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Authors
Grill, Joshua D
Zhou, Yan
Karlawish, Jason
et al.

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Does study partner type impact the rate of Alzheimer's disease progression?

Joshua D. Grill, PhD[*,1], **Yan Zhou, PhD**[1], **Jason Karlawish, MD**[3], and **David Elashoff, PhD**[1,2]

[1]Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA

[2]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

[3]University of Pennsylvania, Perelman School of Medicine, Departments of Medicine, and Medical Ethics and Health Policy, Penn Memory Center, Philadelphia, PA

Abstract

Most patients with Alzheimer's disease (AD) do not have a spouse. Despite this, the majority of AD research participants enroll with a spouse study partner. It remains unclear if differences between AD patients who do and do not have a spouse may bias study results. In this study, we examined whether AD patients with different study partner types (spouse vs adult child) demonstrate different rates of disease progression over two years on three outcome measures commonly used in AD research, including clinical trials. We used data from the National Alzheimer's Coordinating Center Uniform Data Set to examine disease progression in participants age 55–90 with probable AD dementia. We examined disease progression as measured by the Clinical Dementia Rating Scale-Sum of the Boxes score, the Mini Mental Status Examination, and the Functional Assessment Questionnaire. Analyses were performed on data for all available eligible participants from the NACC UDS and after performing a propensity-matching model to better account for inherent differences between the populations of interest. Propensity matching was successful only when models did not include age and gender. For both propensity-matched analyses and those of all available data, we did not observe any differences between the study partner populations for any outcome measure. These results suggest that, if investigators can improve in recruiting AD patients with adult child caregivers to research, the implications to study results may be minimal.

Keywords

Alzheimer's disease; disease progression; caregivers; clinical trial; spouses; adult children

Introduction

Reports from the Alzheimer's Association suggest that more than 17 million Americans care for patients with Alzheimer's disease (AD) and that AD patients more often receive care from non-spouse than spouse caregivers [1]. The quality of care that AD patients receive is likely to have substantial impact on their health and caregiver intervention can improve patient healthcare outcomes, including cognition [2–5]. For example, in one randomized

[*]Corresponding author: Joshua Grill, PhD, UCLA Easton Alzheimer's Center, 10911 Weyburn Ave, Suite 200. Los Angeles, CA 90095, USA. Tel.: (310) 794-2511; fax: (310) 794-3148. jgrill@mednet.ucla.edu.

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trial, AD patients whose caregivers were trained to deliver cognitive therapy showed a mean 2.9-point benefit on the AD Assessment Scale-cognitive subscale (ADAS-cog) over 25 weeks, relative to AD patients whose caregivers were assigned to a control group [6]. Examination of the population-based Cache County Dementia Progression Study found that among possible and probable AD patients, adjusting for age, neuropsychiatric symptoms, disease duration, and baseline severity, those with spouse caregivers experienced a 1.7 point-per-year slower decline measured with the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) and a 1.2 point-per-year slower decline on the Mini-Mental Status Exam (MMSE), relative to those with adult child caregivers [7].

In addition to their critical role in ensuring the health and safety of AD patients, AD caregivers play a vital role in AD research, especially clinical trials of new treatments. AD caregivers serve as trial study partners; they ensure informed consent and trial compliance and serve as the primary informant for a variety of trial outcomes. Recent analyses of AD clinical trials showed differences in the rates of participation and trial completion, based on AD patients' study partner type [8]. These analyses also observed trends toward differences in the rate of decline on the MMSE and ADAS-cog between study partner groups, but with slower progression observed among those with adult child study partners.

Current AD trials are often designed with the goal of demonstrating disease modification, that is, slowing of the rate of cognitive and functional decline in participants randomly assigned to active study medication. To adequately plan such studies, power calculations must be performed based on an anticipated effect size of the treatment under study and the expected decline over time of those assigned placebo. Differences in the rate of decline due to the type or quality of caregiver could impact trial planning and results. In this study, we used data from the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) to examine whether differences in AD progression exist based on the AD participant's type of study partner. We hypothesized that participants with adult child study partners would progress more rapidly than those with spouses.

Materials and Methods

Sample

The National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) is a repository for longitudinal data collected from approximately 34 current or previously NIA-funded AD Centers nationwide (www.alz.washington.edu). The UDS was initiated in 2005. In the current analyses, data collected on or before September 1, 2012 were examined.

Participants

To be included in these analyses, participants needed to have a diagnosis of probable AD and to have enrolled in the NACC UDS with a spouse or an adult child (son, daughter, son-in-law, or daughter-in-law) study partner. We restricted the population to patients age 55–90 who met criteria for dementia and had been enrolled in the NACC UDS with a working diagnosis of probable AD, with a baseline CDR global score of 0.5 or 1.0 and MMSE between 14 and 26. Participants were excluded if they did not have a study partner at baseline that was a spouse or an adult child, if they experienced a change in study partner, or if they had any subsequent diagnosis other than dementia/probable AD. Study baseline was defined as the first eligible visit for which all criteria were met. Because the objective was to examine longitudinal change in measures of cognition and function, we also restricted the population to participants with at least two follow-up visits after a baseline visit in which all other criteria were met and at least two of the MMSE, CDR and Functional Assessment Questionnaire (FAQ) were completed.

Ethics

All participants in the NACC UDS sign an informed consent document approved by an Institutional Review Board (IRB). The current project received an expedited approval from the UCLA IRB.

Study outcomes

We examined the rate of AD progression over two years as measured by three outcome measures. Outcomes with missing data were excluded.

CDR-SB [9]—The CDR is a patient- and informant-based clinical assessment of global cognitive and functional ability that captures and documents information in six unique domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is scored by the investigator as 0 (normal), 0.5 (questionable), 1.0 (mild dementia), 2.0 (moderate dementia), or 3 (severe dementia). The CDR can be used as a global score of disease state, calculated with a scoring algorithm (see http://www.biostat.wustl.edu/adrc/) or by summing the totals of the separate box scores (CDR-SB). We examined the CDR-SB as a measure of disease progression. The CDR-SB has recently been proposed as a potential single primary outcome measure in AD trials [10, 11].

MMSE [12]—The MMSE is the most widely used cognitive assessment tool in dementia research. It uses a 30-point design to assess orientation, short-term and delayed recall, calculations, language interpretation, naming, and praxis. Higher scores represent greater cognitive performance.

***FAQ* [13]—**The FAQ is a 10-item tool based on informant assessment of the patient's ability to complete activities of daily living independently, with assistance, or in a dependent manner. Scores range from 0–30, with higher scores representing greater functional dependence.

Study analyses

We compared the rate of progression between AD participants with spouse and adult child partners using regression models. We identified a sample for analyses in two ways. In addition to modeling disease progression using all available data from all eligible participants, we performed a propensity matching design case-control study. Propensity matching is a technique to remove much of the bias associated with research studies for which randomization is not feasible, such as observational studies [14, 15]. It has been previously used to compare genders [16], populations that did or did not receive treatment [17–19], those with or without access to resources or specialist care [20–22], and a variety of other clinical variables. For each participant (i), a propensity score was computed by constructing a multiple logistic regression model with the equation $e(x_i) = Pr(D_i = 1|X_i = x_i)$, where e_i is the propensity score, D_i is an indicator for study partner type, and the x_i are a set of covariates. The propensity score was modeled to account for education, race, ethnicity, baseline scores on the MMSE, CDR-SB, and NPI, hachinski score, and whether the participant took anti-AD medications. To be considered a match, the propensity score needed to be within 0.05 score distance. Given the abundant number of participants with spouse study partners, each participant with an adult child study partner was matched to two participants with spouses if possible. Participant propensity scores without a match were excluded from analyses. We used the SAS macro program 'gmatch' to carry out the propensity matching (created by Kosanke and Bergstralh, see http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm, accessed 04/01/13).

For both data sets, we used scores at the second follow-up visit (1.5 to 2.5 years from baseline visit) to calculate annualized changes from baseline for each study outcome measure (CDR, MMSE, and FAQ). We performed multiple regression to examine the effects on the annualized change for a number of covariates, including participant gender, participant race, participant ethnicity, participant education, participant age, baseline scores on the outcomes of interest and study partner gender.

To examine potential differences in demographic variables between the study partner groups, we used Chi squared tests (X^2) for dichotomous variables and two sample *t*-tests for continuous variables. All statistical analyses are reported with a significance level of $p<0.05$.

Results

Samples

The descriptive statistics for the sample included in our analyses are presented in Table 1. Table 2 provides descriptive statistics for the study partners. Among those eligible for the current study, there were nearly three times as many AD participants with spouse than adult child study partners. Participants with adult child study partners were older, more often female, more often minority race or ethnicity, and less frequently took anti-AD medications. No differences were observed at baseline in the outcome measures of interest.

The propensity model described in the methods yielded satisfactory matching; on average matching 1.76 AD participants with spouse partners for every participant with an adult child partner. Importantly, when either age or gender were included in the propensity model, the resultant distribution of propensity scores were not sufficiently overlapping to permit adequate matching. Therefore, age and gender were not included in the final propensity model, but were instead adjusted for in the regression models. Consequently, in the propensity-matched sample, those with an adult child study partner remained older and more frequently female than those with spouse study partners. They also had a lower mean level of education ($p=0.03$).

Regression Models

The results of models using only propensity-matched populations and all available data are presented in Tables 3 and 4, respectively. Neither model suggested a difference in the rate of disease progression among the study partner types for any outcome measure. A trend toward an effect of study partner type was observed for the MMSE, whereby decline was slower among participants with an adult child study partner (estimate=0.38; 95% CI: −0.05, 0.80; $p=0.08$; Table 4) in the model of all available data but this trend was not observed for the propensity-matched sample analyses (estimate=0.28; 95% CI: −0.19, 0.75; $p=0.23$). The Figure illustrates the observed changes for the two groups of study partner types for each outcome measure for each data sample (propensity-matched and all available data).

For the CDR-SB and the FAQ, the baseline score predicted the rate of decline, but the effects were in opposite directions between the two outcomes. In both models (Tables 3 and 4), a worse CDR-SB score at baseline predicted greater annualized change over two years. For the FAQ, a worse baseline score predicted smaller change. Greater change (worsening) in the CDR-SB was also associated with female gender in both models and with higher education in the model of all data. Greater change (worsening) in the FAQ was also associated with higher education in the propensity-matched model. For the MMSE, the only significant predictor of the rate of decline was age, with younger age being associated with more rapid decline in both models.

Discussion

Alzheimer's disease (AD) invariably results in decline in cognitive and functional abilities and current clinical trials aim to demonstrate treatment-related slowing of such decline. It remains unclear what factors impact the rate of disease progression, but factors with systematic effects could bias trial results if not adequately controlled. Previous studies suggested that study partner type could affect disease progression. Norton and colleagues found that having a spouse caregiver was associated with slower rate of decline on the ADAS-cog and the CDR-SB in the Cache County study [7]. In contrast, in a sample of AD clinical trials, we observed a trend in which AD patients with adult child study partners exhibited slower cognitive decline, measured with the MMSE and the ADAS-cog, relative to those with spouse study partners, though no differences were observed in the CDR-SB or the ADCS-ADL [8].

In the current analyses, we did not observe differences between study partner types in the rate of disease progression as measured by three common AD clinical trial outcome measures. Therefore, these results do not support the implementation of stratified randomization or inclusion of study partner type in analytic models for AD clinical trials of potential disease modifying therapies. It is of note, however, that this study used a methodology intended to better control for potential covariates, the propensity-matching method, but that the inherent differences between these populations prevented the full utilization of this analytic technique. Specifically, the substantial differences in age and gender between AD participants with adult child and spouse study partners could not be accounted for by propensity matching.

Our results did not replicate the findings of either of the previous discordant studies that suggested differences in disease progression between those with adult child and spousal caregivers/study partners. One potential mechanism to account for differences among these studies is a sample bias. Clinical trials rarely recruit samples representative of the greater disease-suffering population [23], including that they infrequently recruit AD patients who lack a spouse [8]. Trial participants are typically younger, more educated, and more often non-Latino Caucasians than the typical AD patient [24]. The level of involvement of clinical trials (often requiring a large number of clinical visits over a series of months or years) may limit participation to those adult child caregiver/patient dyads that are highly motivated and have the resources to attend visits during the workweek. In contrast, the Cache County study is a natural history study that used community-based recruitment and has a lower burden of participation. The NACC UDS is similar to clinical trials in that recruitment is by convenience and the enrolled sample is highly educated and largely non-Latino Caucasian. The NACC UDS, however, requires only annual visits. Thus, the current results may be explained by differences in the samples of patient/caregiver dyads recruited to participate. Norton and colleagues hypothesized that motivational differences between spouse and non-spouse caregivers result in improved lifestyle, increased cognitive engagement, and other differences that ultimately manifest differences in the rate of AD progression. While these differences may manifest in altered rates of progression in community populations, they may be absent or minimized in research populations, all of whom are motivated to go beyond standard clinical care. This contrast from the general community may be greatest in clinical trials, where adult child caregivers must overcome additional barriers to participation.

Our results do not suggest that systematic differences in the ways that study partners assess patient cognition and function bias assessments. Conde-Sala and colleagues recently showed that adult child caregivers view patient quality of life (as well as their own quality of life) as worse than do comparable spouse caregivers [25–27]. We observed no differences, however,

between the study partner groups on either outcome measures that requires study partner input (the CDR-SB and the FAQ) or clinician-administered outcomes (the MMSE).

Differences were observed in the rates of decline, relative to baseline score, in the CDR-SB and the FAQ. This may have been due to an increased proportion of participants achieving maximum score on the FAQ during the study. Further research is needed to assess the psychometric properties of these scales and the implications to AD research on disease progression.

This study has some limitations. The NACC UDS does not require that the primary caregiver serve as study partner. Our results could be biased if participants with a spouse caregiver were more likely to participate in the study with an adult child as a study partner. Though this information is not systematically captured in the UDS, we anticipate minimal impact of this caveat since we expect that the majority of UDS participants enroll with the primary caregiver.

An ideal design for this study would have examined six outcome measures, balancing for clinician-based and caregiver-based metrics of cognition, function, and global performance. The items examined were chosen for their wide use, ready interpretation, and likelihood for demonstrating change over time. Furthermore, the NACC UDS does not administer the ADAS-cog, the most common measure of cognition in AD trials. Nevertheless, we feel that these results may be instructive to investigators designing future AD dementia treatment trials.

In summary, the results of the current study do not suggest that differences exist in the rate of disease progression, regardless of the means by which disease severity is measured, between AD patients with adult child and spouse study partners. Therefore, AD clinical trials may incur no analytic bias if they can successfully increase the rates of participation among AD patients cared for by their adult children, a significantly underrepresented group. These findings do, however, suggest that differences in research populations may drive differences in study outcomes, emphasizing the need for careful design and enrollment in AD research.

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References

1. Alzheimer's Association and National Alliance for Caregiving. Families care: Alzheimer's disease caregiving in the United States, 2004. 2004. http://www.alz.org
2. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. JAMA. 1996; 276:1725–1731. [PubMed: 8940320]
3. Mittelman MS, Ferris SH, Steinberg G, Shulman E, Mackell JA, Ambinder A, Cohen J. An intervention that delays institutionalization of Alzheimer's disease patients: treatment of spouse-caregivers. Gerontologist. 1993; 33:730–740. [PubMed: 8314099]
4. Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology. 2006; 67:1592–1599. [PubMed: 17101889]

5. Teri L, McCurry SM, Logsdon R, Gibbons LE. Training community consultants to help family members improve dementia care: a randomized controlled trial. Gerontologist. 2005; 45:802–811. [PubMed: 16326662]
6. Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, Lambertucci P, Silveri MC, Bernabei R. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. Br J Psychiatry. 2005; 187:450–455. [PubMed: 16260821]
7. Norton MC, Piercy KW, Rabins PV, Green RC, Breitner JC, Ostbye T, Corcoran C, Welsh-Bohmer KA, Lyketsos CG, Tschanz JT. Caregiver-recipient closeness and symptom progression in Alzheimer disease. The Cache County Dementia Progression Study. J Gerontol B Psychol Sci Soc Sci. 2009; 64:560–568. [PubMed: 19564210]
8. Grill JD, Raman R, Ernstrom K, Aisen P, Karlawish J. Effect of study partner on the conduct of Alzheimer disease clinical trials. Neurology. 2013; 80:282–288. [PubMed: 23255824]
9. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]
10. Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, Vellas B. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement. 2013; 9:S45–55. [PubMed: 22658286]
11. Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the Clinical Dementia Rating-Sum of Boxes as a single primary endpoint for Alzheimer's disease trials. Alzheimers Dement. 2011; 7:602–610. e602. [PubMed: 21745761]
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
13. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329. [PubMed: 7069156]
14. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997; 127:757–763. [PubMed: 9382394]
15. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. Biometrics. 1996; 52:249–264. [PubMed: 8934595]
16. Kendel F, Dunkel A, Muller-Tasch T, Steinberg K, Lehmkuhl E, Hetzer R, Regitz-Zagrosek V. Gender differences in health-related quality of life after coronary bypass surgery: results from a 1-year follow-up in propensity-matched men and women. Psychosom Med. 2011; 73:280–285. [PubMed: 21364199]
17. Walsh P, Shanholtzer L, Loewen M, Trinh K, McEnulty B, Rothenberg SJ. A matched case control study with propensity score balancing examining the protective effect of paracetamol against parentally reported apnoea in infants. Resuscitation. 2011
18. Andrey JL, Romero S, Garcia-Egido A, Escobar MA, Corzo R, Garcia-Dominguez G, Lechuga V, Gomez F. Mortality and morbidity of heart failure treated with digoxin. A propensity-matched study. Int J Clin Pract. 2011; 65:1250–1258. [PubMed: 22093531]
19. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011; 306:1659–1668. [PubMed: 21976615]
20. Webster F, Saposnik G, Kapral MK, Fang J, O'Callaghan C, Hachinski V. Organized outpatient care: stroke prevention clinic referrals are associated with reduced mortality after transient ischemic attack and ischemic stroke. Stroke. 2011; 42:3176–3182. [PubMed: 21921281]
21. Murdoch M, Sayer NA, Spoont MR, Rosenheck R, Noorbaloochi S, Griffin JM, Arbisi PA, Hagel EM. Long-term outcomes of disability benefits in US veterans with posttraumatic stress disorder. Arch Gen Psychiatry. 2011; 68:1072–1080. [PubMed: 21969464]
22. Meret-Hanke LA. Effects of the Program of All-inclusive Care for the Elderly on hospital use. Gerontologist. 2011; 51:774–785. [PubMed: 21737398]
23. Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimers Res Ther. 2010; 2:34. [PubMed: 21172069]

24. Faison WE, Schultz SK, Aerssens J, Alvidrez J, Anand R, Farrer LA, Jarvik L, Manly J, McRae T, Murphy GM Jr, et al. Potential ethnic modifiers in the assessment and treatment of Alzheimer's disease: challenges for the future. Int Psychogeriatr. 2007; 19:539–558. [PubMed: 17451614]

25. Conde-Sala JL, Garre-Olmo J, Turro-Garriga O, Vilalta-Franch J, Lopez-Pousa S. Differential features of burden between spouse and adult-child caregivers of patients with Alzheimer's disease: an exploratory comparative design. Int J Nurs Stud. 2010; 47:1262–1273. [PubMed: 20374966]

26. Conde-Sala JL, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S, Vilalta-Franch J. Factors related to perceived quality of life in patients with Alzheimer's disease: the patient's perception compared with that of caregivers. Int J Geriatr Psychiatry. 2008

27. Conde-Sala JL, Garre-Olmo J, Turro-Garriga O, Vilalta-Franch J, Lopez-Pousa S. Quality of life of patients with Alzheimer's disease: differential perceptions between spouse and adult child caregivers. Dement Geriatr Cogn Disord. 2010; 29:97–108. [PubMed: 20150730]

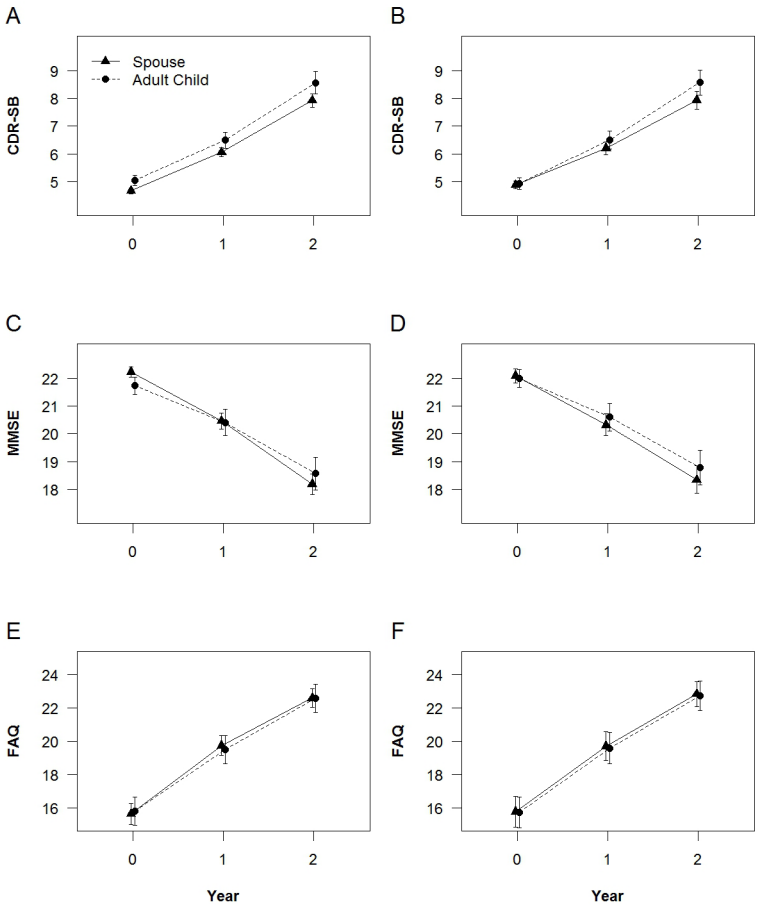

Figure 1.

Figure Mean (± SD) scores are plotted for the groups. Triangles and solid lines represent the spouse study partner groups. Circles and broken lines represent the adult child study partner groups. A and B illustrate scores on the CDR-SB, C and D illustrate scores on the MMSE, and E and F show scores for the FAQ. A, C, and E present plots of the means for all available data, while B, D, and F are plots of the means for only the propensity-matched data.

Table 1

Descriptive statistics of the samples

	Matched sample			All available data		
Characteristic	**Adult child partner**	**Spouse Partner**	**P value (test)**	**Adult child partner**	**Spouse Partner**	**P value (test)**
N (%)	318 (36.3)	559 (63.7)		384 (25.7)	1111 (74.3)	
Age, mean years ± SD	78.8 ± 6.3	73.7 ± 7.79	<0.0001 (*t*-test)	78.6 ± 6.2	73.2 ± 8.0	<0.0001 (*t*-test)
Female, n (%)	266 (83.7)	195 (34.9)	<0.0001 (X^2)	322 (83.9)	377 (33.9)	<0.0001 (X^2)
Minority race, n (%)	64 (20.1)	87 (15.6)	0.08 (X^2)	39 (24.4)	106 (9.5)	<0.0001 (X^2)
Latino ethnicity, n (%)	28 (8.8)	30 (5.4)	0.05 (X^2)	53 (13.9)	33 (3.0)	<0.0001 (X^2)
Education, mean years ± SD	13.6 ± 3.0	14.1 ± 3.1	0.03 (*t*- test)	13.1 ± 3.5	15.2 ± 3.1	<0.0001 (*t*-test)
Baseline global CDR, mean ± SD	0.8 ± 0.2	0.8 ± 0.3	0.32 (*t*- test)	0.8 ± 0.2	0.8 ± 0.3	0.12 (*t*- test)
Baseline CDR- SB, mean ± SD	4.9 ± 1.9	4.9 ± 1.8	0.73 (*t*- test)	5.0 ± 1.9	4.7 ± 1.7	<0.001 (*t*- test)
Baseline MMSE, mean ± SD	22.0 ± 2.9	22.1 ± 3.1	0.63 (*t*- test)	21.7 ± 3.1	22.2 ± 3.2	<0.01 (*t*- test)
Baseline FAQ, mean ± SD	15.7 ± 7.2	15.8 ± 7.4	0.92 (*t*- test)	15.8 ± 7.1	15.6 ± 7.4	0.76 (*t*- test)
Baseline NPI-Q, mean ± SD	4.1 ± 4.0	4.2 ± 4.1	0.66 (*t*- test)	4.2 ± 4.1	3.9 ± 3.8	0.18 (*t*- test)
Baseline Hachinski, mean ± SD	1.0 ± 1.2	0.9 ± 1.2	0.38 (*t*- test)	1.0 ± 1.3	0.7 ± 1.1	<0.001 (*t*- test)
Baseline GDS, mean ± SD	2.3 ± 2.3	2.3 ± 2.4	0.83 (*t*- test)	2.3 ± 2.3	2.1 ± 2.2	0.15 (*t*- test)
Presence of AChEI, n (%)	198 (62.3)	343 (61.4)	0.79 (X^2)	228 (59.8)	732 (65.9)	0.03 (X^2)
Presence of memantine, n (%)	104 (32.7)	175 (31.3)	0.67 (X^2)	115 (30.2)	488 (43.9)	<0.0001 (X^2)

Table 2

Descriptive statistics of the study partners.

	Matched sample			All available data		
Characteristic	**Adult child partner**	**Spouse Partner**	**P value (test)**	**Adult child partner**	**Spouse Partner**	**P value (test)**
Age, mean years ± SD	51.1 ± 7.7	71.1 ± 8.5	<0.0001 (*t*-test)	50.8 ± 7.7	70.6 ± 8.6	<0.0001 (*t*-test)
Female, n (%)	240 (75.5)	367 (65.7)	0.0025 (X^2)	286 (47.5)	733 (66.0)	<0.01 (X^2)
Minority race, n (%)	56 (21.5)	53 (12.3)	0.0013 (X^2)	85 (26.7)	68 (8.2)	<0.0001 (X^2)
Latino ethnicity, n (%)	23 (8.9)	28 (6.5)	0.25 (X^2)	46 (14.3)	35 (4.2)	<0.0001 (X^2)
Education, mean years ± SD	15.9 ± 2.5	14.7 ±2.8	<0.0001 (*t*-test)	15.8 ± 2.6	15.1 ± 2.8	<0.001 (*t*- test)

Table 3

Predictors of the rate of progression 1.5 to 2.5 years from baseline among propensity matched samples.

Variable	CDR-SB, estimate (95% CI)	MMSE, estimate (95% CI)	FAQ, estimate (95% CI)
Adult child study partner type (vs. spouse)	0.03 (−0.26, 0.32)	0.28 (−0.19, 0.75)	−0.31 (−1.04, 0.42)
Female study partner gender (vs. male)	0.19 (−0.10, 0.49)	−0.14 (−0.35, 0.62)	0.09 (−0.64, 0.82)
Female gender (vs. male)	0.40 (0.08, 0.71) *	−0.25 (−0.76, 0.26)	0.50 (−0.30, 1.30)
Caucasian race (vs. non-Caucasian)	0.07 (−0.22, 0.36)	−0.04 (−0.50, 0.42)	0.38 (−0.40, 1.15)
Latino ethnicity (vs. non-Latino)	−0.10 (−0.54, 0.34)	0.61 (−0.09, 1.32)	−0.49 (−1.66, 0.69)
Education	0.03 (−0.01, 0.06)	0.01 (−0.04, 0.07)	0.11 (0.01, 0.21) *
Age	0.002 (−0.01, 0.02)	.04 (0.01, 0.06) *	0.01 (−0.03, 0.05)
Baseline score	0.10 (0.04, 0.16) *	−0.01 (−0.07, 0.05)	−0.22 (−0.26, −0.19)

NOTE: From multiple regression to examine the effects on the annualized change for a number of covariates, including participant gender, participant race, participant ethnicity, participant education, participant age, baseline scores on the outcomes of interest and study partner gender.

* $p<0.05$.

Table 4

Predictors of the rate of progression 1.5 to 2.5 years from baseline among the total data set.

Variable	CDR-SB, estimate (95% CI)	MMSE, estimate (95% CI)	FAQ, estimate (95% CI)
Adult child study partner type (vs. spouse)	−0.05 (−0.32, 0.22)	0.38 (−0.05, 0.80)	−0.34 (−0.98, 0.31)
Female study partner gender (vs. male)	0.23 (−0.05, 0.51)	−0.11 (−0.55, 0.34)	0.30 (−0.36, 0.96)
Female gender (vs. male)	0.38 (0.09, 0.67)	−0.38 (−0.85, 0.08)	0.50 (−0.21, 1.20)
Caucasian race (vs. non-Caucasian)	0.13 (−0.14, 0.40)	−0.05 (−0.47, 0.36)	0.67 (−0.02, 1.36)
Latino ethnicity (vs. non-Latino)	−0.19 (−0.58, 0.21)	0.44 (−0.17, 1.04)	−0.63 (−1.63, 0.38)
Education	0.04 (0.01, 0.06)*	−0.03 (−0.07, 0.02)	0.07 (−0.01, 0.14)
Age	−0.00 (−0.01, 0.01)	0.04 (0.03, 0.06)*	−0.01 (−0.03, 0.02)
Baseline score	0.09 (0.05, 0.14)	0.02 (−0.02, 0.07)	−0.21 (−0.24, −0.19)*

NOTE: From multiple regression to examine the effects on the annualized change for a number of covariates, including participant gender, participant race, participant ethnicity, participant education, participant age, baseline scores on the outcomes of interest and study partner gender.

* $p<0.05$.