Title
Post-disclosure distress among racial and ethnic groups in a preclinical AD trial

Journal
Alzheimer's & Dementia, 20(4)

ISSN
1552-5260

Authors
Ritchie, Marina
Salazar, Christian R
Gillen, Daniel L
et al.

Publication Date
2024-04-01

DOI
10.1002/alz.13726

Peer reviewed

Received: 1 September 2023 | Revised: 13 December 2023 | Accepted: 6 January 2024

DOI: 10.1002/alz.13726

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Post-disclosure distress among racial and ethnic groups in a preclinical AD trial

Marina Ritchie[1,2] | **Christian R. Salazar**[1] | **Daniel L. Gillen**[1,3] | **Joshua D. Grill**[1,2,4]

[1]UC Irvine Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, California, USA

[2]Department of Neurobiology and Behavior, University of California, Irvine, Irvine, California, USA

[3]Department of Statistics, University of California, Irvine, Irvine, California, USA

[4]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, California, USA

Correspondence
Marina Ritchie, UC Irvine Institute for Memory Impairments and Neurological Disorders (UCI MIND), 3230 Biological Sciences III, University of California, Irvine, CA, USA.
Email: mritchie@uci.edu

Funding information
, Grant/Award Number: P30AG066519

Abstract

INTRODUCTION: Trialists need a thorough understanding of whether reactions to Alzheimer's disease (AD) biomarker information differ among racial and ethnic groups in preclinical AD trials.

METHODS: We used data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Study to analyze cognitively unimpaired participants' responses on the Impact of Event Scale (IES) 24 to 72 hours after amyloid disclosure. We fit a linear regression model to test whether mean IES scores differed among participants from specific racial and ethnic groups. We considered potential effect modification by amyloid status.

RESULTS: Reactions to disclosure did not significantly differ among participant groups based on self-reported race and ethnicity. Although the results were not significant when stratified by amyloid status, all racial and ethnic groups except for participants self-reporting Hispanic/Latino ethnicity were observed to have higher mean IES in the elevated amyloid group.

DISCUSSION: These results support continued use of current disclosure methods in preclinical AD trials.

KEYWORDS
biomarker disclosure, clinical trials, preclinical Alzheimer's disease, race and ethnicity

1 | BACKGROUND

In an effort to develop disease-slowing treatments and curb the public health impact of Alzheimer's disease (AD), clinical trials are now testing the safety and efficacy of candidate interventions at preclinical stages of disease.[1] Preclinical AD trials enroll cognitively unimpaired participants who undergo biomarker testing and individual result disclosure, randomizing only those meeting biomarker criteria to treatment or placebo.[2] This aspect of preclinical AD trials is anticipated to guide a clinical practice that includes timely diagnosis and early access to treatments. Ultimately, it will pave the way for widespread biomarker screening, preclinical diagnosis, and the initiation of preventative therapies.[3,4]

The risk and burden of AD are disproportionately greater in Hispanic/Latino and Black communities, compared to the non-Hispanic (NH) White community.[5] Yet, minoritized communities have historically been underrepresented in AD trials.[6,7] To increase the generalizability of trial findings and prevent the perpetuation of health-care disparities, there is an urgent need to increase participant diversity in preclinical AD trials.

Though data are limited, available studies do not find differential interest or willingness to pursue biomarker testing among racial and

ethnic groups.[8–12] Views, understanding, and stigma associated with AD, however, may differ among racial, ethnic, and cultural groups.[13] Race and ethnicity are complex social constructs that associate with cultural differences important to enrollment decisions, attitudes toward disease, and the impact of diagnostic and risk information. To minimize potential barriers to preclinical AD trial enrollment and ensure the cultural sensitivity of trial practices, including approaches to biomarker disclosure, further studies are needed to examine potential differences among racial and ethnic groups. We used data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Study (A4 Study), one of the first and largest preclinical AD trials to date,[2,14] to examine whether short-term disclosure outcomes differed among self-reported racial and ethnic groups after AD biomarker disclosure.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed existing literature using traditional sources (e.g., PubMed) on preclinical Alzheimer's disease (AD) trials and the requirement for participants to undergo biomarker testing and disclosure. Few papers assess reactions to AD biomarker information among participant groups based on self-reported race and ethnicity.
2. **Interpretation**: Overall, the association between racial and ethnic groups and the Impact of Event Scale did not differ by amyloid status, which suggests that current disclosure methods are relatively similar in their effectiveness among these subgroups of participants. We observed that all racial and ethnic groups except for participants self-reporting Hispanic/Latino ethnicity experienced greater distress in the elevated compared to the not elevated amyloid group.
3. **Future directions**: Further studies are needed to examine potential differences in reactions to disclosure among subpopulations within racial and ethnic groups and consider other potential confounding factors such as social determinants of health.

2 | METHODS

2.1 | Data source

We downloaded publicly available screening data of the A4 Study (ClinicalTrials.gov identifier: NCT02008357) from the Laboratory of Neuro Imaging (LONI). The A4 Study was a trial of the anti–amyloid beta monoclonal antibody solanezumab versus placebo.[14] Participants were required to be cognitively unimpaired older adults (based on the Mini-Mental State Examination, Global Clinical Dementia Rating Scale, and Logical Memory II score) ages 65 to 85. Individuals with a diagnosis of dementia or another neurological or psychiatric disorder were ineligible. All participants were required to enroll with a study partner.

Participants were asked to self-report their race and ethnicity. Ethnic categories included Hispanic/Latino, not Hispanic/Latino, and unknown/not reported. Racial categories included American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and unknown or not reported. To test the hypothesis that these groups differed in their short-term reactions to AD biomarker results, we assigned participants to five mutually exclusive groups based on self-reported race and ethnicity: Hispanic/Latino of any race (Hispanic/Latino), non-Hispanic/Latino Asian (NH Asian), non-Hispanic/Latino Black or African American (NH Black), non-Hispanic/Latino White/Caucasian (NH White), and non-Hispanic/Latino "other racial group" (Other NH). The A4 Study was completed in English, Spanish, or Japanese. Participants who completed the study in Japanese were enrolled exclusively in Japan. Given the potential cultural differences for participants in Japan compared to NH Asian participants in North America, we reported the Japanese-speaking and English-speaking NH Asian participants as separate groups.

2.2 | Biomarker disclosure

The A4 Study implemented a protocol-defined disclosure process to ensure participant safety and comprehension.[15] Investigators educated and counseled participants at consent and used the teach-back method to assess and ensure understanding. Participants underwent assessments of anxiety (the State-Trait Anxiety Inventory [STAI]), depression (Geriatric Depression Scale [GDS]), and suicidality (Columbia Suicide Severity Rating Scale [CSSRS]), though the protocol did not explicitly exclude participants based on these assessments. Education and consent, as well as disclosure, were performed on a day separate from amyloid positron emission tomography (PET) imaging. Prior to disclosure, participants reaffirmed their willingness to learn their biomarker status and their understanding of the implications of results. Participants were disclosed their biomarker status in person by a trained and certified study clinician. Results were disclosed as "elevated" or "not elevated" brain amyloid.

2.3 | Primary outcome

One to three days after disclosure, telephone follow-up was used to assess participants' general well-being and to quantify short-term intrusive thoughts and distress using the Impact of Event Scale (IES). The IES is a 15-item questionnaire with two constructs: intrusive thoughts (7 items) and avoidance (8 items)[16] and was the primary outcome for this study. Possible responses included "not at all" = 0, "rarely" = 1, "sometimes" = 3, and "often" = 5. We treated the scores as continuous (range, 0–75 points), with higher scores indicating greater distress.

2.4 | Statistical analyses

We summarized group distributions for sociodemographic and clinical characteristics using frequency tables for discrete covariates, and mean and standard deviation (SD) for continuous covariates. Baseline clinical assessments included the six state items of STAI, the 15-item GDS, and the 14-item Cognitive Function Instrument (CFI), a measure of subjective cognitive complaints. We limited our primary analyses to participants who completed the trial in English and Spanish. One NH White participant was missing more than 40% of IES items and was removed from the analyses. We otherwise imputed missing values for the IES by taking the mean of the participant's available items ($N = 17$). Most of the participants missing IES items self-reported as being NH White ($N = 15$). The remainder of the participants self-reported as being Hispanic/Latino ($N = 1$), NH Black ($N = 1$), and Other NH ($N = 1$). Among the 17 participants with imputed data, 8 participants were missing the *Numb* item and 4 participants were missing the *Avoid* item. No other clear patterns emerged.

Considering the limited availability of data on potential cultural differences by race and ethnicity, we fit a linear regression model to test the two-tailed hypothesis that mean IES scores differed by self-reported racial and ethnic group in our primary analysis. We sought to understand differences in IES scores by race and ethnicity conditional upon amyloid status. As such, we stratified our primary analyses by amyloid status (elevated/not elevated). Our main interest was to understand whether participants from underrepresented racial and ethnic groups differed from NH White participants in their reactions to biomarker information. Given this, and the relative sample sizes of the assigned groups, we used NH White participants as the referent group. Multivariable models adjusted for potential confounding factors including age, sex, years of education, study partner type (spouse, adult child, or other), self-reported family history of dementia or AD, CFI score, and amyloid status. We formally tested for effect modification by amyloid status by including an interaction term between race and ethnicity and amyloid group using a level 0.05 likelihood ratio test.

In a secondary analysis, we re-ran the primary analysis with the addition of 99 participants who completed the trial in Japanese as a separate racial and ethnic group. We also ran a post hoc sensitivity analysis removing all Hispanic/Latino participants who completed the trial in Spanish ($N = 11$) to examine whether language preference impacted the results. In an exploratory analysis, we added baseline GDS and STAI total scores as covariates to the primary model. We then considered subtotal response scores pertaining to intrusion (seven items) and avoidance (eight items) and potential differences by racial and ethnic group with respect to these constructs. We analyzed the mean differences in response between those with elevated and not elevated amyloid status by race and ethnicity for each individual question within the two constructs. We then compared the mean response between the elevated and not elevated groups for each individual question by racial and ethnic group.

3 | RESULTS

3.1 | Participants

IES data were available for 4211 participants who completed the trial in English or Spanish and underwent PET imaging and disclosure (Table 1). Age, baseline STAI, GDS, and CFI mean scores were similar across racial and ethnic groups. Compared to other racial and ethnic groups, we observed a lower proportion of male participants among individuals who self-reported as being NH Black. Years of education were observed to vary by race and ethnicity. The proportion of participants with < 12 years of education were highest in NH Black (2.8% higher than NH White participants) and Hispanic/Latino participant groups (5.4% higher than NH White participants). We note, however, that the NH Black and Hispanic/Latino participants had higher mean education levels compared to the Black and Hispanic population in the United States.[17] The proportion of participants who enrolled in the trial with a spousal study partner also were observed to vary by race and ethnicity. The highest proportion of spouse study partners were observed in Other NH (66.7%) and NH White participants (62.6%) while the lowest was observed in NH Black participants (40.8%). We also observed that the Hispanic/Latino and NH White participants had the highest proportions of family history of dementia (43.7%), while the NH Asian participants who completed the trial in English had the lowest proportion (27.3%).

3.2 | Overall IES comparisons

Table 2 describes mean total IES scores for the racial and ethnic groups, stratified by amyloid status, and Figure 1 illustrates the distribution of total IES scores. The mean score for each racial and ethnic group was below the range of clinical significance (moderate distress score ≥ 26). Hispanic/Latino participants demonstrated the lowest mean IES among those with elevated amyloid, but the highest mean IES among those with not elevated amyloid. NH Asian participants who completed the trial in English demonstrated the highest mean IES scores among those with elevated amyloid. When including participants who completed the trial in Japanese, we found that these participants had the highest mean IES among those with elevated amyloid (mean: 12.10; SD: 7.87). Although the sample size was limited and the results showed wide variance, our assessment of the mean IES scores for participants who completed the trial in Spanish revealed that this group exhibited the highest mean IES among the not elevated amyloid group (Supplemental Material 1 in supporting information). In a regression model, the interaction between racial and ethnic group and amyloid status was not significant ($P = 0.2027$; Table 3). Hispanic/Latino participants in the not elevated amyloid group had a significantly higher mean IES compared to NH White participants (est: 2.23; 95% confidence interval [CI]: 0.41, 4.05; $P = 0.016$). We observed no other statistically significant differences between racial and ethnic groups in either the elevated or the not elevated amyloid groups. Younger age, female sex, higher CFI, and

TABLE 1 Descriptive summary of the participants who completed the trial in English and Spanish ($N = 4211$).

		NH White	NH Black	NH Asian	Hispanic / Latino (any race)	Other NH
	n (%)	3794 (90.1)	147 (3.5)	66 (1.6)	135 (3.2)	69 (1.6)
Age (years)	Mean (SD)	71.3 (4.7)	70.9 (5.0)	70.9 (3.8)	71.7 (4.6)	71.5 (4.1)
Sex	Female, *n* (%)	2259 (59.5)	103 (70.1)	36 (54.5)	81 (60.0)	44 (63.8)
	Male, *n* (%)	1535 (40.5)	44 (29.9)	30 (45.5)	54 (40.0)	25 (36.2)
Education (years)	<12, *n* (%)	358 (9.4)	18 (12.2)	2 (3.0)	20 (14.8)	8 (11.6)
	13–16, *n* (%)	1568 (41.3)	64 (43.5)	24 (36.4)	75 (55.6)	30 (43.5)
	17–19, *n* (%)	1291 (34.0)	51 (34.7)	23 (34.8)	27 (20.0)	19 (27.5)
	≥20, *n* (%)	572 (15.1)	14 (9.5)	17 (25.8)	13 (9.6)	12 (17.4)
	NA, *n* (%)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amyloid status	Elevated, *n* (%)	1176 (31.0)	31 (21.1)	9 (13.6)	38 (28.1)	26 (37.7)
	Not elevated, *n* (%)	2618 (69.0)	116 (78.9)	57 (86.4)	97 (71.9)	43 (62.3)
Family history of dementia	No, *n* (%)	2135 (56.3)	89 (60.5)	48 (72.7)	76 (56.3)	41 (59.4)
	Yes, *n* (%)	1659 (43.7)	58 (39.5)	18 (27.3)	59 (43.7)	28 (40.6)
STAI score	Mean (SD)	9.9 (3.1)	9.5 (3.5)	10.3 (3.4)	9.7 (3.4)	10.1 (3.6)
GDS score	Mean (SD)	1.0 (1.4)	1.0 (1.6)	1.2 (1.7)	1.3 (1.8)	1.4 (1.9)
CFI score	Mean (SD)	1.9 (2.0)	2.1 (2.1)	3.0 (2.6)	2.5 (2.4)	2.1 (2.5)
Partner type	Spouse, *n* (%)	2374 (62.6)	60 (40.8)	41 (62.1)	74 (54.8)	46 (66.7)
	Adult child, n (%)	443 (11.7)	24 (16.3)	11 (16.7)	26 (19.3)	6 (8.7)
	Other, *n* (%)	977 (25.8)	63 (42.9)	14 (21.2)	35 (25.9)	17 (24.6)

Abbreviations: CFI, Cognitive Function Instrument; GDS, Geriatric Depression Scale; NH, non-Hispanic; SD, standard deviation; STAI, State-Trait Anxiety Inventory.

TABLE 2 Mean (SD) IES by race and ethnicity stratified by amyloid status for the participants who completed the trial in English and Spanish.

	NH White	NH Black	NH Asian	Hispanic/Latino	Other NH
Elevated amyloid	10.16 (10.68)	9.77 (12.79)	10.33 (6.54)	8.37 (8.66)	10.15 (13.60)
Not elevated amyloid	6.39 (8.07)	6.32 (9.07)	6.79 (8.68)	8.76 (11.87)	4.93 (6.85)

Abbreviations: IES, Impact of Event Scale; NH, non-Hispanic; SD, standard deviation.

family history of dementia were associated with higher IES (Table 3). When participants who completed the trial in Japanese were included as a separate racial and ethnic group in secondary analysis, we did not observe any significant differences in our findings (Supplemental Material 2 in supporting information).

In sensitivity analyses that removed 11 Hispanic/Latino participants who completed the trial in Spanish, we observed that the adjusted mean IES comparing Hispanic/Latino participants to NH White participants attenuated and was no longer significantly different in the not elevated amyloid group (est: 1.43; 95% CI: −0.44, 3.29; $P = 0.134$; full regression output not shown). In an exploratory regression model with the addition of GDS and STAI as potential confounding variables, GDS was not associated with IES (est: 0.10; CI: −0.11, 0.31; $P = 0.343$), but STAI demonstrated a significant association with IES (est: 0.46; CI: 0.37, 0.55; $P = < 0.001$; Supplemental Material 3 in supporting information).

3.3 | IES constructs

Figure 2 illustrates mean differences between the elevated and not elevated amyloid groups stratified by race and ethnicity for individual questions within the two IES constructs (intrusion and avoidance). For both constructs, Hispanic/Latino participants had the smallest difference between the elevated and not elevated amyloid groups. For the intrusion construct, Hispanic/Latino participants were the only group that showed higher mean scores in the not elevated group than the elevated group. In fact, for six out of seven items, the not

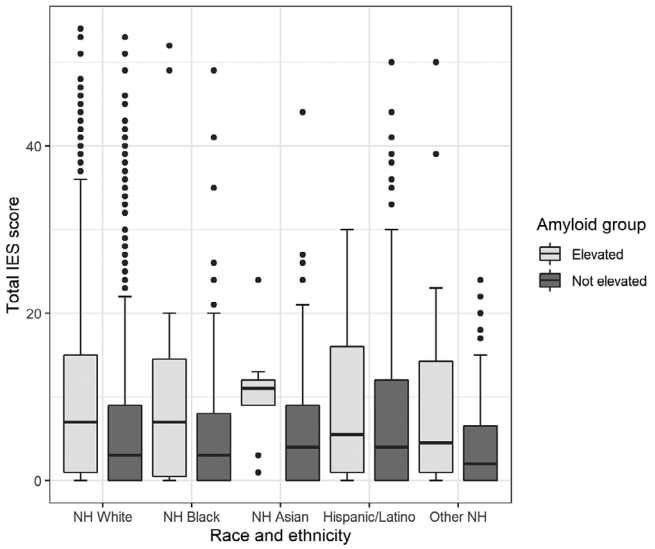

FIGURE 1 Box plot illustrating racial and ethnic group differences in total IES score stratified by amyloid status. The light shade represents the elevated amyloid status group and the darker shade represents the not elevated amyloid status group. IES, Impact of Event Scale; NH, non-Hispanic.

elevated group had a higher mean score than the elevated group among Hispanic/Latino participants.

4 | DISCUSSION

In this study, the occurrence of short-term distress after amyloid disclosure did not appear to differ among groups based on self-reported race and ethnicity in the A4 Study. Specifically, we did not observe a statistically significant interaction effect indicating that the relationship between race and ethnicity varied by amyloid status after controlling for other covariates. Across the racial and ethnic groups, scores were similar and rarely in the range of clinical significance (≥ 26, Figure 1), supporting that the biomarker disclosure process used in the A4 Study was consistently safe among these subgroups of participants.[18]

Although our primary analyses did not suggest significant differences among the racial and ethnic groups, we did observe some potentially important differences among the populations included in this study. NH Asian participants demonstrated the highest mean IES among those with elevated amyloid, although the difference compared to the NH White participants was small and was not significant in our model controlling for covariates. Hispanic/Latino participants demonstrated the lowest mean IES among those with elevated amyloid, but the highest among those with not elevated amyloid and this appeared consistent for the two constructs that make up the IES (Figures 1 and 2). The results of our regression models also suggested that Hispanic/Latino participants, particularly individuals who completed the trial in Spanish, had a higher mean IES score in the not elevated amyloid group compared to NH White participants who completed the trial in English. We are unable to draw definitive conclusions about these differences due to limited sample sizes. Further research is necessary to gain a comprehensive understanding of how acculturation stressors such as discrimination, language barriers, limited access to health care, undocumented status, and economic and occupational hardships may influence responses to amyloid disclosure among Hispanic/Latino and other immigrant populations.[19]

A variety of factors could contribute to differences in disclosure experiences among diverse preclinical AD trial participants. Consistent with earlier studies using the A4 Study data,[18] participant characteristics including female sex, younger age, and higher CFI were significantly

TABLE 3 Adjusted linear regression model of mean total IES score among participants who completed the trial in English and Spanish.

Covariate	Est. diff. in mean IES (95% CI)	*P* value
Not elevated amyloid		
Race and ethnicity*		0.503[a]
—Non-Hispanic White	Referent	
—Hispanic/Latino	2.23 (0.41, 4.05)	0.016
—Non-Hispanic Asian	0.44 (−1.94, 2.82)	0.716
—Non-Hispanic Black	−0.39 (−2.06, 1.28)	0.649
—Other NH	−1.61 (−4.31, 1.08)	0.241
Elevated amyloid		
Race and ethnicity*		
—Non-Hispanic White	Referent	
—Hispanic/Latino	−1.76 (−4.66, 1.14)	0.234
—Non-Hispanic Asian	−0.60 (−6.47, 6.00)	0.972
—Non-Hispanic Black	−0.63 (−3.88, 5.28)	0.842
—Other NH	−0.02 (−3.46, 3.49)	0.993
Age (years)	−0.11 (−0.17, −0.05)	<0.001
Sex (female vs. male)	2.18 (1.59, 2.77)	<0.001
Education (years)		
—<12	Referent	
—13–16	−0.83 (−1.80, 0.15)	0.095
—17–19	−0.26 (−1.35, 0.74)	0.612
—≥20	−0.53 (−1.66, 0.61)	0.361
—Missing	−1.97 (−9.87, 5.92)	0.625
Study partner type		
—Spouse	Referent	
—Adult child	−0.44 (−1.32, 0.43)	0.321
—Other	−0.24 (−0.89, 0.42)	0.475
Family history (yes vs. no)	1.20 (0.63, 1.76)	<0.001
CFI score	0.36 (0.22, 0.50)	<0.001

Note: Amyloid-specific estimates of the association between race and ethnicity and IES based on the interaction between the two are presented.
Abbreviations: CFI, Cognitive Function Instrument; CI, confidence interval; IES, Impact of Event Scale; NH, non-Hispanic.
*P value = 0.2027 for likelihood ratio test of interaction between race and ethnicity and amyloid status.
[a]Likelihood ratio test of the construct of race and ethnicity simultaneously testing for differences between any pair of race and ethnicity groups.

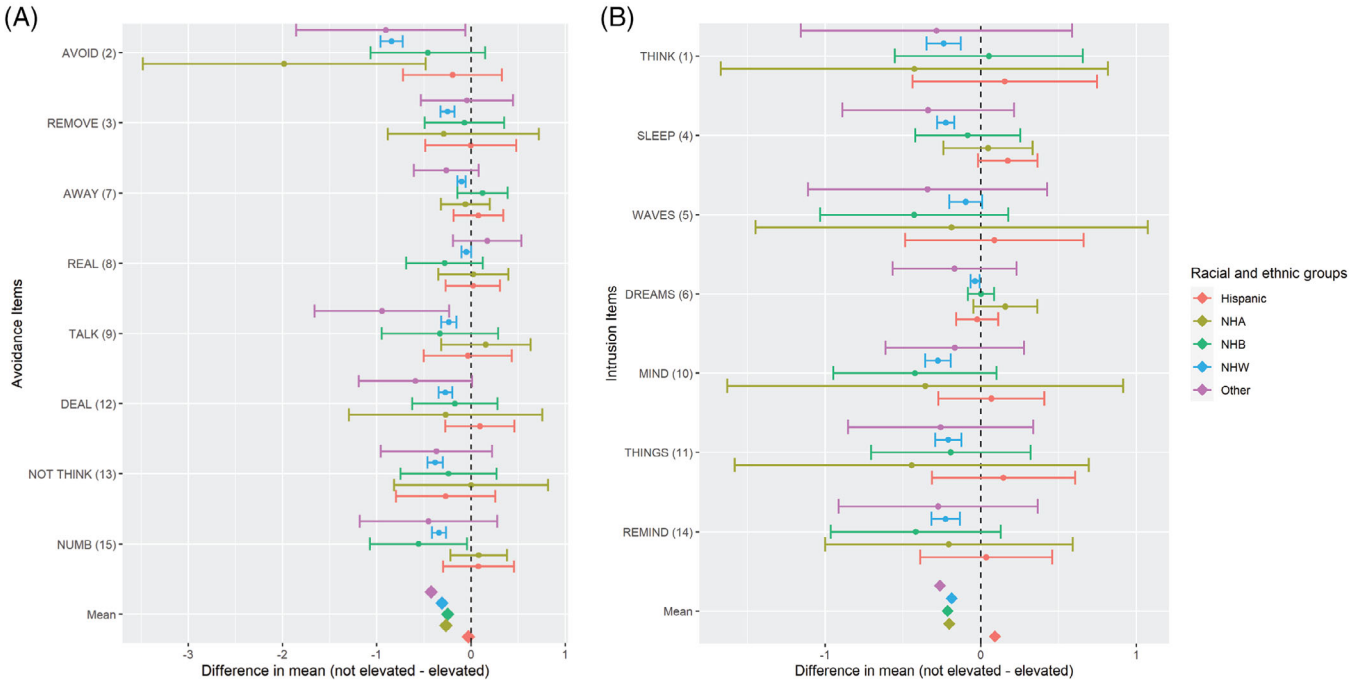

FIGURE 2 Differences in mean between the elevated and not elevated groups for IES questions: (A) pertains to avoidance and (B) to intrusive thoughts. Each dot and line represent the point estimate and 95% confidence interval of the differences in mean IES between the not elevated and elevated amyloid groups for participants from specific racial and ethnic groups. Positive numbers indicate higher IES in the not elevated group and the negative numbers indicate higher IES in the elevated group. The diamonds on the bottom of the figure indicate the mean score of the total IES items for each construct. The colors indicate the different racial and ethnic groups: Hispanic/Latino (Hispanic) in red, NHA in olive green, NHB in lime green, NHW in blue and Other NH (Other) in pink. The full question for each of the abbreviations can be found in Supplemental Material 4 in supporting information. IES, Impact of Event Scale; NH, non-Hispanic; NHA, non-Hispanic Asian; NHB, non-Hispanic Black; NHW, non-Hispanic White.

associated with higher IES in our analysis. In addition to these previously reported covariates, we found that having a family history of dementia was associated with higher IES, an observation that is likely due to the inclusion of a larger sample of participants, compared to previous analyses.[18] These findings suggest that certain personal traits are associated with higher distress levels after amyloid disclosure.

Although we did not observe any significant differences in distress after disclosure among participants based on self-reported racial and ethnic group, other sociocultural constructs may still impact reactions to disclosure. For example, we found that NH Asian participants, particularly those who completed the trial in Japanese, had the highest mean IES across all racial and ethnic groups. These differences in IES scores may be due to cultural differences in views toward and knowledge of AD. Members of some Asian communities may associate dementia with negative mental health stigma, potentially including feelings of embarrassment, shame, and guilt that lead to social avoidance.[20,21]

Previous studies have observed differences among racial and ethnic groups in reactions to receiving bad news. In a study examining the impact of receiving a cancer diagnosis, Black and Hispanic individuals experienced greater distress than did NH White individuals.[22] Hispanic participants reported greater distress compared to other racial and ethnic groups among stroke survivors.[23] Though we did not observe similar differences here, this could be due to differential views specifically toward AD in these groups, such as attributing "God's will" as a risk factor.[24] Our findings may also differ from those in previous studies due to the focus on short-term distress or selection bias, including a willingness to participate in the A4 Study, likely favorable attitudes toward research, and higher education than the general population.[17]

Earlier studies have reported that baseline levels of anxiety and depression may be predictors of distress after amyloid disclosure.[25] While GDS was not associated with IES, STAI was significantly associated with IES in our exploratory analysis. STAI scores did not differ among the groups at baseline, however, and participants were not categorically excluded from the A4 Study for specific scores on GDS or STAI. Nevertheless, these results further emphasize the need to consider these psychological constructs when performing biomarker disclosure. This consideration will be important in future trials and in an eventual clinical practice. Future trials should also consider implementing longitudinal assessments of these constructs. Additional monitoring for those with higher baseline anxiety or depression scores may be important to ensure participant safety.

This study had limitations. Though the parent study enrolled higher numbers of participants from underrepresented racial and ethnic groups than most AD trials, the number and overall proportion of the sample from these groups were still small, particularly as we created further subgroups for these analyses. In the A4 Study, participants from underrepresented racial and ethnic groups were more likely to be ineligible compared to NH White participants.[26] This resulted in

proportionately fewer non-White and Hispanic/Latino participants who were eligible to undergo amyloid biomarker testing, as well as fewer who had elevated amyloid. These results could therefore reflect a selection bias, compared to the full population that screened for A4, let alone the general population. Second, the IES is just one self-reported measure of reaction and may not provide a holistic measure of distress. Given that we observed some differences by self-reported race and ethnicity, more in-depth investigation of the impact of disclosure in a broader variety of participants, including more in-depth qualitative approaches,[27] could yield important findings not demonstrable in the current data. The A4 Study did not evaluate distress using the IES at later time points of the trial. Last, participants were categorized into five mutually exclusive groups for our primary analyses based on self-reported information; however, the available data did not allow for an evaluation of heterogeneity within these groups, including but not limited to countries of origin, cultural background, and immigration status. Our analyses were also limited in potential confounding variables. Individual-level factors, such as comprehension of the disclosed information, primary language, socioeconomic status, and other social determinants of health may be important moderating factors that influence intrusive thoughts and avoidance. Assessments of these constructs were not available in the current dataset.

5 | CONCLUSION

To our knowledge, the A4 Study data represent the largest and most diverse sample of cognitively unimpaired participants to have their AD biomarker results disclosed to them. We found that intrusive thoughts and distress were not significantly higher for participants in underrepresented racial and ethnic groups compared to NH White participants receiving an elevated amyloid result, though some observations may warrant further study.

ACKNOWLEDGMENTS

The A4 Study is a secondary prevention trial in preclinical Alzheimer's disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 Study is funded by a public–private–-philanthropic partnership, including funding from the National Institutes of Health–National Institute on Aging, Eli Lilly and Company, Alzheimer's Association, Accelerating Medicines Partnership, GHR Foundation, an anonymous foundation and additional private donors, with in-kind support from Avid and Cogstate. The companion observational Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) Study is funded by the Alzheimer's Association and GHR Foundation. The A4 and LEARN Studies are led by Reisa Sperling at Brigham and Women's Hospital, Harvard Medical School and Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California. The A4 and LEARN Studies are coordinated by ATRI at the University of Southern California, and the data are made available through the Laboratory for Neuro Imaging at the University of Southern California. The participants screening for the A4 Study provided permission to share their de-identified data to advance the quest to find a successful treatment for Alzheimer's disease. We would like to acknowledge the dedication of all the participants, the site personnel, and all of the partnership team members who continue to make the A4 and LEARN Studies possible. The complete A4 Study Team list is available at: a4study.org/a4-study-team. This study was supported by P30AG066519.

CONFLICT OF INTEREST STATEMENT

Marina Ritchie, Christian R. Salazar, and Daniel L. Gillen report no disclosures relevant to the manuscript. Joshua D. Grill has received research funding from the National Institute on Aging, Alzheimer's Association, BrightFocus Foundation, Eli Lilly, Genentech, Biogen, and Eisai. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Participants in the A4 trial provided written informed consent before enrollment. All participating sites obtained institutional review board approval. The current study did not use any identifiable information and does not meet the criteria for human subjects research.

ORCID

Marina Ritchie https://orcid.org/0000-0002-5844-1293

REFERENCES

1. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12:292-323. doi:10.1016/j.jalz.2016.02.002
2. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6:228fs13. doi:10.1126/scitranslmed.3007941
3. Sperling RA, Karlawish J, Johnson KA. Preclinical Alzheimer disease-the challenges ahead. *Nat Rev Neurol*. 2013;9:54-58. doi:10.1038/nrneurol.2012.241
4. Karlawish J. Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. *Neurology*. 2011;77:1487-1493. doi:10.1212/WNL.0b013e318232ac1a
5. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19:1598-1695. doi:10.1002/alz.13016
6. Franzen S, Smith JE, den Berg E, et al. Diversity in Alzheimer's disease drug trials: the importance of eligibility criteria. *Alzheimers Dement*. 2022;18:810-823. doi:10.1002/alz.12433
7. Faison WE, Schultz SK, Aerssens J, et al. Potential ethnic modifiers in the assessment and treatment of Alzheimer's disease: challenges for the future. *Int Psychogeriatr*. 2007;19:539-558. doi:10.1017/S104161020700511X
8. Zhou Y, Elashoff D, Kremen S, Teng E, Karlawish J, Grill JD. African Americans are less likely to enroll in preclinical Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2016;3:57-64. doi:10.1016/j.trci.2016.09.004
9. Wikler EM, Blendon RJ, Benson JM. Would you want to know? Public attitudes on early diagnostic testing for Alzheimer's disease. *Alzheimers Res Ther*. 2013;5:43. doi:10.1186/alzrt206
10. Eliacin J, Hathaway E, Wang S, O'Connor C, Saykin AJ, Cameron KA. Factors influencing the participation of Black and White Americans in Alzheimer's disease biomarker research. *Alzheimers Dement (Amst)*. 2022;14:e12384. doi:10.1002/dad2.12384
11. Ketchum FB, Erickson CM, Chin NA, et al. What Influences the willingness of Blacks and African Americans to enroll in preclinical Alzheimer's disease biomarker research? A qualitative vignette analysis. *J Alzheimers Dis*. 2022;87:1167-1179. doi:10.3233/JAD-215521

12. Erickson CM, Chin NA, Ketchum FB, et al. Predictors of willingness to enroll in hypothetical Alzheimer disease biomarker studies that disclose personal results. *Alzheimer Dis Assoc Disord*. 2022;36:125-132. doi:10.1097/WAD.0000000000000490
13. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021;17:327-406. doi:10.1002/alz.12328
14. Sperling RA, Donohue MC, Raman R, et al. Association of factors with elevated amyloid burden in clinically normal older individuals. *JAMA Neurol*. 2020;77:735-745. doi:10.1001/jamaneurol.2020.0387
15. Harkins K, Sankar P, Sperling R, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimers Res Ther*. 2015;7:26. doi:10.1186/s13195-015-0112-7
16. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. *Psychosom Med*. 1979;41:209-218. doi:10.1097/00006842-197905000-00004
17. Manly JJ, Gilmore-Bykovskyi A, Deters KD. Inclusion of underrepresented groups in preclinical Alzheimer disease trials-opportunities abound. *JAMA Netw Open*. 2021;4:e2114606. doi:10.1001/jamanetworkopen.2021.14606
18. Grill JD, Raman R, Ernstrom K, et al. Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment. *JAMA Neurol*. 2020;77:1-10. doi:10.1001/jamaneurol.2020.2734
19. Ornelas IJ, Yamanis TJ, Ruiz RA. The health of undocumented latinx immigrants: what we know and future directions. *Annu Rev Public Health*. 2020;41:289-308. doi:10.1146/annurev-publhealth-040119-094211
20. Liang J, Jang Y, Aranda MP. Stigmatising beliefs about Alzheimer's disease: findings from the Asian American quality of life survey. *Health Soc Care Community*. 2021;29:1483-1490. doi:10.1111/hsc.13208
21. Lim S, Mohaimin S, Min D, et al. Alzheimer's disease and its related dementias among Asian Americans, Native Hawaiians, and Pacific Islanders: a scoping review. *J Alzheimers Dis*. 2020;77:523-537. doi:10.3233/JAD-200509
22. Alcalá HE. Differential mental health impact of cancer across racial/ethnic groups: findings from a population-based study in California. *BMC Public Health*. 2014;14:930. doi:10.1186/1471-2458-14-930
23. Skolarus LE, Lisabeth LD, Burke JF, et al. Racial and ethnic differences in mental distress among stroke survivors. *Ethn Dis*. 2015;25:138-144.
24. Glover CM, CoCroft S, James BD, Barnes LL. Perceptions of risk factors for Alzheimer disease among community-dwelling, nondemented older African Americans. *Alzheimer Dis Assoc Disord*. 2019;33:254-259. doi:10.1097/WAD.0000000000000314
25. Burns JM, Johnson DK, Liebmann E, Bothwell R, Morris JK, Vidoni ED. Safety of disclosing amyloid status in cognitively normal older adults. *Alzheimers Dement*. 2017;13:1024-1030. doi:10.1016/j.jalz.2017.01.022
26. Raman R, Quiroz YT, Langford O, et al. Disparities by race and ethnicity among adults recruited for a preclinical Alzheimer disease trial. *JAMA Netw Open*. 2021;4:e2114364. doi:10.1001/jamanetworkopen.2021.14364
27. Largent EA, Harkins K, van Dyck CH, Hachey S, Sankar P, Karlawish J. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. *PLoS ONE*. 2020;15:e0229137. doi:10.1371/journal.pone.0229137

SUPPORTING INFORMATION

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

How to cite this article: Ritchie M, Salazar CR, Gillen DL, Grill JD. Post-disclosure distress among racial and ethnic groups in a preclinical AD trial. *Alzheimer's Dement*. 2024;20:2508–2515. https://doi.org/10.1002/alz.13726