

SHORT REPORT

A randomized controlled trial of amyloid positron emission tomography results disclosure in mild cognitive impairment

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Abstract

Introduction: Recent studies suggest that Alzheimer's disease (AD) biomarker disclosure has no discernable psychological impact on cognitively healthy persons. Far less is known about how such results affect symptomatic individuals and their caregivers.

Methods: Randomized controlled trial of 82 mild cognitive impairment (MCI) patient and caregiver dyads (total n = 164) to determine the effect of receiving amyloid positron emission tomography results on understanding of, and perceived efficacy to cope with, MCI over 52 weeks of follow-up.

Results: Gains in the primary outcomes were not consistently observed. Amyloid negative patients reported greater perceived ambiguity regarding MCI at follow-up, while moderate and sustained emotional distress was observed in patients, and to a lesser extent, caregivers, of those who were amyloid positive. There was no corresponding increase in depressive symptoms.

Discussion: These findings point to the possibility that both MCI patients and caregivers may need emotional support after the disclosure of amyloid scan results.

KEYWORDS

amyloid positron emission tomography, biomarker disclosure, caregiving, ethics, mild cognitive impairment

1 | INTRODUCTION

Biomarker tests of Alzheimer's disease (AD) pathology can provide critical insights into the etiology of cognitive decline,¹⁻³ and sharing such information with patients and families affected by mild cognitive impairment (MCI) could lessen their sense of ambiguity regarding the syndrome.

We tested the hypotheses that, irrespective of scan results, giving patients the opportunity to learn their brain amyloid status would enhance understanding of and decrease perceived ambiguity regarding MCI, and empower both patients with MCI and their family caregivers to cope more effectively with its challenges.

2 | METHODS

2.1 | Design and participants

The Return of Amyloid Imaging Scan Results (RAISR) Study enrolled participants from the University of Pittsburgh Alzheimer Disease Research Center (ADRC) between September 2014 and September 2018. Eligible participants and their family caregivers were allocated as dyads in a 1:1 ratio to a scan group or comparison group (Figure 1). Details of the study design and protocols for MCI education (comparison group) and pre-testing counseling (scan group), amyloid positron emission tomography (PET) results disclosure, and adverse event monitoring have been previously described.⁴⁻⁶ Briefly, we included patients

with all MCI subtypes and excluded those with active untreated mood disorders. Caregivers were 18 years of age or older. All participants provided written informed consent and demonstrated decisional capacity.

RAISR was approved by the University of Pittsburgh Institutional Review Board and registered at ClinicalTrials.gov.

2.2 | Intervention

Scan group dyads received pre-test counseling including content on normal aging, MCI, and AD, amyloid PET, and information about the limitations of knowledge to be gained. Participants were encouraged to consider possible reactions to potential scan result scenarios before deciding whether to proceed. Comparison group dyads received an MCI education session with no option of amyloid PET. PET scans were acquired using a standard florbetapir F18 injection protocol⁷ and rated using a validated binary visual read method.^{8,9}

The disclosure protocol included: verbal and visual presentations of scan results using "significant amyloid buildup," or lack thereof, to describe positive and negative scans; short-term risk estimates for conversion to AD; brain health information; and follow-up monitoring instructions.⁴ Participants were randomly assigned to one of three clinically licensed, formally trained results disclosers. Disclosure sessions were audited for protocol adherence and participants' comprehension of information presented was verified.⁴

2.3 | Primary outcomes

Outcomes measures were administered at baseline and weeks 4, 24, and 52 post-disclosure (scan group) or MCI education session (comparison group). Objective knowledge of MCI was measured using the MCI/AD Knowledge Assessment from the Risk Evaluation and Education for Alzheimer's Disease IV (REVEAL IV) protocol.¹⁰ Perceived ambiguity about what MCI means was measured using the Illness Coherence Subscale of the Revised Illness Perception Questionnaire (IPQ-R).¹¹ Self-efficacy for coping was measured by the Coping Self-Efficacy Scale (CSE).¹²

2.4 | Psychological safety

Depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CESD).¹³ State anxiety was measured by the Spielberger State Anxiety Inventory (STAI).¹⁴ Emotional impact was measured by the 15-item Impact of Event Scale (IES).¹⁵ The Distress and Positive Impact subscales of the Impact of Genetic Testing-Alzheimer's Disease (IGT-AD) were also administered,¹⁶ substituting "test result" for "genetic test."

2.5 | Statistical analyses

Intention-to-treat (ITT) analyses of primary outcomes were conducted based on an a priori power analysis indicating that 40 subjects per

HIGHLIGHTS

- First randomized controlled trial of amyloid imaging results disclosure in mild cognitive impairment (MCI).
- The vast majority of those who were eligible opted to receive amyloid positron emission tomography with results disclosure.
- Contrary to our hypothesis, learning one's brain amyloid status did not improve understanding of, or capacity to cope with, the uncertainty of an MCI diagnosis.
- Rather, significant test-related distress was present in amyloid positive patients and caregivers, with caregivers feeling less able to cope with MCI after learning that it is likely a prodrome to Alzheimer's disease.

RESEARCH IN CONTEXT

1. Systematic review: Searching combinations of the keywords "amyloid imaging," "mild cognitive impairment," and "ethics" yielded six observational studies of psychological reactions to disclosing amyloid imaging results plus two reports of comprehension of amyloid imaging results. These studies suggest that receiving amyloid positron emission tomography (PET) results has little to no psychological impact on recipients of such information.
2. Interpretation: This randomized controlled trial examined outcomes of distinct relevance to persons, and care partners of those, living with the uncertainty of a mild cognitive impairment (MCI) diagnosis. We tested the hypothesis that amyloid PET results disclosure would improve understanding of and self-efficacy for coping with the syndrome among MCI care dyads. These hypotheses were not supported. Rather, we found that a negative emotional response is possible.
3. Future Directions: Our findings suggest that MCI care dyads may benefit from monitoring and emotional support after disclosure of biomarker test results.

group would yield 80% power to detect a medium effect size of 0.64 (from a behavioral science perspective) at a two-tailed significance level of .05. This estimation is conservative given RAISR's repeated measures design, which can detect effect sizes as small as 0.32.

After screening, transformations were applied to normalize skewed residuals where encountered (eg, CESD, STAI). Group comparisons of participant characteristics were performed using two-sample t-tests (or Mann-Whitney U-tests) and chi-square tests (or Fisher exact tests). Linear mixed modeling with fixed effects for group and

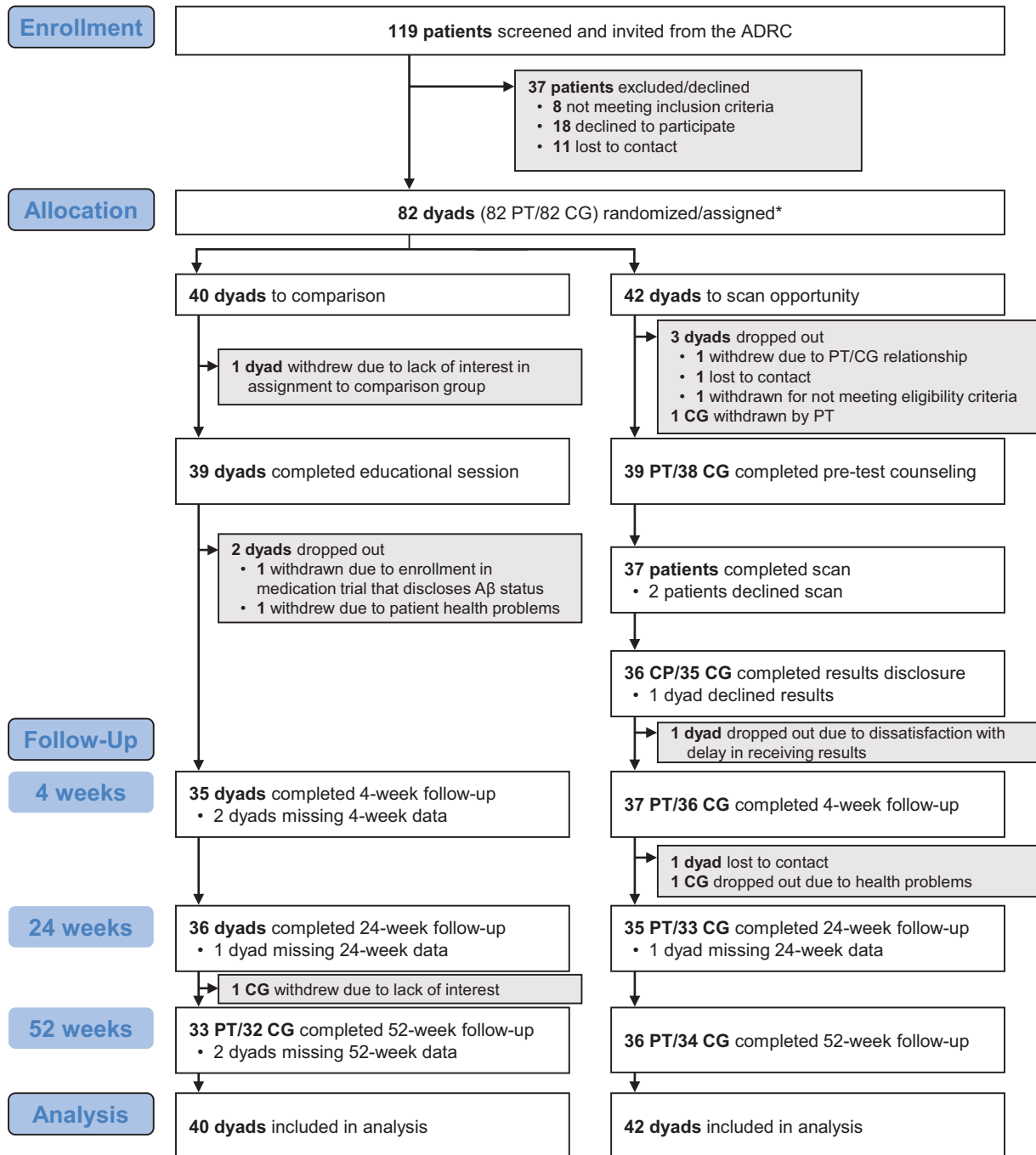


FIGURE 1 Consort diagram. ADRC, Alzheimer Disease Research Center (University of Pittsburgh); PT, patient; CG, caregiver. *N = 12 patients had previously undergone a research positron emission tomography (PET) amyloid scan under a protocol that precluded results disclosure. The randomization process was overridden in these cases and participants were assigned to the scan group, with the opportunity to undergo a new amyloid PET scan and results disclosure. This deviation did not impact the balance of the study groups (including the subgroups of amyloid positive and negative cases) on key baseline characteristics or primary outcomes measures

time and their interaction, and random effects for participant, were used to examine change in the dependent variables. Least squares means and their corresponding standard errors were reported by group and time point along with means and standard errors from within-group linear contrasts. Linear mixed modeling was also used

to examine psychological safety by scan result. All 164 participants were included and the significance level was set at $P < .05$ for two-sided hypothesis testing. Results based on untransformed dependent variables are reported as findings were similar using transformed data.

TABLE 1 Sample characteristics by study group

Variable	Patient participants			Caregiver participants		
	All patient (N = 82)	Scan opportunity (n = 42)	Comparison (n = 40)	All Caregiver (N = 82)	Scan opportunity (n = 42)	Comparison (n = 40)
Mean age in years (SD)	72.6 (8.80)	73.2 (8.19)	72.0 (9.47)	66.8 (12.56)	67.8 (11.59)	65.8 (13.58)
Education, n (%)						
< High school	1 (1%)	0 (0%)	1 (2%)	1 (1%)	1 (2%)	0 (0%)
High school/GED	13 (16%)	7 (17%)	6 (15%)	15 (18%)	5 (12%)	10 (25%)
Technical school or college	23 (28%)	10 (24%)	13 (33%)	38 (46%)	18 (43%)	20 (50%)
Graduate school	45 (55%)	25 (59%)	20 (50%)	28 (34%)	18 (43%)	10 (25%)
Sex, n (%)						
Female	33 (40%)	19 (45%)	14 (35%)	62 (76%)	31 (74%)	31 (77%)
Male	49 (60%)	23 (55%)	26 (65%)	20 (24%)	11 (26%)	8 (23%)
Race/ethnicity, n (%)						
White	75 (92%)	37 (88%)	38 (95%)	74 (90%)	37 (88%)	37 (92%)
Black/African American	6 (7%)	4 (10%)	2 (5%)	5 (6%)	4 (9.5%)	1 (3%)
Asian/Pacific Islander	1 (1%)	1 (2%)	0 (0%)	1 (1%)	1 (2%)	0 (0%)
Multiracial	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
MCI subtype, n (%)						
Amnestic	71 (87%)	37 (88%)	34 (85%)	n/a	n/a	n/a
Non-amnestic	11 (13%)	5 (12%)	6 (15%)			
Relationship, n (%)						
Spouse/partner	n/a	n/a	n/a	60 (73%)	28 (67%)	32 (87%)
Adult child				9 (11%)	7 (17%)	2 (5%)
Other				13 (16%)	7 (17%)	6 (15%)
Mean interest in amyloid PET at baseline ^a (SD)	9.2 (1.59)	9.0 (1.96)	9.4 (1.06)	8.9 (2.50)	8.6 (2.65)	9.1 (2.35)
Mean UBACC score (SD)	18.9 (1.43)	18.9 (1.32)	18.9 (1.56)	19.1 (1.43)	18.8 (1.51)	19.3 (1.31)

Abbreviations: GED, general education diploma; MCI, mild cognitive impairment; PET, positron emission tomography; SD, standard deviation; UBACC, University of San Diego Brief Capacity to Consent.

^aRating of interest in PET amyloid PET on 10-point scale.

*p type = >.05 difference between scan and comparison groups using chi-square or t-test; post-hoc comparisons of demographic characteristics of amyloid negative and amyloid positive scan group participants were also non-significant

3 | RESULTS

The sample included 164 individuals (n = 82 patients; n = 82 caregivers) who completed baseline data collection before allocation to the scan opportunity (n = 42 dyads) or comparison condition (n = 40 dyads). Characteristics of the sample are shown in Table 1. Most patients were highly interested (M = 9.2 on a 10-point scale) in learning their brain amyloid status upon enrollment. Of the 39 scan group patients who completed pre-test counseling, 37 proceeded with the scan, and 36 received results. Reasons for declining included concerns about radiation exposure and the potential for a negative emotional reaction.

3.1 | Primary outcomes

Among patient participants, there were no significant time or group by time effects for any of the three primary endpoints (Table 2). Findings were similar among caregivers. However, a time effect was observed

for objective knowledge of MCI/AD, with scores increasing from baseline among caregivers in both groups ($F_T = 5.12, P = .002$). A within group time effect was observed for self-efficacy for coping with MCI; caregivers in the scan group reported decreased self-efficacy for coping with their relatives' MCI at 4 weeks post results disclosure (mean difference = $-12.35 \pm -5.12; P < .05$), with the decrease persisting at week 52 (mean difference = $-14.98 \pm -6.67; P < .05$).

3.2 | Safety outcomes and subgroup analyses

There were no consistent differences in depressive symptoms in either patients or caregivers, and patients' ratings of state anxiety were stable over time across groups (Figure 2). Caregivers' state anxiety levels were increased from baseline at both 4 and 24 weeks of follow-up, returning to baseline at week 52 ($F_T = 3.16, P = .031$). Mean scores on both the depression and anxiety measures were below cut-points for clinical significance across all participant groupings and time points (Table S1 in supporting information).

TABLE 2 Primary outcomes

Variable	Patient			Caregiver		
	Scan		F-value, p-value	Scan Opportunity		F-value, p-value
	Opportunity (n = 42)	Comparison (n = 40)		(n = 42)	Comparison (n = 40)	
mean ± SE	mean ± SE	mean ± SE	mean ± SE	mean ± SE		
IPQ Coherence			$F_G = 0.00, P = .955$			$F_G = 0.00, P = .947$
Baseline (T ₁)	14.69 ± 0.57	14.03 ± 0.58	$F_T = 0.96, P = .412$	12.38 ± 0.49	12.65 ± 0.50	$F_T = 1.54, P = .207$
4 weeks (T ₂)	14.39 ± 0.59	14.27 ± 0.60	$F_{G \times T} = 1.21, P = .306$	13.26 ± 0.52	12.55 ± 0.53	$F_{G \times T} = 0.82, P = .486$
24 weeks (T ₃)	13.77 ± 0.62	14.57 ± 0.62		11.85 ± 0.55	12.26 ± 0.55	
52 weeks (T ₄)	13.72 ± 0.59	13.86 ± 0.60		12.43 ± 0.53	12.31 ± 0.53	
Change (T ₂ -T ₁)	-0.30 ± 0.52	0.25 ± 0.53		0.87 ± 0.53	-0.10 ± 0.54	
Change (T ₃ -T ₁)	-0.92 ± 0.55	0.54 ± 0.55		-0.54 ± 0.56	-0.39 ± 0.55	
Change (T ₄ -T ₁)	-0.97 ± 0.52	-0.16 ± 0.53		0.05 ± 0.54	-0.34 ± 0.54	
Knowledge			$F_G = 1.64, P = .204$			$F_G = 0.03, P = .871$
Baseline (T ₁)	8.90 ± 0.22	8.90 ± 0.22	$F_T = 0.25, P = .863$	8.79 ± 0.23	8.80 ± 0.24	$F_T = 5.12, P = .002^{**}$
4 weeks (T ₂)	8.75 ± 0.23	9.34 ± 0.24	$F_{G \times T} = 1.38, P = .249$	9.29 ± 0.24	9.47 ± 0.25	$F_{G \times T} = 0.91, P = .436$
24 weeks (T ₃)	8.90 ± 0.24	9.00 ± 0.25		9.43 ± 0.26	9.14 ± 0.26	
52 weeks (T ₄)	8.65 ± 0.23	9.19 ± 0.24		9.15 ± 0.25	9.43 ± 0.25	
Change (T ₂ -T ₁)	-0.16 ± 0.25	0.44 ± 0.26		0.51 ± 0.24	0.67 ± 0.24	
Change (T ₃ -T ₁)	0.00 ± 0.26	0.10 ± 0.27		0.64 ± 0.25	0.34 ± 0.25	
Change (T ₄ -T ₁)	-0.26 ± 0.25	0.29 ± 0.26		0.37 ± 0.24	0.63 ± 0.24	
Coping Self-Efficacy			$F_G = 0.37, P = .543$			$F_G = 0.04, P = .852$
Baseline (T ₁)	204.92 ± 5.12	202.13 ± 5.25	$F_T = 0.14, P = .936$	204.05 ± 4.99	200.76 ± 6.50	$F_T = 2.19, P = .100$
4 weeks (T ₂)	205.45 ± 5.27	202.02 ± 5.39	$F_{G \times T} = 0.66, P = .578$	191.70 ± 7.42	191.13 ± 10.61	$F_{G \times T} = 1.33, P = .274$
24 weeks (T ₃)	205.91 ± 5.41	204.57 ± 5.52		196.64 ± 6.47	195.23 ± 9.35	
52 weeks (T ₄)	208.73 ± 5.3	199.91 ± 5.39		189.07 ± 8.44	201.23 ± 6.97	
Change (T ₂ -T ₁)	0.53 ± 3.83	-0.11 ± 3.91		-12.35 ± 5.12	-9.63 ± 8.26	
Change (T ₃ -T ₁)	0.99 ± 4.03	2.45 ± 4.08		-7.41 ± 4.52	-5.53 ± 7.90	
Change (T ₄ -T ₁)	3.81 ± 3.87	2.22 ± 3.91		-14.98 ± 6.67	0.47 ± 5.06	

Abbreviations: IPQ, Illness Perception Questionnaire; SE, standard error.

* $P < .05$.

** $P < .01$.

Subgroup analyses showed increasing perceived ambiguity about MCI among amyloid negative patients ($P < .05$) and revealed that decreased self-efficacy for coping was most pronounced among caregivers of amyloid positive individuals at 4 weeks post disclosure (mean difference = -14.83 ± 7.22 ; $P < .05$), and those of amyloid negative patients at 24 weeks post disclosure (mean difference = -12.22 ± 5.83 ; $P < .05$).

At all follow-up assessments, IES ratings were higher among amyloid positive patients versus amyloid negative patients. These scores declined over time ($F_T = 5.42, P = .008$), but between group differences persisted (Figure 3). Similar patterns were observed on IGT-AD distress ratings, with the greatest difference at week 4 at which amyloid positive patients had mean IGT-AD scores averaging three times higher than amyloid negative patients. IGT-AD positive scores were elevated and stable among amyloid positive patients but increased at each follow-up point among amyloid negative patients, whose scores grew closer to those of the amyloid positive patients over time (see supporting information).

Analyses of caregiver post-disclosure distress revealed group differences on the IGT-AD distress and positive subscales, with caregivers

of amyloid positive individuals reacting more negatively to test results (Figure 3).

4 | DISCUSSION

We hypothesized that, irrespective of scan results, having the opportunity to learn more about the potential etiology of cognitive symptoms would improve patients' and caregivers' overall understanding of, and self-efficacy for coping with, MCI. However, learning one's brain amyloid status was no more effective than an MCI education session for increasing caregivers' knowledge about MCI, and patients' knowledge scores were unchanged regardless of group assignment. Subgroup analysis showed that perceived ambiguity regarding MCI increased in amyloid negative patients, suggesting that such individuals likely understood that their symptoms remained unexplained.

Contrary to our hypothesized increase, we observed decreased self-efficacy for coping with MCI among caregivers of scan group participants, a finding which was present, at varying time points, among

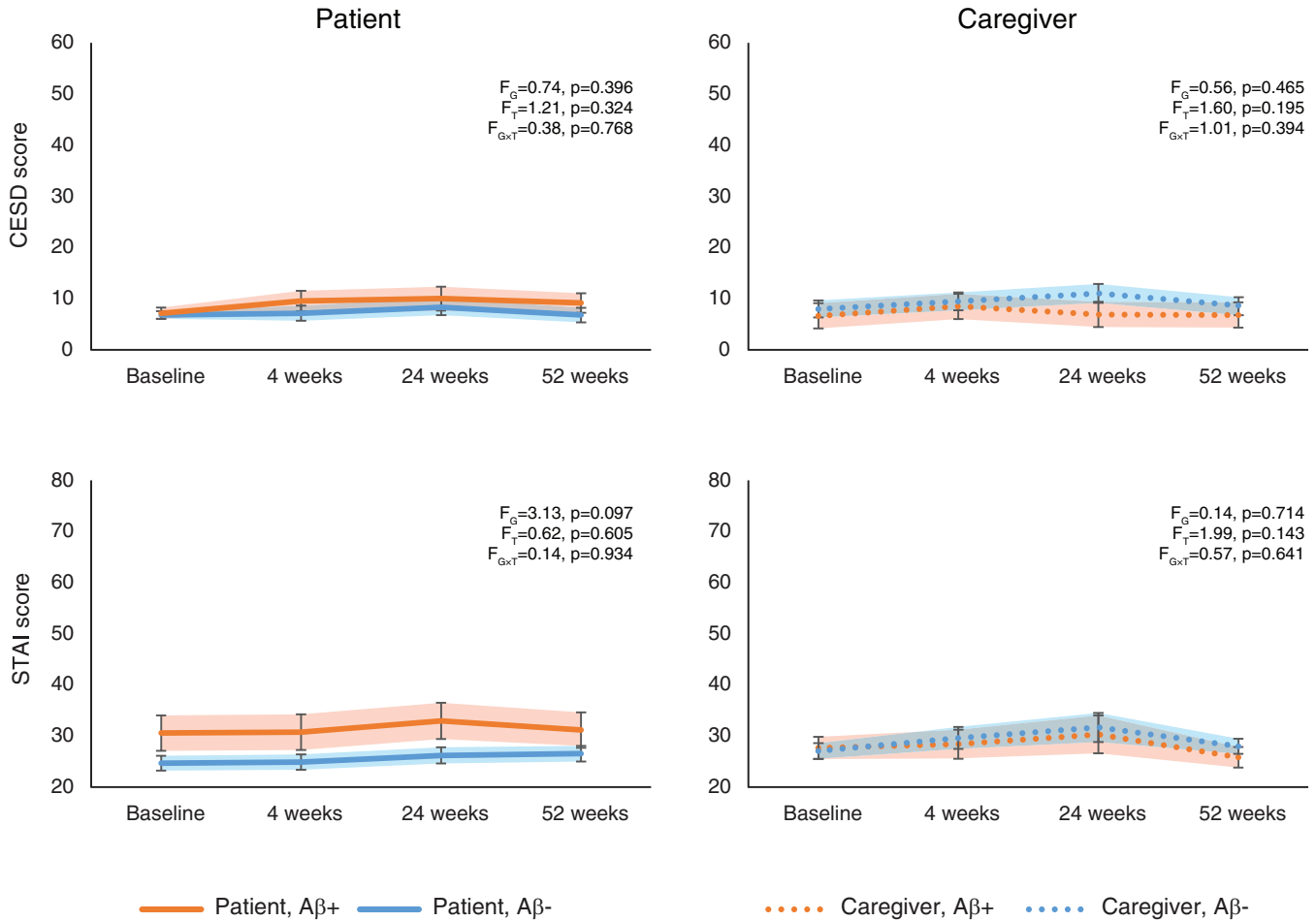


FIGURE 2 Psychological safety. Measures of mood over time. CESD, Center for Epidemiological Studies Depression Scale; STAI, Spielberger State Anxiety Inventory; A β , amyloid beta

caregivers of participants with both positive and negative results. This unstable decrease in self-efficacy could potentially reflect feelings of unpreparedness regarding the prospect of one's relative progressing to AD (amyloid-positive group) as well as increased uncertainty about the cause of the symptoms (amyloid-negative group).

Although emerging literature suggests that disclosing brain amyloid status to cognitively normal adults and those with subjective cognitive impairment has no discernable effect on psychological well-being, evidence in overtly symptomatic populations and family caregivers is limited.¹⁷ Consistent with prior investigations of unimpaired persons,¹⁸ we found no significant differences in mood between amyloid positive and negative individuals. However, we observed significant and sustained levels of event-related distress among MCI care dyads who learned of amyloid positivity, with ratings notably higher than those reported in asymptomatic samples.

Overall, our findings raise the possibility that emotional support interventions may be indicated upon biomarker testing in MCI, although needs may vary depending on one's perspective (patient or caregiver) and scan result.

Given the self-selection bias associated with ADRC participation, there is a critical need for additional studies with more diverse samples who may be less receptive, or may respond differently, to AD biomarker testing. Importantly, RAISR excluded individuals with active untreated mood disorders, which are prevalent among cognitively impaired individuals. Therefore, our exploratory findings regarding psychological safety may not extend to all MCI patients meeting Appropriate Use Criteria for amyloid PET.^{19,20}

ACKNOWLEDGMENTS

The authors gratefully acknowledge the participants who volunteered for this research. We also thank Drs. Meghan Mattos and Jonna Morris and Ms. Sarah Goldberg for their efforts as pre-test counselors. This study was supported by NIH/NIA R01AG046906-01, NIH/NIA, P50 AG05133, and NIH/NIA P30 AG053760. Flortetapir F 18 Injection doses in this study are supplied at no cost by Avid Radiopharmaceuticals a wholly owned subsidiary of Eli Lilly, Inc. The week-4 follow-up data reported in this manuscript were first presented at the 2019 Alzheimer's Association International Conference.

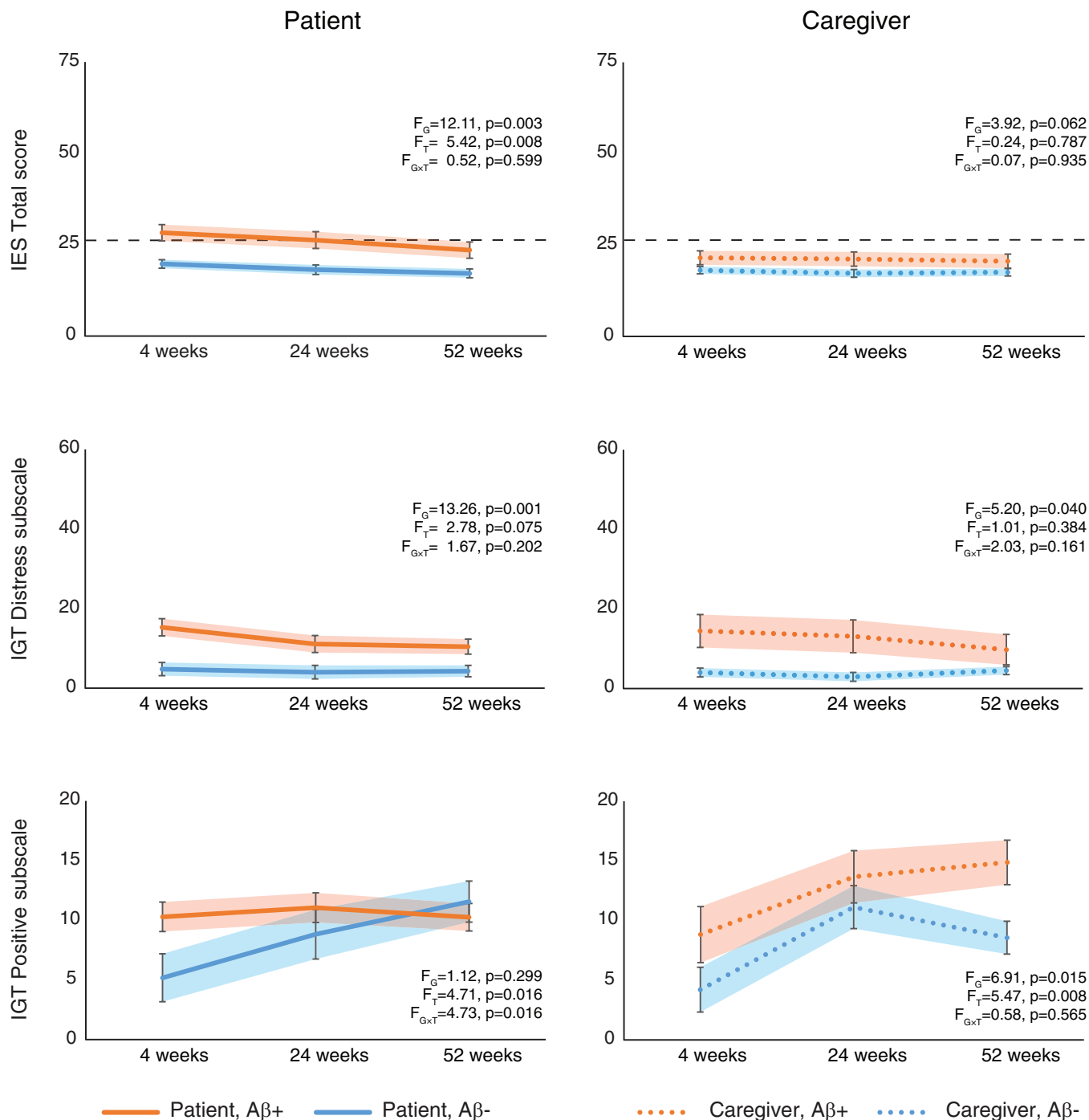


FIGURE 3 Post-disclosure impact of event scores over time. IES, Impact of Events Scale; IGT, Impact of Genetic Testing Scale; Aβ, amyloid beta. An IES total score cut-off point of 26 is noted by a dashed line above which a moderate or severe impact may be indicated

CONFLICTS OF INTEREST

Florbetapir F 18 Injection doses in this study are supplied at no cost by Avid Radiopharmaceuticals a wholly owned subsidiary of Eli Lilly, Inc. Dr. Lopez provides consultation to Grifols, Inc.

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SUPPORTING INFORMATION

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

How to cite this article: Lingler JH, Sereika SM, Butters MA, et al. A randomized controlled trial of amyloid positron emission tomography results disclosure in mild cognitive impairment. *Alzheimer's Dement*. 2020;16:1330-1337. <https://doi.org/10.1002/alz.12129>