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RESEARCH ARTICLE

Impact of study partner replacement in a mild cognitive impairment clinical trial

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Abstract

BACKGROUND: In Alzheimer's disease (AD) clinical trials, including trials enrolling patients with mild cognitive impairment (MCI), participants must enroll with a study partner (SP). SPs ensure compliance and are a source of study data, including assessments of the participant's cognition and function. Consistency in SP reporting is essential to trial data integrity.

METHODS: We quantified SP replacement and its impact on bias and variance of SP-reported AD Cooperative Study Activities of Daily Living for MCI (ADCS-ADL-MCI) in the ADCS Vitamin E/Donepezil MCI Trial. We used logistic regression to estimate the association between SP type (spouse or non-spouse) and the odds of experiencing SP change. We used generalized estimating equations to longitudinally model the differences in consecutively recorded ADCS-ADL-MCI scores as a function of whether SP change occurred. We used a similar model to quantify end-of-study change from baseline in ADCS-ADL-MCI scores.

RESULTS: Among 768 participants, 40 (5%) experienced at least one SP change. We estimated that the odds of experiencing a SP change were 65% lower for spousal dyads when compared to non-spousal dyads (odds ratio [OR] = 0.35; 95% confidence interval [CI]: [0.18–0.67]). Compared to those with a consistent SP, participants who experienced a SP change had, on average, a consecutive visit absolute score difference that was 1.60 points greater in magnitude (95% CI: [0.62–2.57]), suggesting greater volatility. ADCS-ADL-MCI scores were neither systematically higher nor lower when SP change occurred, on average (-0.23; 95% CI: [-1.60, 1.14]), suggesting minimal bias. The estimated difference in variance for end-of-study change from baseline ADCS-ADL-MCI was observed to be higher for those with SP change compared to those without, but the difference was not statistically significant (1.29; 95% CI: [0.47–1.17]).

CONCLUSION: SP replacement occurred for a meaningful number of participants but did not result in systematic bias on a functional outcome in this trial, but it did increase variability.

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KEYWORDS
ADCS-ADL-MCI, Alzheimer's disease, mild cognitive impairment, partner-reported outcomes, study partner replacement

Highlights

- Among participants in a mild cognitive impairment trial, approximately 5% experienced at least one study partner replacement.
- The estimated odds of replacement were 60% lower for participants with a spousal study partner at baseline, compared to those with a non-spouse partner.
- We observed increased variance, but not bias, in the mean within-participant change in consecutive ADCS-ADL-MCI scores among participants experiencing study partner replacement.
- We observed greater variance for end-of-study change from baseline ADCS-ADL-MCI for those who experienced a study partner replacement, compared to those who did not.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative condition that impairs cognition and daily function and is the most common cause of dementia. Dementia is a syndrome defined by cognitive impairment that is sufficient to impair activities of daily living (ADLs).[1] AD is an active area of drug development,[2] with more recent AD clinical trials including patients with cognitive impairment not sufficient to affect ADLs,[3] referred to as mild cognitive impairment (MCI).[1,4,5]

In MCI trials, like in AD dementia trials, participants must enroll with a study partner. The role of the study partner is to ensure protocol compliance and provide additional assessments of a participant's cognitive and functional performance.[6–9] These study partner reports are often used as primary or secondary outcomes in MCI trials. For example, the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) is a widely used co-primary outcome measure in AD trials, where assessments are obtained through interviews with participants' study partners.[10] The ADCS-ADL was adapted for use in MCI trials (ADCS-ADL-MCI), emphasizing potential subtle impairments, especially to instrumental ADLs.[10] Given that outcomes like the ADCS-ADL-MCI are used to determine drug efficacy, consistency in the reporting of information by study partners in these instruments is essential to trial data integrity.

The study partner role is typically filled by the participant's spouse or adult child in AD trials.[11,12] One potential source of bias in study partner-reported outcomes is the possibility that the individual filling the role could need to be replaced after randomization. That is, the participant remains on study protocol, but the study partner can no longer fulfill their role and must be replaced by another individual. We previously found that study partner replacement was common (15%) in a longitudinal observational study and less common (5%) in a meta-analysis of four AD trials.[13–15] Both analyses of replacement were associated with increased variation and inflated measures of change in study partner-reported functional assessments.[13,16] It is unclear, however, how often study partner replacement occurs in MCI trials and whether the introduction of a new study partner systematically biases partner-reported outcomes or impacts their volatility. It is also unclear whether the relationship between a trial participant and their study partner (spousal, parent-child, etc.) influences the frequency with which replacement occurs, the severity of potential bias, or volatility of outcome measures.

In this study, we quantified the frequency, likelihood, and impact of study partner replacement on bias and variance of partner-reported scores in a large Phase 3 MCI trial. We hypothesized that the probability of study partner replacement is higher among trial participants without a spousal study partner, and that study partner replacement impacts both the bias and the precision of partner-reported ADCS-ADL-MCI scores.

2 | METHODS

2.1 | Data source

Data used in the preparation of this manuscript were obtained from the University of California, San Diego ADCS Legacy database. We used data from the ADCS Vitamin E/Donepezil MCI Trial. Criteria for enrollment included that participants be between the ages 55 and 90 years, have a Clinical Dementia Rating scale global score of 0.5, and have a study partner at baseline who agreed to attend all study visits with the participant.[4] The original goal of this randomized placebo-controlled trial was to determine whether vitamin E or donepezil could delay progression to AD dementia, compared to placebo, up to 36 months post-randomization. Secondary outcomes included partner-reported participant function, quantified with the ADCS-ADL-MCI. A total of 769 participants were enrolled in the original trial; one participant was

excluded from our analysis due to missing ADCS-ADL-MCI at all visits. Participants signed Institutional Review Board approved consent forms before enrollment in the original study. The current study utilized only deidentified data and therefore does not qualify as human subjects' research.

2.2 | ADCS-ADL-MCI

The ADCS-ADL-MCI is a questionnaire that utilizes informant reporting to assess participants' performance of activities that they would likely encounter during their everyday life.[10,17,18] It is comprised of 36 items with a range of 53 possible points across 8 subscores, with higher scores indicating better function. The instrument was collected at study baseline (time of randomization) and every 6 months until treatment termination, up to 36 months after baseline.

2.3 | Participant and study partner demographics

Participant and study partner demographic information, such as sex, age, years of education, race and ethnicity, study partner type, and number of hours per week the study partner spent with the participant, were recorded at the screening visit. Participants self-reported their race and ethnicity as one of the following categories: American Indian or Alaskan Native, Asian or Pacific Islander, Hispanic, non-Hispanic Black, non-Hispanic White, or other/unknown. For completeness, we reported demographic information for all categories in Table 1 but, due to sparsity in several race and ethnicity categories, we created three mutually exclusive groups (non-Hispanic White, Hispanic, non-Hispanic, and non-White) for modeling analyses. Due to sparsity in individual relationship categories, we defined study partners as being spousal, including husbands and wives, or non-spousal, including all other participant-partner relationships. In the event of a study partner replacement, demographic information was collected on the new study partner, along with the visit number in which the new study partner was first observed.

2.4 | Statistical analyses

2.4.1 | Associations with study partner replacement

We used a logistic regression model to assess the association between study partner type (spousal vs. non-spousal) at baseline and the odds of experiencing a study partner replacement at any point during the trial. We adjusted for a priori identified confounding factors including participant age, participant race and ethnicity, participant sex, baseline ADCS-ADL-MCI score, study partner education level (in years), and the interaction between participant age and dyad type.

2.4.2 | Impact of study partner replacement on bias and variance in ADCS-ADL-MCI scores

To assess the impact of study partner replacement on bias in ADCS-ADL-MCI scores, we used generalized estimating equations (GEEs) to longitudinally model the difference in ADCS-ADL-MCI scores recorded at consecutive visits (directional change) as a function of whether a study partner replacement occurred. We also assessed the impact of replacement on ADCS-ADL-MCI score variability via GEE by longitudinally modeling the absolute difference in ADCS-ADL-MCI scores between consecutive visits (mean absolute change) as a function of whether a study partner replacement occurred. Both models adjusted for confounding factors, including study partner type at the previous visit, participant age, months since baseline visit, participant sex, and ADCS-ADL-MCI score at the previous visit. We specified an exchangeable working covariance structure to account for correlation between consecutive visits for a single participant and used robust variance estimators[19] for all inference.

RESEARCH IN CONTEXT

1. **Systematic review**: In Alzheimer's disease (AD) clinical trials, including trials enrolling patients with mild cognitive impairment (MCI), participants must enroll with a study partner (SP). SPs ensure compliance and are a source of study data, including assessments of the participant's cognition and function. It is unclear, however, how often SP replacement occurs in MCI trials and whether the introduction of a new SP systematically biases partner-reported outcomes or impacts their volatility.
2. **Interpretation**: SP replacement occurred for a meaningful number of participants but did not result in systematic bias on a functional outcome in this trial, but it did increase variability.
3. **Future directions**: Efforts to reduce replacement and account for resulting variance may be necessary.

2.4.3 | End-of-study variability

We used an F-test to compare the variances of the end-of-study change from baseline ADCS-ADL-MCI scores for those with and without study partner replacements during the course of the trial. We then fit a linear regression model to assess the impact of replacement on end-of-study change from baseline ADCS-ADL-MCI score, adjusting for participant age and study partner type. We restricted these analyses to participants who completed at least two visits.

2.4.4 | Missing data and influence diagnostics

We imputed missing ADCS-ADL-MCI scores using hot deck imputation.[20] We applied this method to observations where seven out of the eight ADCS-ADL-MCI subscores were available, and ran-

domly sampled a match for the missing subscore from the entire study pool. The final ADCS-ADL-MCI score was obtained by summing the eight subscores together. If participants were missing more than one ADCS-ADL-MCI subscore, their data at that visit were excluded from our analysis. We used Cook's Distance to assess influential observations; we did not find evidence of outsized influence from any data points in our analyses.

All statistical analyses were conducted using R version 4.0.3.[21] With the exception of F-tests for variance, all statistical inference utilized Wald-based tests with a two-sided alpha level of 0.05 and corresponding 95% confidence intervals (CIs) are reported.

3 | RESULTS

3.1 | Descriptive statistics and demographic information

Table 1 describes the demographics of the 768 participants included in our analyses, stratified by whether they experienced a study partner replacement at any point in the trial. Forty participants (5%) experienced at least one study partner replacement. A smaller proportion of participants who experienced at least one study partner replacement had spousal study partners at baseline compared to participants who did not experience a replacement (50% vs. 74%). Participants who experienced at least one study partner replacement also tended to be older (76.4 vs. 72.8) and more often female (67.5% vs. 44.6%) than those with stable study partners. The mean baseline ADCS-ADL-MCI score was slightly higher for those who experienced at least one study partner replacement (47.1 vs. 45.9).

Among the 40 participants who experienced a study partner replacement, 36 experienced one replacement and four experienced two replacements (44 total replacement events). Table 2 describes the type of replacements that occurred in terms of dyadic relationship. Most replacements were transitions to a non-spouse partner.

3.2 | Association with replacement

We fit a logistic regression model that included an interaction between study partner replacement and mean-centered participant age along with adjustment for baseline ADCS-ADL-MCI, sex, study partner years of education, participant years of education, and race/ethnicity. From this model, the estimated odds of study partner replacement were 60% lower for average age participants (73 years) with a spousal study partner at baseline, compared to those with a non-spouse partner (odds ratio [OR] = 0.40; 95% CI: [0.18–0.88]; Table 3). Among participants with a spousal study partner at baseline, we estimated 93% greater odds of study partner replacement comparing participants who differed in age by 5 years (OR = 1.93; 95% CI: [1.40–2.67]; Table 3); though it did not reach statistical significance, we estimated a 17% higher odds of study partner replacement comparing participants who had a non-spousal study partner at baseline but differed in age by 5 years (OR = 1.17; 95% CI [0.85–1.62]; Table 3). The overall test for the interaction term was not statistically significant ($p = 0.053$). The estimated odds of study partner replacement among male participants were 54% lower than female participants with similar characteristics (OR = 0.46; 95% CI: [0.21–0.97]; Table 3). No other characteristics demonstrated a significant association.

TABLE 1 Characteristics of participants and SPs analyzed

Patient characteristics	No SP replacement ($n = 728$)	At least one SP replacement ($n = 40$)	Total ($n = 768$)
Sex			
Male	403 (55.4)	13 (35.5)	416 (54.2)
Female	325 (44.6)	27 (67.5)	352 (45.8)
Race/ethnicity			
American Indian or Alaskan Native	3 (0.4)	0 (0.0)	3 (0.4)
Asian/Pacific Islander	6 (0.8)	1 (2.5)	7 (0.9)
Hispanic	28 (3.9)	2 (5.0)	30 (3.9)
Non-Hispanic Black	16 (2.2)	2 (5.0)	18 (2.3)
Non-Hispanic White	673 (92.4)	35 (87.5)	708 (92.2)
Other/Unknown	2 (0.3)	0 (0.3)	0 (0.3)
Baseline SP type			
Spousal	539 (74.0)	20 (50.0)	559 (72.8)
Non-spousal	189 (25.9)	20 (50.0)	209 (27.2)
Child	101 (13.9)	10 (25.0)	111 (14.5)
Friend/companion	60 (8.2)	4 (10.0)	64 (8.3)
Other	28 (3.8)	6 (15.0)	34 (4.4)
Age			
Participant age	72.8 (7.3)	76.4 (5.5)	72.8 (7.3)
Baseline SP age	65.4 (12.2)	66.0 (17.9)	65.5 (12.6)
Baseline ADCS-ADL-MCI	45.9 (4.8)	47.1 (4.2)	46 (4.8)
Years of education			
Participant	14.6 (3.1)	14.5 (3.1)	14.7 (3)
Baseline study partner	14.6 (2.8)	14.1 (3.0)	14.6 (2.8)

Note: Continuous variables are summarized as means (standard deviation), while discrete variables are summarized as counts (%).
Abbreviations: ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment; SP, study partner.

TABLE 2 Type of replacement at each SP replacement occurrence

Type of SP replacement	Number of occurrences *N* (%)
Spousal to non-spousal	21 (47.7)
Non-spousal to non-spousal	18 (40.9)
Non-spousal to spousal	5 (11.4)
Total	44

Abbreviation: SP, study partner.

TABLE 3 Estimated odds ratios for logistic regression model assessing the relationship between ever experiencing a SP replacement and baseline dyad type

	SP replaced by final visit		
Parameter	Estimated odds ratio	95% Confidence interval	*p*-Value
Spousal SP (age of 73)	0.40	(0.18–0.88)	0.022
Participant age (per 5 years)			
Spousal SP	1.93	(1.40–2.67)	<0.001
Non-spousal SP	1.17	(0.85–1.62)	0.338[a]
Baseline ADCS-ADL-MCI	1.07	(0.98–1.15)	0.104
Male	0.46	(0.21–0.97)	0.042
SP years of education	0.89	(0.79–1.01)	0.076
Participant years of education	1.05	(0.93–1.19)	0.421
Non-Hispanic White	0.80	(0.27–2.37)	0.656

The referent group is participants with non-spousal SPs.
[a]The *p*-value for the interaction between age and partner type is 0.053.
Abbreviations: ACDS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment; SP, study partner.

Figure 1 depicts an overall positive association between the odds of study partner replacement, comparing participants with spousal study partners versus non-spousal study partners and participant age. It shows that, compared to those with non-spousal study partners at baseline, the odds of a study partner replacement for those with a baseline spousal study partner increases with participant age.

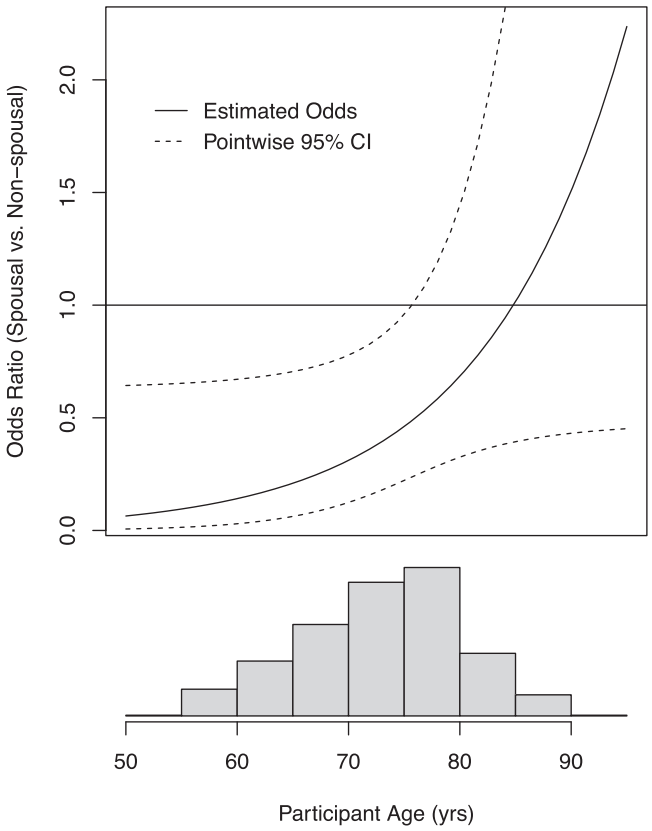

FIGURE 1 Interaction of age and study partner dyad type. Odds ratio of study partner replacement comparing patients with spousal to non-spousal study partners as a function of participant age.

3.3 | Short-term impact of replacement

Table 4 contains a summary of the GEE regression results for between-visit mean difference (bias) and absolute difference (volatility) in ADCS-ADL-MCI scores, adjusting for ADCS-ADL-MCI at the previous visit, months since baseline, participant age, and study partner dyad type at the previous visit. We found that mean within-participant change in consecutive ADCS-ADL-MCI scores did not vary significantly by study partner replacement status (-0.23; 95% CI: [-1.60, 1.14]; Table 4, columns 1–2). Mean within-participant absolute change in ADCS-ADL-MCI scores did, however, vary significantly by study partner replacement status. Compared to those participants with consistent study partners at consecutive visits, participants who experienced study partner replacement had, on average, an absolute difference in consecutive ADCS-ADL-MCI scores that was 1.60 points larger in magnitude (95% CI: [0.62–2.57]; Table 4, columns 3–4). In contrast, the results of the between-visit mean difference model did not indicate that this difference was consistently in a higher or lower direction.

3.4 | Long-term impact of replacement

On average, participants who experienced at least one study partner replacement had a larger decline in ADCS-ADL-MCI from baseline to the end-of-study (-6.05; 95% CI: [-9.3, -2.73] vs. -4.88; 95% CI: [-5.54, -4.11]). Although it was not statistically significant, the variance of the end-of-study change from baseline ADCS-ADL-MCI scores was observed to be higher among those who experienced at least one replacement (variance ratio = 1.27; 95% CI: [0.84–2.10]).

Table 5 contains estimates from modeling the association between study partner replacement and the end-of-study change from baseline ADCS-ADL-MCI scores, adjusting for baseline dyad type and participant age. Participants who experienced study partner replacement had an end-of-study change from baseline ADCS-ADL-MCI score that was, on average, 0.33 points smaller than participants who did not experience a study partner replacement (-0.33; 95% CI: [-3.32, 2.66]; Table 5).

4 | DISCUSSION

To our knowledge, this is the first systematic assessment of study partner replacement in an MCI trial. Of the 768 analyzed participants, 40 (5%) experienced at least one study partner replacement—a rate potentially meaningful to trial outcomes and data integrity. Though we did not find evidence of directional bias associated with study partner replacement, variance and volatility were increased.

TABLE 4 Estimated associations for longitudinal regression models assessing the relationship of SP replacement with relative (left) and absolute (right) differences in consecutive ADCS-ADL-MCI scores.

	Difference in consecutive ADCS-ADL-MCI		Absolute difference in consecutive ADCS-ADL-MCI	
Parameter	Coefficient estimate	95% confidence interval	Coefficient estimate	95% Confidence interval
SP replacement	−0.23	(−1.60, 1.14)	1.60	(0.62–2.57)
Previous visit ADCS-ADL-MCI	−0.03	(−0.05, 0.00)	−0.12	(−0.14, −0.10)
Time	−0.04	(−0.06, −0.02)	0.00	(−0.01, 0.01)
Participant age	−0.06	(−0.08, −0.04)	0.04	(0.02, 0.06)
Spousal SP	−0.13	(−0.47, 0.22)	−0.37	(−0.68, −0.07)

Abbreviations: ACDS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment; SP, study partner.

TABLE 5 Estimated associations for regression model assessing the relationship of SP replacement and end-of-study change from baseline ADCS-ADL-MCI scores

	End-of-study change from baseline ADCS-ADL-MCI	
Parameter	Coefficient estimate	95% confidence interval
SP replacement	−0.33	(−3.32, 2.66)
Baseline spousal SP	−0.94	(−2.51, 0.64)
Participant age	−0.26	(−0.36, −0.16)

Abbreviations: ACDS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment; SP, study partner.

The observed rate of study partner replacement in this study was markedly less than previously reported in an observational study,[13] though is consistent with those reported in Alzheimer's dementia trials.[14,15] Explanations for this discrepancy may include that the previous observational study involved only annual visits, was of a longer duration, and had potentially less stringent protocols for maintaining the same study partner. In addition, the previous study was conducted in a dementia population, while the current trial under investigation included only individuals with MCI. We note, however, despite a lower frequency of replacement, that the current study shows that relationship to the study partner was still a risk factor for replacement. Specifically, the odds of replacement were estimated to be lower for those enrolled with a spousal partner for nearly all ages. The observed lower rate of replacement among participants with spousal study partners could be explained by stronger personal motivation of spousal study partners,[22] although our data do not directly address this.

We found that the magnitude of the association between dyad type and study partner replacement was modified by participant age. Overall, older participants had greater odds of study partner replacement. This observation was limited to spousal dyads, however; no significant age effect was observed among non-spousal dyads. Although no data were available to explain reasons for study partner replacements, it is possible that these replacements related to study partner age more so than participant age. Members of spousal dyads typically have similar ages, compared to the frequent generational age difference between members of non-spousal dyads. Increasing age brings challenges to participation for older study partners, including potential logistical, mobility, and health issues (and even death).[6] In contrast, age was not associated with replacement for non-spousal dyads. This likely results from the predominance of adult children among non-spousal partners and the wide ranging but overall young age range among these partners, regardless of the participant's age.

In contrast to our hypothesis, we did not observe a significant acute bias in ADCS-ADL-MCI scores after study partner replacement: consecutive-visit score differences were neither systematically larger nor smaller, on average, after a study partner replacement. We also observed no bias when examining the effects of study partner replacement on end-of-study change-from-baseline outcomes. These observations indicate that the risk of bias in MCI trials, if, for example, replacement were unbalanced by study arm, may be minimal. On the other hand, we note that there is a complex relationship between the amount of sustained or daily contact with the participant and the assessment of participant function and cognition.[23,24] While we did not observe a statistically significant difference, previous literature has found that spousal study partners, or partners with sustained contact with the participant, tend to underestimate functional outcomes compared to non-spousal study partners.[23,25–27]

We did observe a statistically significant impact on the variance of partner-reported ADCS-ADL-MCI scores acutely after a study partner was replaced. We also observed a greater variability in end-of-study change from baseline ADCS-ADL-MCI, on average, for participants who experienced at least one study partner replacement. This observation may be particularly important for investigators conducting AD trials, where unexpected rates of study partner replacement could conceivably reduce trial power to demonstrate a treatment effect.

The observed acute variation in ADCS-ADL-MCI suggests increased efforts during MCI trials are needed to retain study partners, particularly among those with non-spousal partners. Potential interventions to reduce replacement could include more explicitly outlining the expectations of study partners in the enrollment and consent

processes. As with efforts to recruit and retain participant dyads, interventions to reduce the burden of participation may also be key to lower replacement rates.[6,28–30] Further investigation into why some study partners can no longer fill their role is also needed, as this may reveal common stress points for study partners that may be actionable for trial teams.[8] This is particularly important because participants from historically underrepresented racial and ethnic groups are more often members of non-spousal dyads than their non-Hispanic White counterparts.[31,32] Even in this study, which overall lacked diversity, we observed differences in the racial and ethnic representations of participants who experienced replacement compared to those who did not.

An additional solution may be to consider the impact of study partner replacement on endpoint precision before the trial begins by incorporating differential variation in sample size calculations in trial planning stages. A current barrier to this proactive planning is a lack of publicly available historical information on the frequency and impact of partner replacement on study endpoints. Assessing study partner replacement frequency, analyzing its impact on short-term change in outcome measures, and publishing such results in future AD trials may also help to sustain study integrity for the greater AD and related dementias trial community. Providing investigators with reported metrics on frequency and variance in previous studies for reference may make it easier to incorporate study partner replacement in future study planning. While this information may be incorporated into sample size calculations via simulation, there is no explicit closed-form calculation that can accommodate these differential variances, particularly if differential variance in multiple respects are of interest. Further methodological investigation is needed to determine the best way to incorporate this information at the study planning stage.

We note some limitations to this work. While the low frequency with which study partner replacement occurred in our study sample (5%) was not a limitation in and of itself, it limited our ability to obtain narrow precision on our estimates. Study partner replacement may be associated with factors such as travel constraints or burden to the study partner, but would require a larger, more diverse sample to draw more definitive conclusions. Our analysis was performed using results from a single MCI trial. This limits our ability to understand how study partner replacement may impact variability in study partner-reported outcomes in MCI trials more broadly or in the more recently used "early AD" trials that include individuals with MCI and patients with mild dementia.[33] The ADCS MCI Donepezil trial also consisted mostly of non-Hispanic White participants, limiting our ability to assess potential subgroup differences in these observations.

5 | CONCLUSION

Our results show that when planning future AD trials, efforts to reduce or otherwise account for variability caused by study partner replacement may be necessary.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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