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Frequency and impact of informant replacement in Alzheimer's disease research

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Abstract

Informants serve an essential role in Alzheimer's disease (AD) research. Were an informant to be replaced during a longitudinal study, this could have negative implications. We used data from the National Alzheimer's Coordinating Center Uniform Data Set to examine the frequency of informant replacement among AD dementia participants, whether patient and informant characteristics were associated with replacement, and how replacement affected research outcome measures. Informant replacement was common (15.5%) and typically occurred after the first or the second research visit. Adult child (24%) and other (38%) informants were more frequently replaced than spouse informants (10%). Older spouse informant age and younger adult child informant age were associated with replacement. The between-visit change in Functional Assessment Questionnaire (FAQ) scores was greater in patients who replaced informants than in those with stable informants. Clinical Dementia Rating-Sum of Boxes, FAQ, and Neuropsychiatric Inventory scores showed greater variability in between-visit change in patients who replaced informants compared to those with stable informants. These findings suggest that informant replacement is relatively common, may have implications to study analyses, and warrant further examination in the setting of clinical trials.

Keywords

Alzheimer's disease; caregivers; research; informant; spouses; adult children; outcome measurements

Background

Alzheimer's disease (AD) research, especially dementia clinical trials, relies on accurate assessment of longitudinal patient change.[1–2] Informants may be better at assessing disease-

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related symptoms and changes in those symptoms than are patients themselves.[3] Informant-based AD research scales assess patients' cognitive domains, neuropsychiatric symptoms, occupational and community activities, and basic and instrumental activities of daily living. Informant-based measures of patient performance offer advantages, relative to direct patient testing. They are associated with less patient burden, may be less susceptible to cultural and educational bias, can incorporate change in performance in single time point ratings, and may be more relevant to everyday function.[4] Informant-based measures of patient performance have disadvantages as well. To be effective, these scales depend on accurate and consistent ratings by informants, and some informants may provide more valid data than others.

Factors that affect informant accuracy could bias study results and lead to error. Previous studies suggest that particular informant and patient characteristics may be associated with informant accuracy, both for subjective outcomes such as depression and quality of life,[5–7] and for more objective constructs such as cognition and daily function.[8–11] For example, spouses may provide more accurate data on patient cognition, compared to non-spousal relatives.[8–10] Informants under greater caregiver stress may rate patient function as worse[12] and may be more likely to differ from patient self-report[5, 11–12] or direct patient measures.[11, 13] Disease severity may also impact informant accuracy. In one study, informant reports more poorly predicted patient cognitive performance in mild (global Clinical Dementia Rating [CDR] scale=1), compared to very mild, dementia (global CDR=0.5).[10]

Another factor that might impact accuracy is replacing an informant. Replacement would require a new informant to complete research assessments, from which change scores would be calculated as if a consistent source had provided the data. Unfortunately, how often replacement occurs and how replacing an informant affects study outcome measures are unknown. Understanding the implications of switching informants is important to data interpretation in AD research, especially dementia registration trials, where one co-primary outcome to establish drug efficacy is typically informant-based.

We used data from the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) to examine the frequency of informant replacement in longitudinal AD research. We examined which participants most frequently experience informant turnover and assessed the impact that replacing an AD research informant has on study outcome measures. We hypothesized that, since they are at greater risk for dropout in the setting of AD trials,[14] patients with nonspousal informants would be at increased risk for replacement, and that informant replacement would be associated with differences in change scores on informant-dependent research outcome measures.

Materials and Methods

Data source

Initiated in 2005, the NACC UDS is a repository for longitudinal data collected from approximately 34 current or previously NIA-funded AD Centers (www.alz.washington.edu).[15–16] UDS participants undergo clinical and neuropsychological

assessment on an annual basis. The acceptable visit window is ±3 months, relative to the annual baseline visit anniversary. We examined data collected on or before June 1, 2013.

Participants

Eligible participants were subjects with a diagnosis of probable AD dementia, age 55–90, and a baseline CDR global score of 0.5 or 1.0 who had at least one follow-up visit. Participants were excluded if they had any subsequent neurodegenerative diagnosis other than dementia/probable AD. Study baseline was defined as the first eligible visit for which all criteria were met.

The NACC UDS requires participants to have a reliable informant who accompanies them to study visits and completes a variety of outcomes. At each visit, informants are categorized based on their relationship to the participant: spouse, adult child, or other (neither spouse nor adult child) and the UDS variable *NEWINF*, "is this a new informant?" captures whether an informant was replaced, compared to the prior visit. We excluded data from 361 (16.5%) participants for whom (1) the informant was identified as new but the relation to the participant and the informant birth month and year were unchanged, (2) the informant relation or birth month and year were different from the previous visit but the informant was not listed as new, or (3) the relationship of the informant to the participant at baseline for this study was unknown. The final set for analysis included 1536 participants with stable informants, 218 participants who experienced informant replacement once, and 64 participants who experienced informant replacement more than once.

Measures

Patient demographics—We examined participant age; sex; years of education; race, characterized as Caucasian or non-Caucasian; and ethnicity, categorized as Latino or non-Latino. To examine participant fatigue over time, we also included the overall UDS visit number, since some participants first enrolled in the UDS prior to meeting criteria for this study. Additionally, in some analyses we examined the visit number for this study; that is, relative to the first visit for which the participant met eligibility criteria.

Informant demographics—We examined informant age, sex, race, ethnicity, and the relationship of the informant to the patient, categorized as spouse, adult child, or other.

Clinical outcomes

Clinical Dementia Rating-Sum of Boxes (CDR-SB)[17]: The CDR is a clinical assessment of global cognitive and functional ability that documents information in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. After interviewing both the patient and the informant, an investigator scores each domain as 0 (not demented), 0.5 (questionable dementia), 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).

Functional Assessment Questionnaire (FAQ)[18]: The FAQ is a 10-item tool based solely on informant assessment of the patient's ability to complete activities of daily living. Items are scored as 0 (normal), 1 (has difficulty but does by self), 2 (with assistance), or 3 (in a dependent manner). Scores range from 0 to 30, with higher scores representing greater functional dependence. In the UDS, missing FAQ values are not permitted but "not applicable" (e.g., never did) is an alternative response. We replaced not-applicable responses with the mean of available items, if at least five items were completed.[19]

Neuropsychiatric Inventory (NPI-Q)[20–21]: The NPI is an informant-based instrument that assesses delusions, hallucinations, dysphoria, anxiety, euphoria, aggression, apathy, irritability, disinhibition, aberrant motor behaviors, nighttime behaviors, and eating and appetite. The informant rates each item as present or absent. If present, the item is rated for its frequency, severity, and the distress it causes the informant.[20] The UDS collects the NPI-Q, a brief version of the NPI that only assesses the presence and severity of behavioral symptoms.[21] Present symptoms are scored as mild (1 point), moderate (2 points), or severe (3 points), providing an NPI-Q total score ranging from 0 to 36.

Mini-Mental State Exam (MMSE)[22]: 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. The researcher administers the scale to the patient participant. The MMSE was used as an objective covariate in analytic models (see below).

Statistical analyses

We examined the frequency of informant replacement in UDS among AD participants in three groups based on baseline informant relationship to the patient participant. Within each informant type, we compared demographic and clinical characteristics at baseline in participants who replaced informants versus those with stable informants, using two-sample t-tests for continuous variables and Chi-square (X^2) tests or Fisher's exact tests for categorical variables. The NPI total score had a highly skewed distribution whereby the majority (69%) of participants had scores of zero, so we used Chi-square tests for the frequency of NPI-Q total scores greater than zero.

We used logistic regression with stepwise selection, using significance levels of 0.05 as criteria to add or remove variables, to identify the variables associated with the outcome of informant replacement. Due to systematic differences among informant groups in demographic characteristics (e.g., participants with adult child informants are older than participants with spouse informants, and adult child informants are younger than spouse informants[23]) and potentially different mechanisms that drive the replacement, we constructed models separately within each informant group. The pool of candidate variables included patient race and ethnicity, overall UDS visit number, baseline MMSE, CDR, FAQ, and NPI scores, and informant age and sex. For the spouse and adult child groups, patient and informant age were highly correlated (r=0.75 and r=0.78, respectively), so only informant age was included. Similarly, patient and informant sex are associated for the

spouse group, so only informant sex was included. For participants who experienced informant replacement more than once, we used their first replacement.

The next series of analyses examined change in informant-based outcome measures and associated factors. We calculated the change in each outcome measure by subtracting scores for the visit immediately preceding informant replacement from the scores for the first visit with the new informant. To select two comparable visits in the group with stable informants, we performed a visit number matching procedure so that the two groups had equal proportions of participants examined at each visit number relative to baseline. This was made possible by first matching participants at the longest duration time points. Participant data from the two consecutive visits selected by the matching procedure were used to compute the change scores. Because of the need to match based on visit number, these analyses excluded participants who experienced informant replacement more than once. To ensure that the comparison was not biased by the difference in the time elapsed between visits, we used actual visit dates and computed a precise time interval for every participant. Two sample t-tests were used to compare the mean of CDR, FAQ, and NPI-Q change scores between the new and stable informant groups. Tests for the equality of variances were used to compare the variance of the change scores for each outcome. In the setting of equal variance, pooled t-tests were performed. In the setting of unequal variance, Satterthwaite t-tests were performed. The same analysis was carried out among those with informant changes to compare those participants whose new informant was an adult child to those with any other type of new informant.

Linear regression models were used to further examine whether change in these informant-based outcome scores was associated with informant replacement when adjusting for covariates of interest. Models were run for each outcome measure and covariates included: whether replacement occurred, sex, patient age, precise time since the previous visit, and type of informant and MMSE score at the visit prior to replacement (or the matched visit in the group with stable informants). An interaction term *informant replacement*baseline informant type* was included to examine whether the effect of informant replacement differed by baseline informant type. All analyses were performed in SAS v.9.3 (Cary, NC). All statistical analyses are reported with a significance level of 0.05.

Ethics

All participants and informants in the NACC UDS sign an informed consent document approved by an Institutional Review Board (IRB). The current project was approved the UCLA IRB (#13-001015).

Results

Frequency of informant replacement

1,818 UDS AD dementia participants met study eligibility criteria; 282 (15.5%) had experienced informant replacement at least once. Among the 218 participants who experienced replacement once, most (73%) informant replacement occurred between the baseline and first follow-up visits (42%) or between the first and second follow-up visits

(31%). Fifteen percent of informant replacement occurred after the second follow-up visit, 7% after the third visit, and 3% after the fourth visit. The pattern of informant replacement based on overall UDS visit number was similar. Sixty-five percent of replacement occurred prior to the first or second follow-up visit (data not shown).

Among patients with a spouse informant at baseline, 9.7% experienced informant replacement (Table 1). Participants with adult child (23.7%) and other informants (37.9%) at baseline more frequently replaced informants than those with spouses (X^2=113, p<0.001). New informants were typically adult children (68%). Adult children replaced 80% of spouse informants, 64% of adult child informants, and 53% of other informants.

Participants with spouse informants at baseline

Table 1 shows the patient participants' demographic and clinical characteristics at baseline and Table 2 shows their informants' characteristics at baseline. Patients whose spouse informants were replaced were older (t-test, p<0.001), more often female (X^2, p<0.001), more frequently Latino ethnicity (Fisher's exact test, p<0.001), and had lower education (t-test, p=0.009) than their counterparts with stable informants. Spouse informants who were replaced were older (t-test, p<0.001), more often male (X^2, p<0.001), and were more frequently minority race (X^2, p=0.02) and Latino ethnicity (Fisher's exact test, p=0.002) than their consistent counterparts.

The final logistic regression model resulting from the stepwise procedure showed that Latino ethnicity (OR=3.67, 95% CI: 1.39–9.69), older informant age (OR=1.07, 95% CI: 1.04–1.10), and male informant sex (OR=1.60, 95% CI: 1.03–2.50) were significantly associated with replacing a spouse informant.

Participants with adult child informants at baseline

We found no demographic or clinical differences at baseline between patient participants with adult child informants who were replaced and those whose informants were stable (Table 1). Replaced adult child informants were younger than their stable counterparts (Table 2; t-test, p=0.02).

Logistic regression showed that informant age was a significant predictor of adult child informant replacement (OR=0.97, 95% CI: 0.95 – 0.999), but in the opposite direction from that seen for spouses. No other variable reached statistical significance.

Participants with other informants at baseline

Participants who replaced an informant who was neither spouse nor adult child were more frequently Latino (X^2, p=0.01), had lower education (t-test, p=0.01), and had milder scores on the global CDR (t-test, p=0.03), CDR-SB (t-test, p=0.02), and FAQ (t-test, p=0.001) compared to those with stable other informants (Table 1). Other informants who were replaced were more often Latino (X^2, p<0.01) and had lower education (t-test, p<0.05) than their stable counterparts (Table 2).

Among participants with other informants, lower scores on the FAQ (OR=0.88, 95% CI: 0.83–0.93) and higher scores on the NPI-Q (OR=1.64, 95% CI: 1.09 – 2.45) at baseline were associated with replacing the informant in the logistic regression.

Outcome measure change scores

Among all participants, regardless of informant type, there was no difference in the mean change in CDR-SB or the NPI-Q for those who did, compared to those who did not, have a new informant. The change in FAQ score, however, was significantly greater for the group with a new informant (4.48 vs 3.45, p=0.02). The new informant group also demonstrated significantly greater variance for change in all three informant-based outcome measures examined (Table 3). The time elapsed between visits was longer on average and exhibited greater variation for the new informant group than for the stable informant group (1.23 ± 0.51 years vs. 1.13 ± 0.36 years).

Table 3 displays the mean between-visit changes in outcomes for those who replaced versus those with stable informants for the different baseline informant type groups. In the group with spouses at baseline (n=97 replaced; n=1100 stable), the results were similar to those for the entire population; FAQ change scores were greater in the replaced group (5.18 vs. 3.58, p=0.03) and the variance was increased for each outcome. For those with adult child (n=74 new; n=341 stable) and other informants at baseline (n=47 new; n=95 stable), no differences were observed in the mean change scores for any outcome measure; the variance associated with between-visit change was greater for the replaced adult child informant group for the NPI-Q and for the replaced other informant group for the FAQ. The time elapsed between visits was different between replaced versus stable informant groups in those with adult child (1.33 ± 0.65 years vs. 1.14 ± 0.33 years) but not those with spouse (1.20 ± 0.44 years vs. 1.13 ± 0.38 years) or other informants (1.15 ± 0.39 years vs. 1.07 ± 0.23 years) at baseline.

When we compared those participants whose new informant was an adult child to those with another type of new informant, we found no differences between the groups in the mean between-visit change for any outcome and a difference in the variances only for the CDR-SB (data not shown).

In regression models adjusting for the time elapsed between visits, MMSE score at the visit prior to replacement, and participant age and gender (see Table 4), the main effect of replacement held for change scores in FAQ (p=0.02). The interaction term *informant replacement*baseline informant type* was not significant for change scores in any of the three outcomes, suggesting that the effect of replacement did not differ by baseline informant type. In addition, greater change in CDR-SB and FAQ were significantly associated with longer time between visits (p<0.0001); both were also associated with MMSE scores at the visit before replacement, but in opposite directions. Those with spouse informants at baseline experienced greater change in FAQ than those with other informants at baseline (p=0.01). Change in NPI-Q was only associated with gender, with females showing greater increase in neuropsychiatric symptoms (p=0.02).

Discussion

These findings suggest that the replacement of informants in longitudinal AD research may be a common occurrence. In the NACC UDS, 15% of dementia participants replaced their informants. The majority of replacement occurred early in participation, after the first or second research visit, suggesting that factors other than research fatigue resulted in replacement. In fact, particular patient and informant characteristics were associated with replacement.

Replacement was less frequent for those with spouse informants than for those with nonspouse informants. Among spouse informants, however, Latino ethnicity, male informant sex, and older informant age were associated with informant replacement. Latinos and male informants are less common than non-Latino Caucasians and female informants in AD research.[14, 24–26] The aspects of caregiving and research participation that act as barriers to enrollment in these spouses[27–28] may also increase the risk of their replacement mid-study. The age-associated risk of spouse replacement suggests that death or disability in an aging spouse may necessitate a new informant. In contrast, younger age was associated with adult child informant replacement. Nonspousal informants may have different attitudes toward AD research than do spouses.[29] AD patients lacking a spouse participate in research at lower rates[14, 24] and may be at increased risk for dropping out when they do.[14] These results add to a literature that suggests that careful consideration of which patient-informant dyads to enroll and methods to retain particular dyads especially may be needed to reduce informant replacement and study dropout.

These results may also suggest that informant replacement could affect study data. We observed more than 1-point greater decline between visits on the FAQ in those who replaced, compared to those with stable, informants, after adjusting for covariates (Table 4). Informant replacement, however, was not associated with change in CDR-SB or NPI-Q. Whereas the FAQ is based entirely informant report, the CDR-SB incorporates both informant interview and patient observation. This difference may account for the discrepancy in observations for these two scales, though in the regression model the effect of informant replacement did approach significance for the CDR-SB (p=0.06). The NPI-Q, like the FAQ, is entirely informant-dependent. Though behavioral symptoms become increasingly common with disease progression, NPI-Q measures over time also include fluctuations and reoccurrence.[30] In fact, our regression model suggested that only patient sex was associated with change in NPI-Q between visits.

In our models, greater time between visits was also associated with greater change in FAQ and CDR. Interestingly, the total time elapsed between visits was greater for those replacing versus those with stable adult child informants. Differences in time between visits were not observed for those replacing spouse or other informants, further suggesting (in addition to the regression model) that time alone does not drive the observed effect of replacement on FAQ change scores.

Descriptive statistics suggested that the effect of replacement on FAQ change scores was present in those replacing spouse informants, but absent in those replacing adult child

informants. Because of this, we included the baseline informant type and an interaction term for *informant replacement*baseline informant type* in our models. Neither baseline informant type nor this interaction term, however, reached significance for any outcome (data not shown), suggesting that the effect of replacement is not unique to patients who replace particular informants. The model did suggest that those with spouse informants demonstrated greater between-visit change on the FAQ than those with other informants, a group not examined in a previous study that found no difference in the rate of change between those with spouse versus those with adult child informants.[23]

For each outcome measure, the variability associated with between-visit change scores was greater in those replacing informants than those with consistent informants. Increased variance was also observed for each outcome when limiting analyses to those with spouse informants at baseline. Increased variance was observed for the NPI-Q for those replacing adult child informants, and for the FAQ for those replacing nonspouse, non-adult child informants.

The observed differences in changes in outcome measures and the increased variance for those replacing informants could reduce statistical power to observe differences between research study groups, such as those receiving an intervention versus a control.

Limitations

It is likely that for many AD dementia research participants, the loss of a primary caregiver results in study drop out. Participants who dropped out were not included in the current analyses. We did, however, observe that the most common new informants were adult children. This may suggest that participants who have adult children, in addition to their informant, may be at reduced risk to drop out.

Although the NACC UDS is an ample data source, some of the subgroup analyses included low numbers of cases (e.g., other informant replacement). These analyses may have been underpowered.

Our data do not offer insight into the reasons that informant replacement occurred. The UDS does not collect information on caregiver burden or stress, but previous results suggest that measures of patient function and discrepancies between informant and patient ratings of patient function may be predicted by caregiver burden.[12–13] It is possible that burden due to changes in participant function resulted in replacement, rather than replacement resulting in inflated scoring of patient worsening. Additionally, baseline MMSE score was not predictive of replacement and MMSE change scores were no different in those replacing versus those with stable informants (data not show). These findings may suggest that informant replacement is not due to disease progression.

Whereas lower MMSE scores were associated with greater change in the CDR-SB, higher MMSE scores were associated with greater change in the FAQ between visits. This is likely due to a ceiling effect in the population studied for the FAQ, as has been previously observed.[19, 23, 31] Additionally, among those with non-spouse, non-adult child informants,

milder scores on the FAQ were associated with replacement. While intriguing, further study will be necessary to elucidate this relationship.

Finally, given that the UDS includes annual follow-up over many years, it is unclear to what extent these results will generalize to other research studies, in particular dementia clinical trials, which are frequently 18 or 24 months in total length and have much more frequent visits and evaluations. Though the outcome measures we examined are commonly used in clinical trials, others, such as the AD Cooperative Study-Activities of Daily Living scale[32] or the AD Assessment Scale-cognitive subscale,[33] are not collected in the UDS.

Conclusions

These findings suggest that informant replacement is common and that particular research participants may be at risk for loss of informant. The loss of informant may result in inconsistent data reporting and exploratory analyses suggest that replacement may result in inflated measures of change in patient function and increased outcome measure variance. Such effects could have implications in data analyses and study interpretation. These observations warrant further study in AD dementia treatment trials. Investigators need to know the frequency of informant replacement, whether similar characteristics predict its occurrence, and if replacement impacts trial data. In addition to potential implications to outcome data, informant replacement could impact study completion rates, adverse event reporting, and other variables critical to trial success.

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Table 1

Descriptive statistics of patient participants who did and did not experience informant replacement, categorized by baseline informant type (*p<0.05 based on two-sample t-test or X^2 test or Fisher's exact test, relative to stable group).

Baseline informant:	**Spouse**		**Adult child**		**Other**	
Follow-up informant:	**Stable**	**New**	**Stable**	**New**	**Stable**	**New**
N (%)	1100 (90.3)	118 (9.7)	341 (76.3)	106 (23.7)	95 (62.1)	58 (37.9)
Age, mean years ± SD	73.3 ± 8.2	76.0 ± 7.1*	78.9 ± 6.9	77.7 ± 7.6	75.2 ± 9.2	77.5 ± 8.5
Female, n (%)	387 (35.2)	63 (53.4)*	291 (85.3)	88 (83.0)	71 (74.7)	46 (79.3)
Non-Caucasian race, n (%)	101 (9.2)	14 (12.4)	71 (21.3)	21 (21.7)	22 (23.4)	13 (26.5)
Latino ethnicity, n (%)	26 (2.4)	12 (10.2)*	39 (11.6)	18 (17.1)	9 (9.6)	14 (24.6)*
Education, mean years ± SD	15.4 ± 2.9	14.5 ± 3.5*	13.1 ± 3.6	13.0 ± 4.1	14.5 ± 3.7	12.5 ± 5.0*
Baseline global CDR, mean ± SD	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.3*
Baseline CDR-SB, mean ± SD	4.5 ± 1.8	4.7 ± 1.9	5.0 ± 2.0	4.6 ± 1.6	5.0 ± 2.0	4.1 ± 2.3*
Baseline MMSE, mean ± SD	22.6 ± 4.1	22.7 ± 3.6	21.7 ± 4.2	22.0 ± 3.7	21.6 ± 4.4	22.4 ± 5.5
Baseline FAQ, mean ± SD	13.6 ± 7.2	14.0 ± 7.0	15.0 ± 7.3	15.0 ± 7.3	16.2 ± 7.2	11.9 ± 8.4*
Baseline NPI-Q, mean ± SD	0.48 ± 0.86	0.56 ± 1.02	0.66 ± 1.10	0.64 ± 1.02	0.42 ± 0.89	0.65 ± 1.04

Table 2

Descriptive statistics of the baseline informants who were and were not replaced, categorized by baseline informant type (*p<0.05 based on two-sample t-test or X^2 test or Fisher's exact test, relative to stable group).

Baseline informant:	**Spouse**		**Adult child**		**Other**	
Follow-up informant:	**Stable**	**New**	**Stable**	**New**	**Stable**	**New**
Age, mean years ± SD	70.6 ± 8.8	75.7 ± 9.3*	51.4 ± 8.4	49.2 ± 8.7*	62.8 ± 12.8	58.7 ± 14.8
Female, n (%)	708 (64.4)	54 (45.8)*	260 (76.3)	72 (67.9)	75 (79.0)	43 (74.1)
Non-Caucasian race, n (%)	76 (7.0)	15 (13.2)*	77 (23.0)	29 (28.4)	22 (23.4)	21 (36.8)
Latino ethnicity, n (%)	29 (2.7)	10 (8.9)*	42 (12.5)	18 (17.7)	7 (7.5)	14 (24.1)*
Education, mean years ± SD	15.1 ± 2.8	14.8 ± 3.1	15.9 ± 2.7	15.6 ± 2.6	15.6 ± 2.8	14.5 ± 3.1*

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Table 3

Between-visit change in informant-based outcome measure scores (*p<0.05).

Group	Outcome measure	Stable informant, mean±SD	New informant, mean±SD	t-test, p value	Test of equal variance, p value
All participants	CDR-SB	2.01±2.57	2.37±3.07	0.10	0.0002*
	FAQ	3.45±5.02	4.48±6.39	0.02*	<0.0001*
	NPI-Q	0.11±1.14	0.13±1.38	0.81	<0.0001*
Spouse informant	CDR-SB	2.06±2.56	2.74±3.43	0.06	<0.0001*
	FAQ	3.58±5.03	5.18±6.74	0.03*	<0.0001*
	NPI-Q	0.11±1.08	0.24±1.33	0.34	0.002*
Adult child informant	CDR-SB	1.96±2.65	1.95±2.90	0.95	0.27
	FAQ	3.40±5.23	3.97±5.14	0.39	0.97
	NPI	0.12±1.28	0.09±1.58	0.87	0.01*
Other informant	CDR-SB	1.52±2.37	2.38±2.56	0.06	0.53
	FAQ	1.99±3.72	4.09±7.51	0.08	<0.0001*
	NPI-Q	0.13±1.27	−0.02±1.08	0.48	0.23

Table 4

Results of regression models for change in each informant-based outcome measure.

Variable	Estimate (95% C.I.) *p<0.05		
	CDR-SB	FAQ	NPI-Q
Time (years)	1.63 (1.32, 1.95)*	1.87 (1.21, 2.53)*	0.003 (−0.14, 0.15)
MMSE score	−0.12 (−0.15, −0.10)*	0.07 (0.02, 0.12)*	0.008 (−0.003, 0.018)
Female gender	−0.07 (−0.20, 0.34)	0.13 (−0.45, 0.70)	0.15 (0.02, 0.28)*
Age (years)	0.008 (−0.014, 0.016)	−0.0003 (−0.033, 0.032)	0.001 (−0.006, 0.008)
Replacement	0.50 (−0.04, 1.04)	1.35 (0.20, 2.50)*	0.05 (−0.21, 0.30)
Informant type (reference=spouse): child	−0.19 (−0.56, 0.17)	−0.22 (−0.99, 0.54)	−0.05 (−0.22, 0.12)
Informant type (reference=spouse): other	−0.42 (−0.99, 0.15)	−1.53 (−2.73, −0.33)*	−0.09 (−0.36, 0.17)
Informant type × Replacement (reference=spouse): child	−0.48 (−1.31, 0.36)	−1.63 (−3.39, 0.14)	−0.07 (−0.46, 0.32)
Informant type × Replacement (reference=spouse): other	0.16 (−0.90, 1.22)	0.85 (−1.40, 3.10)	−0.18 (−0.68, 0.31)