD biomarkers, a construct referred to as MCI due to AD[45] or prodromal AD.[46] We lacked data to consider the implications of these biomarker criteria. Furthermore, factors that impact study partner type are likely to include those beyond

the available data, such as comorbidities, socioeconomic status, family size, geographic proximity to the participant, and study partner employment status and other responsibilities that could restrict availability. We did, however, have the ability to adjust for what are likely to be some of the largest confounding factors that play a role in the estimated associations. In the donepezil and vitamin E trial, gender was recorded as female or male. We recognize that gender and sex are separate constructs;[47] when this trial was recruiting, distinctions between gender and sex were less common. For our analyses, we assumed that gender recorded as female or male was meant to represent biological sex. Lastly, we did not have the screening data for individuals who were not randomized, which would have allowed us to compare reasons for screen failure across dyad types.

Enrolling a representative sample from the target patient population is paramount for external validity of MCI trial results. We found associations between participant characteristics (race and ethnicity, age, and APOE ε4 carrier status) and dyad type. One way to improve representativeness by race and ethnicity in MCI trials is to continue efforts to identify and overcome barriers for non-spousal dyads. In planning future trials, investigators may wish to consider the pros and cons of potential inclusion/exclusion criteria and recruitment strategies based on baseline participant characteristics and study partner type. The resultant distributions of study partner dyad types may have implications to inclusivity, power, and generalizability. Hence, we recommend sponsors and investigators consider the following when designing future MCI trials:

- Expand recruitment strategies to include: open-access screening programs[48] (to improve chances of identifying individuals who may not be seen at a research-affiliated clinics), community-based strategies[49] (to recruit from sites including churches and senior centers), and population-based methods such as random digit dialing.
- Modify eligibility criteria as appropriate, especially with respect to what determines an eligible study partner, to limit potential barriers for study partners to enroll in trials.
- Reduce the burden on study partners of enrolling and staying in trials via remote consenting, in-home treatment administration (e.g., for infused therapies), incentives and compensation for time on study and time off work, and online or telephone assessments whenever possible.[50]

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Conflicts of Interest and Source of Funding:

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Data Availability Statement:

The datasets generated during and/or analyzed during the current study are not publicly available. They were made available through the University of California, San Diego ADCS Legacy database.

Abbreviations

AD	Alzheimer's disease
ADCS	Alzheimer's Disease Cooperative Study
APOE	Apolipoprotein E
CDR	Clinical dementia rating
CI	Confidence interval
FDA	Food and Drug Administration
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
NIH	National Institutes of Health
OR	Odds ratio
SD	Standard deviation

References

1. Largent EA, Karlawish J, Grill JD. Study partners: essential collaborators in discovering treatments for Alzheimer's disease. Alzheimer's research & therapy. 2018;10(1):1–7.
2. Black BS, Taylor H, Rabins PV, Karlawish J. Researchers' perspectives on the role of study partners in dementia research. International psychogeriatrics/IPA. 2014;26(10):1649.
3. Black BS, Taylor HA, Rabins PV, Karlawish J. Study partners perform essential tasks in dementia research and can experience burdens and benefits in this role. Dementia. 2018;17(4):494–514.
4. Karlawish JH, Casarett D, Klocinski J, Sankar P. How do AD patients and their caregivers decide whether to enroll in a clinical trial? Neurology. 2001;56(6):789–792. [PubMed: 11274319]
5. Grill JD, Raman R, Ernstrom K, Aisen P, Karlawish J. Effect of study partner on the conduct of Alzheimer disease clinical trials. Neurology. 2013;80(3):282–288. [PubMed: 23255824]
6. Alzheimer's Association. 2021 Alzheimer's Disease Facts and Figures. Alzheimers Dement; 2021; 17(3).
7. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Archives of neurology. 1999;56(3):303–308. [PubMed: 10190820]
8. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. New England Journal of Medicine. 2005;352(23):2379–2388. [PubMed: 15829527]

9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. 1984;34(7):939–939. doi:10.1212/wnl.34.7.939
10. Bonferroni C. Teoria statistica delle classi e calcolo delle probabilita. Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commericiali di Firenze. 1936;8:3–62.
11. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics. 1979:65–70.
12. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica: journal of the Econometric Society. 1980:817–838.
13. de Brey C, Musu L, McFarland J, et al. Status and Trends in the Education of Racial and Ethnic Groups 2018. NCES 2019–038. National Center for Education Statistics. 2019;
14. Cook R. Detection of influential observations in linear regression, in "Technometric", 19. I5–18. 1977;
15. R Core Team. R: A language and environment for statistical computing. https://www.R-project.org/: R Foundation for Statistical Computing, Vienna, Austria; 2020.
16. Bernstein OM, Grill JD, Gillen DL. Recruitment and retention of participant and study partner dyads in two multinational Alzheimer's disease registration trials. Alzheimer's Research & Therapy. 2021;13(1):1–11.
17. Locke DE, Greenaway MC, Duncan N, et al. A patient-centered analysis of enrollment and retention in a randomized behavioral trial of two cognitive rehabilitation interventions for Mild Cognitive Impairment. The journal of prevention of Alzheimer's disease. 2014;1(3):143.
18. Lingler JH, Terhorst L, Schulz R, Gentry A, Lopez O. Dyadic analysis of illness perceptions among persons with mild cognitive impairment and their family members. The Gerontologist. 2016;56(5):886–895. [PubMed: 26035901]
19. Chandler MJ, Locke DE, Crook JE, et al. Comparative effectiveness of behavioral interventions on quality of life for older adults with mild cognitive impairment: a randomized clinical trial. JAMA network open. 2019;2(5):e193016–e193016. [PubMed: 31099860]
20. Lingler JH, Sereika SM, Butters MA, et al. A randomized controlled trial of amyloid positron emission tomography results disclosure in mild cognitive impairment. Alzheimer's & Dementia. 2020;16(9):1330–1337.
21. Grill JD, Monsell S, Karlawish J. Are patients whose study partners are spouses more likely to be eligible for Alzheimer's disease clinical trials. Dementia and geriatric cognitive disorders. 2012;33(5):334–340. [PubMed: 22759982]
22. Cary MS, Rubright JD, Grill JD, Karlawish J. Why are spousal caregivers more prevalent than nonspousal caregivers as study partners in AD dementia clinical trials? Alzheimer disease and associated disorders. 2015;29(1):70. [PubMed: 24805971]
23. Cox CG, Ryan MM, Gillen DL, Grill JD. A preliminary study of clinical trial enrollment decisions among people with mild cognitive impairment and their study partners. The American Journal of Geriatric Psychiatry. 2019;27(3):322–332. [PubMed: 30522811]
24. Watson JL, Ryan L, Silverberg N, Cahan V, Bernard MA. Obstacles and opportunities in Alzheimer's clinical trial recruitment. Health Affairs. 2014;33(4):574–579. [PubMed: 24711317]
25. Canevelli M, Bruno G, Grande G, et al. Race reporting and disparities in clinical trials on Alzheimer's disease: a systematic review. Neuroscience & Biobehavioral Reviews. 2019;101:122–128. [PubMed: 30946856]
26. 2020 Profile of Older Americans. US Department of Health and Human Services. Administration for Community Living. Published May 2021. Accessed December 23, 2021. https://acl.gov/sites/default/files/Aging%20and%20Disability%20in%20America/2020ProfileOlderAmericans.Final_.pdf
27. Tang M-X, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean hispanics, and caucasians in northern Manhattan. Neurology. 2001;56(1):49–56. [PubMed: 11148235]
28. Combined FDA and Applicant Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Briefing Document - Aducanumab. United States Food and Drug Administration

and the Applicant (Biogen). Published November 6, 2020. Accessed December 22, 2021. https://www.fda.gov/media/143502/download

29. Amendment: NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research. National Institutes of Health. Published October 9, 2001. Accessed December 26, 2021. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
30. Collection of Race and Ethnicity Data in Clinical Trials – Guidance for Industry. US Food and Drug Administration. Published October 26, 2016. Accessed December 22, 2021. https://www.fda.gov/media/75453/download
31. Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. US Food and Drug Administration. Pubnlished November 2020. Accessed December 22, 2021. https://www.fda.gov/media/127712/download
32. Oh SS, Galanter J, Thakur N, et al. Diversity in clinical and biomedical research: a promise yet to be fulfilled. PLoS medicine. 2015;12(12):e1001918. [PubMed: 26671224]
33. Bernick C, Cummings J, Raman R, Sun X, Aisen P. Age and Rate of Cognitive Decline in Alzheimer Disease: Implications for Clinical Trials. Archives of Neurology. 2012;69(7):901–905. doi:10.1001/archneurol.2011.3758 [PubMed: 22431834]
34. Schneider LS, Kennedy RE, Wang G, Cutter GR. Differences in Alzheimer disease clinical trial outcomes based on age of the participants. Neurology. 2015;84(11):1121–1127. [PubMed: 25681452]
35. Li J-Q, Tan L, Wang H-F, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. Journal of Neurology, Neurosurgery & Psychiatry. 2016;87(5):476–484. [PubMed: 26001840]
36. Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects. National Institutes of Health. Published December 19, 2017. Accessed March 27, 2021. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html
37. Gillis C, Mirzaei F, Potashman M, Ikram MA, Maserejian N. The incidence of mild cognitive impairment: A systematic review and data synthesis. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2019;11:248–256.
38. Bernard MA, Clayton JA, Lauer MS. Inclusion Across the Lifespan: NIH Policy for Clinical Research. JAMA. 2018;320(15):1535–1536. doi:10.1001/jama.2018.12368 [PubMed: 30326521]
39. Rajan KB, Barnes LL, Wilson RS, et al. Racial differences in the association between apolipoprotein E risk alleles and overall and total cardiovascular mortality over 18 years. Journal of the American Geriatrics Society. 2017;65(11):2425–2430. [PubMed: 28898389]
40. Kunkle BW, Schmidt M, Klein H-U, et al. Novel Alzheimer disease risk loci and pathways in african American individuals using the African genome resources panel: a meta-analysis. JAMA neurology. 2021;78(1):102–113. [PubMed: 33074286]
41. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ϵ4, and the risk of late-onset Alzheimer disease in African Americans. Jama. 2013;309(14):1483–1492. [PubMed: 23571587]
42. Granot-Hershkovitz E, Tarraf W, Kurniansyah N, et al. APOE alleles' association with cognitive function differs across Hispanic/Latino groups and genetic ancestry in the study of Latinos-investigation of neurocognitive aging (HCHS/SOL). Alzheimer's & Dementia. 2020;
43. González HM, Tarraf W, Schneiderman N, et al. Prevalence and correlates of mild cognitive impairment among diverse Hispanics/Latinos: Study of Latinos-Investigation of Neurocognitive Aging results. Alzheimer's & dementia. 2019;15(12):1507–1515.
44. Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET imaging in self-identified non-Hispanic Black participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study. Neurology. 2021;96(11):e1491–e1500. [PubMed: 33568538]
45. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia. 2011;7(3):270–279.

46. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. The Lancet Neurology. 2010;9(11):1118–1127. [PubMed: 20934914]

47. Torgrimson BN, Minson CT. Sex and gender: what is the difference? Journal of Applied Physiology. 2005;99(3):785–787. doi:10.1152/japplphysiol.00376.2005 [PubMed: 16103514]

48. Wójcik D, Szczechowiak K, Zboch M, Pikala M. Effectiveness of the Open Screening Programs in Recruiting Subjects to Prodromal and Mild Alzheimer's Disease Clinical Trials. The Journal of Prevention of Alzheimer's Disease. 2020;7(4):251–255.

49. Rovner BW, Casten RJ, Hegel MT, Leiby BE. Preventing cognitive decline in older African Americans with mild cognitive impairment: design and methods of a randomized clinical trial. Contemporary Clinical Trials. 2012;33(4):712–720. [PubMed: 22406101]

50. Grill J. Alzheimer's Disease Clinical Trial Study Partners. In: Cummings JKJ, Fillit H, eds., ed. Alzheimer's Disease Drug Development: Research and Development Ecosystem. Cambridge University Press; 2022:333–342:chap 29.

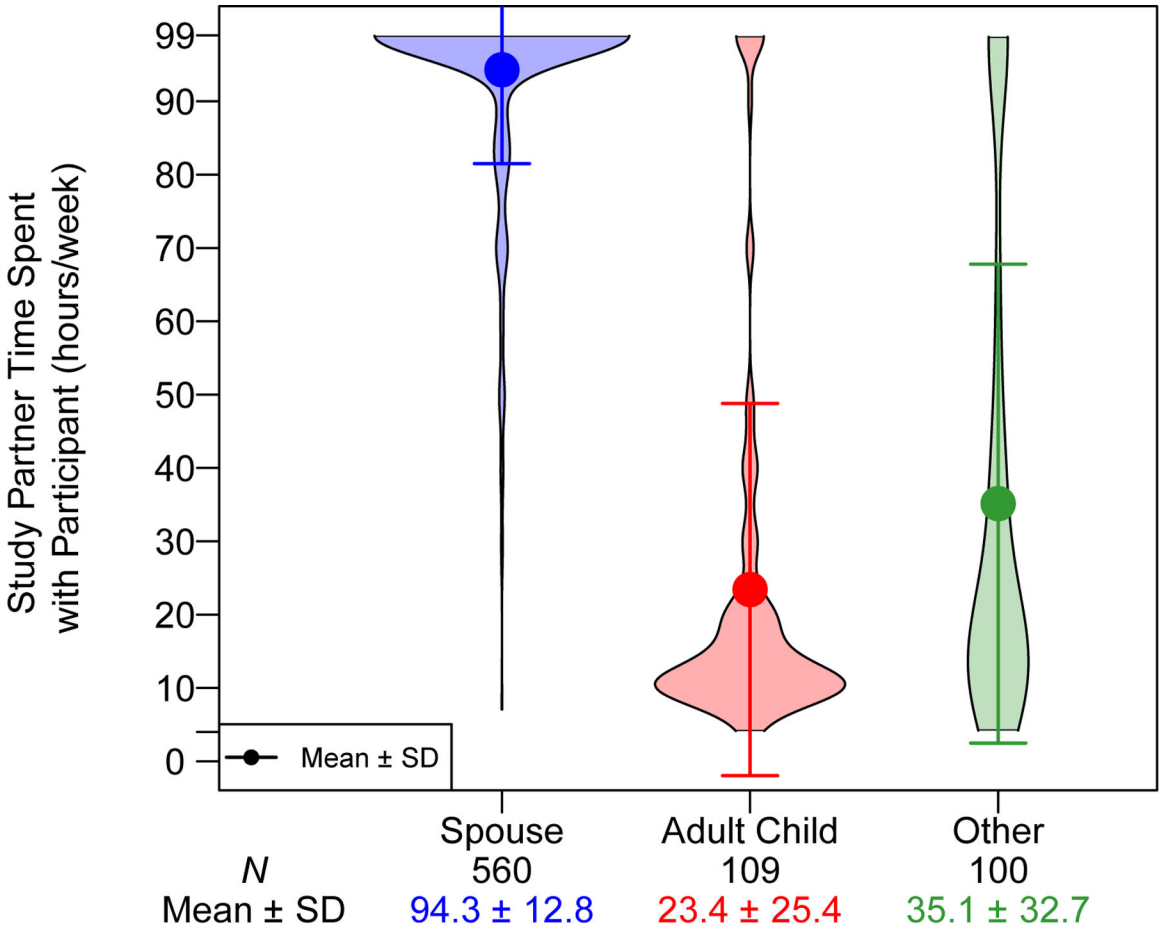

Figure 1:
Violin plots of baseline study partner time spent with participant (hours/week; range: 0–99 hours/week) by dyad type. Number of participants and mean ± SD of time spent are reported by dyad type.

Table 1.

Baseline participant and study partner characteristics by dyad type.

	Total	Study Partner Type		
		Spouse	Adult Child	Other
	(*N* = 769)	(*N* = 560)	(*N* = 109)	(*N* = 100)
Participant Characteristic [a]				
Age, years	73.0 ± 7.3	72.4 ± 6.9	75.6 ± 7.3	73.9 ± 8.9
Female sex (vs. male)	352 (45.8)	205 (36.6)	87 (79.8)	60 (60.0)
Race and Ethnicity [b]				
Non-Hispanic White	708 (92.1)	537 (95.9)	92 (84.4)	79 (79.0)
Hispanic	30 (3.9)	12 (2.1)	9 (8.3)	9 (9.0)
Non-Hispanic Black	18 (2.3)	6 (1.1)	3 (2.8)	9 (9.0)
Asian or Pacific Islander	7 (0.9)	2 (0.4)	4 (3.7)	1 (1.0)
American Indian or Alaskan Native	3 (0.4)	2 (0.4)	1 (0.9)	0 (0.0)
Other or unknown	3 (0.4)	1 (0.2)	0 (0.0)	2 (2.0)
APOE ε4 carrier (vs. non-carrier)	424 (55.1)	329 (58.8)	53 (48.6)	42 (42.0)
Education, years	14.6 ± 3.1	14.8 ± 3.0	13.9 ± 2.9	14.3 ± 3.5
Residence Type [b]				
House	566 (73.6)	435 (77.7)	75 (68.8)	56 (56.0)
Condominium/ apartment	150 (19.5)	95 (17.0)	22 (20.2)	33 (33.0)
Retirement community	33 (4.3)	21 (3.8)	7 (6.4)	5 (5.0)
Trailer	12 (1.6)	5 (0.9)	2 (1.8)	5 (5.0)
Other	5 (0.7)	4 (0.7)	0 (0.0)	1 (1.0)
Assisted living	3 (0.4)	0 (0.0)	3 (2.8)	0 (0.0)
Marital Status [b]				
Married	597 (77.6)	559 (99.8)	29 (26.6)	9 (9.0)
Widowed	97 (12.6)	1 (0.2)	60 (55.0)	36 (36.0)
Divorced	53 (6.9)	0 (0.0)	20 (18.3)	33 (33.0)
Never married	21 (2.7)	0 (0.0)	0 (0.0)	21 (21.0)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.0)
Study Partner Characteristic [a,c]				
Age, years	65.5 ± 12.4	69.5 ± 8.7	45.9 ± 8.2	64.4 ± 14.0
Education, years	14.5 ± 2.8	14.4 ± 2.8	15.2 ± 2.3	14.4 ± 2.9

[a] Continuous characteristics summarized with mean ± standard deviation and categorical characteristics summarized with *N* (column %).

[b] Ordered by descending frequency based on total counts.

[c] One spouse study partner had missing age and one adult child study partner had missing age and education.

Table 2.

Inferential summaries from unadjusted and adjusted multinomial regression analyses.

Covariate[a]	Unadjusted					Adjusted				
	Adult Child vs. Spouse		Other vs. Spouse			Adult Child vs. Spouse		Other vs. Spouse		
	OR[b] (95% CI)	*p*	OR[b] (95% CI)	*p*	Global *p*[c,d]	OR[b] (95% CI)	*p*	OR[b] (95% CI)	*p*	Global *p*[c,d]
Age, 5-year difference	1.38 (1.19, 1.61)	<.001	1.15 (0.99, 1.34)	0.060	<.001	1.46 (1.23, 1.73)	<.001	1.23 (1.05, 1.44)	0.012	<.001
Female sex	6.85 (4.16, 11.3)	<.001	2.60 (1.68, 4.01)	<.001	<.001	6.89 (4.10, 11.6)	<.001	2.65 (1.66, 4.22)	<.001	<.001
Racial and ethnic background		0.001		<.001	<.001		0.001		<.001	<.001
Non-Hispanic White	1.0		1.0			1.0		1.0		
Hispanic	4.38 (1.79, 10.7)	0.001	5.10 (2.08, 12.5)	<.001		5.86 (2.09, 16.5)	0.001	4.95 (1.83, 13.4)	0.002	
Non-Hispanic Black	2.92 (0.72, 11.9)	0.135	10.2 (3.53, 29.4)	<.001		3.26 (0.73, 14.6)	0.123	11.4 (3.69, 35.2)	<.001	
Asian or Pacific Islander	11.7 (2.11, 64.7)	0.005	3.40 (0.30, 37.9)	0.32		9.23 (1.37, 62.1)	0.022	2.64 (0.23, 30.8)	0.439	
AIAN, other, or unknown	1.95 (0.20, 18.9)	0.566	4.53 (0.75, 27.5)	0.101		1.67 (0.15, 19.3)	0.680	4.45 (0.67, 29.7)	0.123	
APOE ε4 carrier	0.66 (0.44, 1.00)	0.052	0.51 (0.33, 0.78)	0.002	0.003	0.67 (0.42, 1.06)	0.085	0.50 (0.31, 0.79)	0.003	0.007
Education, 1-year difference	0.91 (0.85, 0.97)	0.004	0.94 (0.88, 1.01)	0.094	0.007	0.95 (0.88, 1.03)	0.222	0.99 (0.92, 1.07)	0.850	0.470
Residence type		0.065		<.001	<.001		0.428		0.001	0.005
House	1.0		1.0			1.0		1.0		
Condo, apartment, or trailer	1.39 (0.84, 2.31)	0.202	2.95 (1.85, 4.70)	<.001		1.15 (0.66, 1.99)	0.626	2.51 (1.53, 4.13)	<.001	
Assisted living, retirement community, or other	2.32 (1.07, 5.03)	0.033	1.86 (0.73, 4.74)	0.191		1.77 (0.74, 4.24)	0.203	1.62 (0.61, 4.33)	0.333	

[a] All are baseline participant characteristics.

[b] Estimated odds ratio (OR) from a multinomial regression model.

[c] Based on a multivariate Wald test with the null hypothesis that the log odds of having an adult child study partner = log odds of having an other study partner = 0.

[d] Holm-Bonferroni corrected statistical significance thresholds to compare these *p* values (from smallest to largest) are 0.008, 0.01, 0.013, 0.017, 0.025, 0.05, respectively.

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Table 3.

Secondary regression analyses with baseline participant characteristic as the outcome and dyad type as the predictor of interest.

Outcome[a]	Predictor of Interest		
	Adult Child	Other	
	OR[e] (95% CI)	OR[e] (95% CI)	Global *p*[g]
Racial and ethnic background (referent: Non-Hispanic White)			
Unadjusted			
Hispanic	4.38 (1.79, 10.7)	5.10 (2.08, 12.5)	<.001
Non-Hispanic Black	2.92 (0.72, 11.9)	10.2 (3.53, 29.4)	<.001
Asian or Pacific Islander	11.7 (2.11, 64.6)	3.40 (0.30, 37.9)	0.018
AIAN, other or unknown	1.95 (0.20, 18.9)	4.53 (0.75, 27.5)	0.260
Female sex			
Unadjusted	6.85 (4.16, 11.3)	2.60 (1.68, 4.02)	<.001
APOE ε4 carrier			
Unadjusted	0.66 (0.44, 1.00)	0.51 (0.33, 0.78)	0.003
Adjusted[b]	0.62 (0.40, 0.96)	0.48 (0.30, 0.75)	0.002
	Estimate[f] (95% CI)	**Estimate[f] (95% CI)**	**Global *p*[g]**
Age, years			
Unadjusted	3.23 (1.75, 4.71)	1.50 (−0.34, 3.33)	<.001
Adjusted[c]	3.97 (2.43, 5.52)	2.41 (0.65, 4.18)	<.001
Education, years			
Unadjusted	−0.94 (−1.55, −0.34)	−0.55 (−1.27, 0.17)	0.005
Adjusted[d]	−0.44 (−1.08, 0.20)	−0.16 (−0.83, 0.51)	0.386

[a] All are baseline participant characteristics.

[b] Adjusted for participant sex and racial and ethnic background.

[c] Adjusted for participant sex, APOE ε4 carrier status, and racial and ethnic background.

[d] Adjusted for participant age, sex, and racial and ethnic background.

[e] Estimated odds ratio (OR) from a logistic regression model.

[f] Difference in mean outcome from a linear regression model using robust standard errors.

[g] Based on a multivariate Wald test (null hypothesis: no difference in the difference in means or log odds of the outcome across three dyad types).