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RESEARCH ARTICLE

Reasons for undergoing amyloid imaging among cognitively unimpaired older adults

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Abstract

Objectives: Preclinical Alzheimer's disease (AD) clinical trials screen cognitively unimpaired older adults for biomarker criteria and disclose their results. We examined whether participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease Study with "elevated" and "not elevated" amyloid differed in scores on the "Views and Perceptions of Amyloid Imaging" questionnaire. We hypothesized that, prior to disclosure, those with elevated amyloid would score higher than those with not elevated amyloid. We also quantified how responses changed after result disclosure. **Methods:** We assessed data from 4327 individuals who completed the questionnaire at screening visit 1 and after amyloid disclosure. We used linear regression models to assess the relationship between questionnaire category scores and amyloid status. We also quantified the relationship between category score changes and amyloid status. **Results:** Overall, participants scored altruism and contribution to research as the strongest motivations for undergoing amyloid imaging. Those with elevated amyloid scored 0.23 points higher in the Perceived Risk category, on average, than those who had not elevated amyloid prior to disclosure; this effect attenuated towards zero after adjusting for Cognitive Function Instrument score. After disclosure, participants with elevated amyloid demonstrated less within-subject change in Perceived Risk, on average, compared to those with similar pre-disclosure scores who had not elevated amyloid, while demonstrating greater changes in the altruism and planning categories. **Interpretation:** Altruism and learning disease risk motivated enrollment in this preclinical AD trial. Participants with elevated amyloid differed from their not elevated counterparts in their perceptions of amyloid imaging, even before undergoing the procedure.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by gradual cognitive and functional decline, eventually resulting in dementia and death. While clinical symptoms of sporadic AD typically begin after age 65,¹ brain changes associated with disease, such as accumulation of amyloid plaques in the brain, may begin as early as 20 years before symptom onset.² In an effort to intervene earlier in the disease process, researchers have begun performing clinical trials that enroll patients who show no clinical symptoms of AD but who demonstrate biomarker evidence of the disease such as elevated brain amyloid, which can be observed through the use of neuroimaging. This construct has been named "preclinical AD."³

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Study is a fully enrolled ongoing phase 3 preclinical AD clinical trial of the investigational drug solanezumab.⁴ Cognitively unimpaired older adults were screened in A4 to see if they demonstrated elevated brain amyloid on positron emission tomography (PET) imaging and were therefore eligible for randomization. The screening phase of A4 incorporated the Views and Perceptions of Amyloid Imaging questionnaire. The questionnaire asks participants to score how strongly they identify or agree with a series of reasons for undergoing amyloid imaging as personal motivating factors. Participants were administered the questionnaire before and after undergoing amyloid PET during screening.

Knowledge of why participants undergo amyloid imaging in preclinical AD trials could help researchers develop targeted recruitment strategies and improve biomarker disclosure processes for future studies. Improved recruitment of underrepresented populations⁵ and assurance of sensitive disclosure of biomarker results among differing cultures⁶ are particular areas of need. We therefore sought to characterize responses to the Views and Perceptions of Amyloid Imaging scale in the A4 Study and determine if participants with elevated and not elevated amyloid differed from each other. Since A4 participants have shown other differences prior to their amyloid result,⁴ we hypothesized that, prior to learning their biomarker status, those with elevated amyloid would identify with presented motivations more strongly than those with not elevated amyloid. In particular, we expected that differences would be apparent in Perceived Risk components, due to known associations with higher brain amyloid levels such as family history of disease and subjective cognitive complaints.^{4,7} We further hypothesized that this association would manifest, at least in part, via participant responses to the Cognitive Function Instrument (CFI),⁸ a subjective cognitive performance scale. Finally, we sought to quantify how responses to the Views and

Perceptions of Amyloid Imaging questionnaire changed after participants were told their amyloid result. Since learning amyloid status impacts perception of AD risk and self,⁹ we hypothesized that those with elevated amyloid would have greater within-subject score change than those with not elevated amyloid.

Materials and Methods

Data collection

The A4 Study screened individuals from 67 clinical trial sites in the US, Canada, Australia, and Japan.⁴ Screening eligibility criteria for A4 were that participants were between age 65 and 85 years, were assessed to be cognitively unimpaired, were living independently, and had a study partner capable of serving annually to complete informant-based assessments of participant cognition and function. Six screening visits (see Fig. 1) were used to determine whether participants met inclusion criteria for the A4 Study's randomization phase. The analyses performed in our study used a subset of the data collected from the A4 screening visits. Criteria for our analyses were that screened participants had an available PET standardized uptake value ratio (SUVr) observation and had completed the Views and Perceptions of Amyloid Imaging questionnaire both at screening visit 1 and after amyloid result disclosure (screening visit 3; see Fig. 1).

Amyloid levels

In the A4 Study, participants were told they had "elevated" or "not elevated" brain amyloid levels based on their PET result. Participants with PET SUVr greater than 1.15 were categorized as elevated amyloid. Participants with PET SUVr less than 1.10 were categorized as not elevated amyloid. Participants with PET SUVr between 1.10 and 1.15 required an additional visual read to determine amyloid eligibility in A4, with those with at least a two-reader consensus being included in the elevated amyloid group (i.e., eligible for further screening and randomization).⁴

Views and perceptions of amyloid imaging

The primary outcomes of interest in this analysis were item scores in the Views and Perceptions of Amyloid Imaging questionnaire. The questionnaire was adapted from previous work¹⁰ for the A4 Study. Thus, these are among the first data using this instrument, to our knowledge. Participants scored how strongly they identified with each of nine reasons for undergoing amyloid imaging on 5-point Likert scales, with a score of 1 indicating the participant identifies with the presented motivation

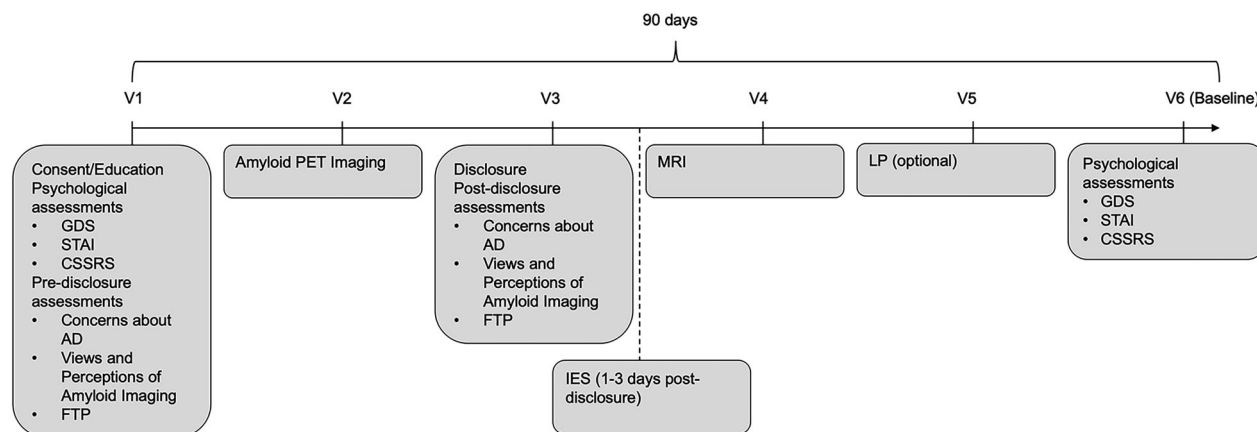


Figure 1. Screening timeline for the A4 Study. Screening required 4 to 5 visits depending on whether the participant completed an optional lumbar puncture (LP). Education, informed consent, and psychological and pre-disclosure assessments were completed at screening visit 1. Amyloid results were disclosed at visit 3. The Views and Perceptions of Amyloid Imaging questionnaire was completed at screening visits 1 and 3. CSSRS indicates Columbia Suicide Severity Rating Scale; FTP, future time perspective; GDS, Geriatric Depression Scale; IES, Impact of Events Scale; MRI, magnetic resonance imaging; PET, positron emission tomography; STAI, State-Trait Anxiety Scale; V, visit.

“Not at all” and a score of 5 indicating the participant “Extremely” identifies with the presented motivation. The questionnaire also has a tenth open-response question that we did not include in this analysis.

We a priori grouped the items from the questionnaire into four thematic categories (see Table 1): Perceived Risk (Items 2, 7; category score range: 2–10), Altruism/Contribute to Research (Items 4, 5; category score range: 2–10), Plan/Prepare (Items 1, 6, 8; category score range: 3–15), and Curiosity (Items 3, 9; category score range: 2–10). Individual item scores in each category were summed to create total category scores. For example, the Curiosity category combines a participant’s scores from Items 3 and 9; the lowest score one can give each item is 1, meaning the minimum score the category as a whole can receive is 2; likewise, 5 is the highest score one can give each item, creating

a category maximum of 10. Thematic categories grouping more items (i.e., Plan/Prepare) subsequently had larger category minimums and maximums. Changes in scores were calculated by subtracting the score at screening visit 1 from the post-disclosure score. For summary tables and statistical models, we used the raw category scores; for plotting purposes, we transformed category scores to normalized Z-scores by subtracting the average category score across visits from a participant’s category score and then dividing by the category standard error.

Statistical analyses

For analysis purposes, participants who selected their race as Native American/Alaska Native, Native Hawaiian/Pacific Islander, Other, a combination of two or more

Table 1. A priori grouping of Views and Perceptions of Amyloid Imaging questionnaire items into thematic categories.

Category	Questionnaire Item (Numbering from original scale)
Perceived risk (category score range: 2–10)	2. To put my mind at ease if I found out I do not have elevated amyloid on my PET scan 7. To confirm the feeling that I might already be developing symptoms of Alzheimer’s disease dementia
Altruism/contribute to research (category score range: 2–10)	4. To be able to participate in anti-amyloid clinical trials (such as the A4 trial) 5. The desire to contribute to research on Alzheimer’s disease
Plan/prepare (category score range: 3–15)	1. To seek information on preventative measures (e.g., change diet, exercise, or other lifestyle changes) 6. To arrange my personal affairs 8. To prepare my family for my possible illness in the future
Curiosity (category score range: 2–10)	3. To know more about my risk of developing Alzheimer’s disease dementia 9. Curiosity

Item scores in each category were summed to create total category scores.

racers, or selected “refused to answer” for either race or ethnicity were categorized as “Other.” Mutually exclusive ethnorracial categories (non-Hispanic [NH] white, NH Black, NH Asian, Hispanic/Latino, Other) were created by combining race and ethnicity information for the remaining participants.

In the primary analysis, we used linear regression models to assess the relationship between questionnaire category scores recorded at screening visit 1 as the response and amyloid status as the independent variable of interest. Participant age, years of education, sex, ethnorracial group, and family history of AD were adjusted for in all models as potential confounding variables. Age and education were treated as continuous, while NH white was used as an ethnorracial reference group for comparisons. Previous research has shown that participants with spousal study partners make clinical trial enrollment decisions largely in tandem, particularly when biomarker testing is necessary.^{11–13} This dynamic may impact participants’ views and perceptions of undergoing amyloid imaging,¹⁴ thus study partner type (dichotomized as spouse or non-spouse) was also adjusted for in all models as a potential confounding variable. CFI scores were adjusted for as a potential mediator in follow-up analyses to determine if the relationship between amyloid status and first-visit category scores was independent of subjective memory concerns. In secondary analyses, we used similar linear regression models to assess the relationship between changes in category scores and amyloid status. Potential confounding variables similar to those in the primary analyses were adjusted for in the secondary models, with the addition of first-visit category score. We quantified uncertainty in all analyses with 95% confidence intervals. Statistical analyses were conducted using R version 3.6.2.¹⁵

Results

Participants

Table 2 describes the demographics of 4327 individuals from the screening phase of the A4 Study used in this analysis. Just under a third of participants (29.6%; $n = 1280$) were categorized as elevated amyloid, while more than two-thirds (70.4%; $n = 3047$) were categorized as not elevated amyloid. Overall, the sample was mostly female (59.3%; $n = 2566$) and NH white (88.8%; $n = 3807$).

As has been reported elsewhere,⁴ participants who had elevated amyloid were observed to be less often NH Black (2.4%) or NH Asian (2.3%) than those with not elevated amyloid (3.9% and 4.6%, respectively). They were also observed to be slightly older and to more often have a family history of AD (48.9% vs. 40.3%).

Table 2. Characteristics of analysis participants.

	Elevated amyloid ($n = 1280$)	Not elevated amyloid ($n = 3047$)	Total ($n = 4327$)
Male	530 (41.4%)	1231 (40.4%)	1761 (40.7%)
Family history of AD	626 (48.9%)	1228 (40.3%)	1854 (42.9%)
Age	72.04 (4.87)	70.93 (4.51)	71.26 (4.65)
Years of education	16.54 (2.81)	16.59 (2.85)	16.57 (2.84)
Ethnorracial group			
NH white	1159 (91.6%)	2648 (87.6%)	3807 (88.8%)
NH Black	30 (2.4%)	117 (3.9%)	147 (3.4%)
NH Asian	29 (2.3%)	138 (4.6%)	167 (3.9%)
Hispanic	37 (2.9%)	96 (3.2%)	132 (3.1%)
Other	11 (0.9%)	24 (0.8%)	35 (0.8%)
Missing	14 (1.1%)	24 (0.8%)	38 (0.9%)
APOE $\epsilon 4$ carrier	738 (58.2%)	762 (25.3%)	1500 (35.0%)
CFI	2.24 (2.12)	1.80 (1.97)	1.93 (2.02)

Continuous variables are summarized as means (SD), while discrete variables are summarized as counts (%).

Perceptions of amyloid imaging prior to disclosure

Table 3 describes the Views and Perceptions of Amyloid Imaging category scores by amyloid group. The Plan/Prepare and Altruism/Contribute to Research categories had the highest average visit 1 scores in both amyloid groups as well as overall, though the Plan/Prepare category had a larger maximum score of 15 (instead of 10). The Altruism/Contribute to Research category achieved the highest average normalized Z-scores (Fig. 2A).

In regression models, participants who had elevated amyloid scored 0.23 points higher in the Perceived Risk category, on average, than those with similar demographic characteristics who had not elevated amyloid (95% CI: [0.09, 0.37]) prior to imaging and disclosure (Fig. 3A). No differences between the groups were observed in the Altruism/Contribute to Research category, the Plan/Prepare category, or the Curiosity category (Fig. 3B–D).

NH Black and Hispanic participants scored higher compared to NH whites in the Perceived Risk (NH Black: 1.01 points, 95% CI: [0.67, 1.35]; Hispanic: 1.02 points, 95% CI: [0.63, 1.41]; Fig. 3A), Plan/Prepare (NH Black: 1.34 points, 95% CI: [0.82, 1.86]; Hispanic: 1.56 points, 95% CI: [0.97, 2.15]; Fig. 3C), and Curiosity (NH Black: 0.55 points, 95% CI: [0.26, 0.85]; Hispanic: 0.39, 95% CI: [0.06, 0.72]; Fig. 3D) categories. NH Asians scored 0.48 points higher in the Perceived Risk category (95% CI: [0.15, 0.80]; Fig. 3A) and 0.63 points higher in the Plan/

Table 3. Views and Perceptions of Amyloid Imaging category scores by amyloid elevation group summarized as mean (SD).

	Elevated amyloid (<i>n</i> = 1280)	Not elevated amyloid (<i>n</i> = 3047)	Total (<i>n</i> = 4327)
Perceived risk			
Visit 1	6.19 (2.10)	5.97 (2.14)	6.03 (2.13)
Post-disclosure	6.24 (2.16)	6.47 (2.19)	6.40 (2.18)
Altruism/contribute to research			
Visit 1	8.52 (1.35)	8.45 (1.47)	8.47 (1.44)
Post-disclosure	8.67 (1.37)	8.52 (1.47)	8.56 (1.45)
Plan/prepare			
Visit 1	9.28 (3.13)	9.21 (3.27)	9.23 (3.23)
Post-disclosure	9.80 (3.10)	9.59 (3.38)	9.65 (3.30)
Curiosity			
Visit 1	7.16 (1.77)	7.28 (1.80)	7.25 (1.79)
Post-disclosure	7.28 (1.80)	7.39 (1.82)	7.36 (1.81)

Prepare category (95% CI: [0.14, 1.13]; Fig. 3C), while scoring 1.19 points lower in the Altruism/Contribute to Research category (95% CI: [−1.40, −0.97]; Fig. 3B) and 0.36 points lower in the Curiosity category (95% CI: [−0.64, −0.08]; Fig. 3D) compared to NH whites. Those with a family history of AD scored between 0.18 and 0.41 higher in every category except Curiosity where they scored 0.13 points lower, compared to those with no family history (Fig. 3A–C).

When CFI scores were added as a potential mediator, the significant effect for both amyloid status and the NH Asian ethnographic group attenuated towards zero in Perceived Risk category (Elevated Amyloid: 0.12, 95% CI: [−0.02, 0.25]; NH Asian: 0.17, 95% CI: [−0.14, 0.49]). The significant effect for NH Asian also attenuated toward zero in the Plan/Prepare category (0.41; 95% CI: [−0.09, 0.90]). None of the other observed effects shifted significantly with the adjustment of CFI scores, though the effect for amyloid status in the Curiosity category did become statistically significant (−0.13; 95% CI: [−0.24, −0.01]; see Table S1).

Attitudes after disclosure

Scores generally increased from visit 1 to the post-disclosure visit 3 across categories and biomarker groups (Table 3). The highest average post-disclosure scores were in the Plan/Prepare and Altruism/Contribute to Research categories. As seen in Figure 2B, Altruism/Contribute to Research remained the category with the highest average normalized Z-scores. We also observed that there was a noticeable disparity in normalized Curiosity scores between the biomarker groups, whereby not elevated participants were observed to rate Curiosity higher than elevated participants.

After disclosure, participants with elevated amyloid demonstrated a lower within-subject change in score in the Perceived Risk category, on average, compared to those with similar visit 1 scores who had not elevated amyloid (−0.35; 95% CI: [−0.46, −0.24]; Fig. 4A). Participants with elevated amyloid demonstrated greater within-subject changes in the Altruism/Contribute to Research (0.11; 95% CI: [0.02, 0.19]; Fig. 4B) and Plan/Prepare (0.21; 95% CI: [0.03, 0.38]; Fig. 4C) categories, compared to those with similar visit 1 scores who had not elevated amyloid. There was no difference between the amyloid groups in the change in the Curiosity category.

Discussion

These are among the first findings to examine participants' motivations for undergoing amyloid imaging in a preclinical AD trial and how motivations change after biomarker disclosure. Overall, participants in this study rated the Altruism/Contribute to Research category as the most important reasons for undergoing amyloid imaging. Participants with elevated amyloid more strongly rated the Perceived Risk category prior to disclosure compared to their counterparts with not elevated amyloid. Average category scores increased after disclosure of individual amyloid imaging results across all categories and groups, signaling that, after biomarker disclosure, participants as a whole identified more strongly with all categories than they did prior to disclosure. Disclosure of amyloid status produced unique changes in the scale between the amyloid groups. We observed that Perceived Risk increased marginally in both elevated and not elevated amyloid groups but that this change differed between groups; those with not elevated amyloid showed larger within-subject increases in Perceived Risk than did those with elevated amyloid.

These results may inform future preclinical AD trial recruitment practices. Appealing to altruism may have the broadest utility. Recruitment messages focusing on concerns about perceived risk for AD, such as clinical referrals of “worried well” and campaigns inviting those with memory concerns to screen, however, may more specifically target biomarker eligible participants¹⁶ since participants in the A4 Study with elevated amyloid more strongly identified confirming or assuaging concerns of AD risk as reasons for undergoing amyloid imaging. In particular, this difference was likely due to the perceived cognitive problems of those with elevated amyloid (despite performing normally on objective tests^{7,8}), as the effect disappeared after adjusting for the CFI, a subjective cognitive function scale, as we hypothesized.

It is well known that diverse racial and ethnic groups are vastly underrepresented in AD trials.¹⁷ As the analysis

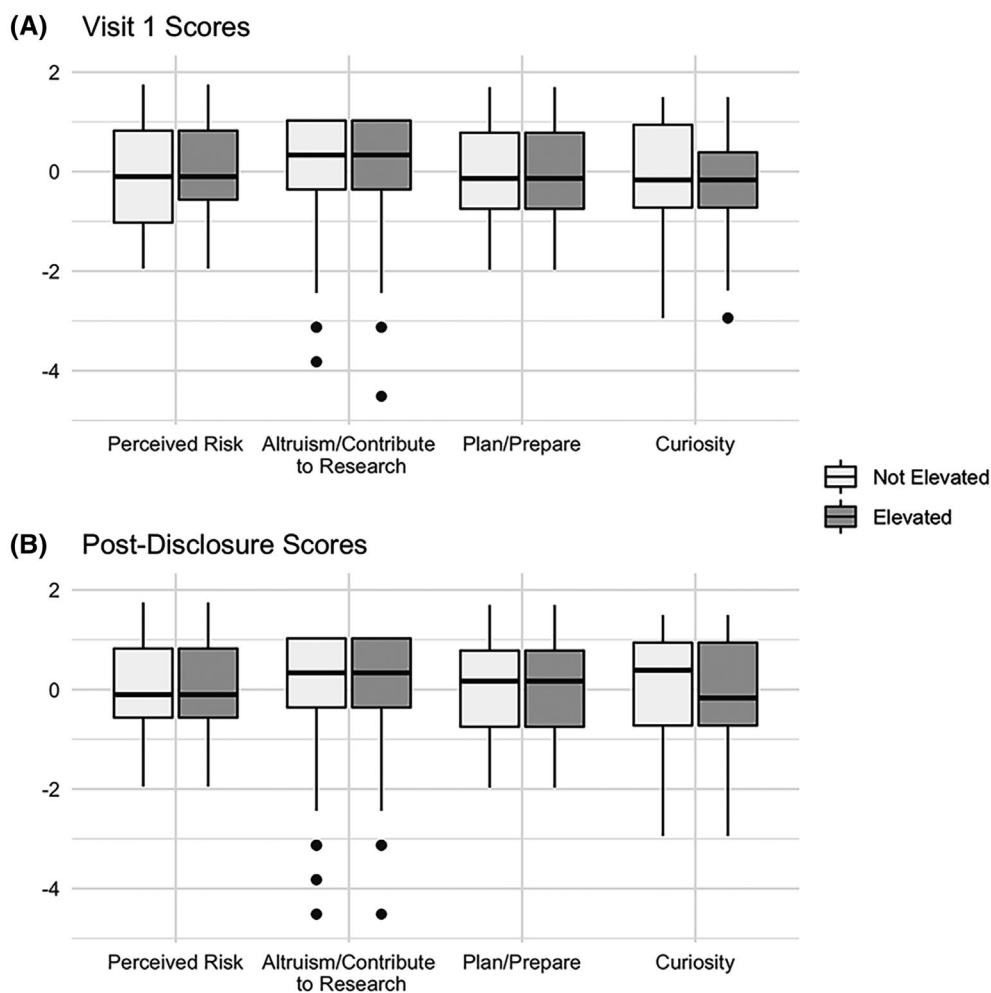


Figure 2. Boxplots of normalized Views and Perceptions of Amyloid Imaging category scores stratified by amyloid elevation status at visits 1 (A) and 3 (B). Scores were transformed into normalized Z-scores by subtracting the average category score across visits from a participant's category score, then dividing by the category standard error. Solid dots represent outliers.

models considered in this study were not designed to properly analyze the relationship between ethnoracial groups and amyloid imaging views, these results should be used for the purposes of hypothesis generation and should be confirmed with future studies. Nonetheless, NH Black and Hispanic participants rated the Perceived Risk category, but also the Plan/Prepare category, as more important than NH whites prior to amyloid disclosure, while NH Asians rated the Altruism/Contribute to Research category lower than NH whites. Thus, in addition to well-described efforts to engage communities and establish trust,^{5,18} these results may indicate that strategic, culturally specific efforts may be needed to improve diversity within preclinical AD trials. These efforts may need to be combined with larger scale educational programs, given especially that diverse groups have been

shown previously to perceive their risk for AD as lower than that for NH Whites.^{19–22}

Multiple studies support that disclosing amyloid imaging biomarkers to cognitively unimpaired individuals does not increase anxiety, depression, or suicidal thoughts.^{6,23} Nevertheless, the current results support the notion that the delivery of amyloid results does differentially impact participants, depending on their specific result. The results may also be important to consider as future similar trials disclose biomarker results to participants.

After disclosure, participants with elevated amyloid increased their endorsement of Altruism/Contribution and Planning/Preparation more than their not elevated counterparts. This may be a positive indication that participants intend to use the results to prepare for a possible future that includes cognitive decline and dementia.²⁴

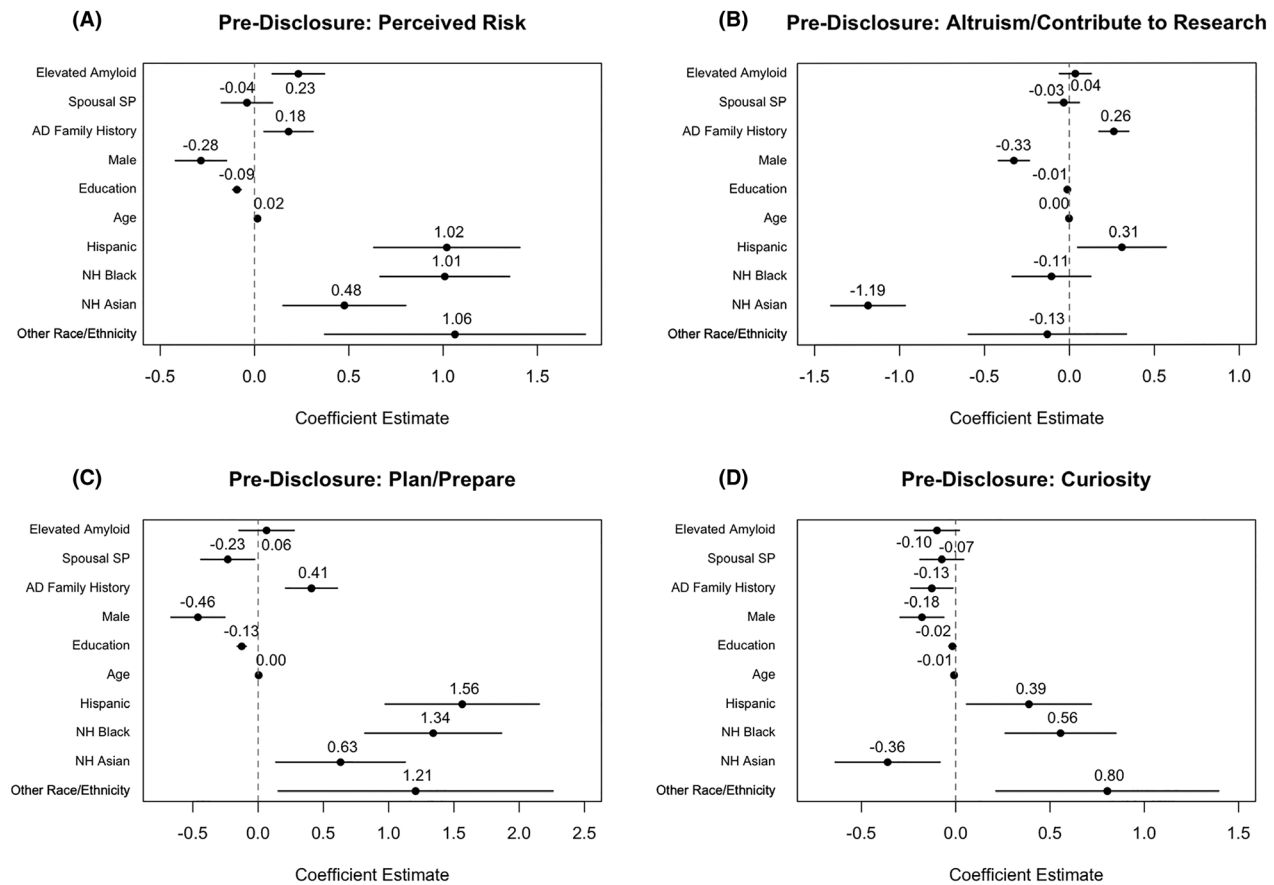


Figure 3. Estimated associations for pre-disclosure regression model assessing the relationship of amyloid status with perceived risk (A), altruism/contribute to research (B), plan/prepare (C), and curiosity (D) category scores. Points represent estimated score difference and solid lines represent estimated 95% confidence interval.

The A4 disclosure process included in-person informed consent and education sessions, where an investigator discussed AD symptoms and the fact that elevated amyloid increases risk but does not guarantee future dementia.²⁵ The educational materials did not cover risk reduction measures or steps one might take to prepare for the potential onset of dementia later in life such as financial planning, discussing future living arrangements, or purchasing long term care (LTC) insurance. Participants with elevated amyloid reported contemplating these issues in the Study of Knowledge and Reactions to Amyloid Testing (SOKRATES), an ancillary interview study with A4 participants.⁹ Including planning and preparation information in the disclosure session or providing informational material for future reference might better support feelings of needing to plan and prepare, which may intensify after disclosure for participants with elevated amyloid. Although participants with not elevated amyloid did not increase their endorsement of Planning/Preparation as much as those with elevated amyloid, they did

demonstrate an absolute increase in endorsement of these items. It is possible that this could have been in response to planning for a future that was less likely to include dementia, since it has been shown that these participants also demonstrated an increase in Future Time Perspective (FTP) scale score.⁶

Participants with elevated amyloid demonstrated less change in their endorsement of the Perceived Risk category, compared to those with not elevated amyloid, suggesting that they were unsurprised by the result. This may have been driven by differential responses for the two items in this category. Specifically, both amyloid groups demonstrated increased scores for Item 7 ("To confirm the feeling that I might already be developing symptoms of Alzheimer's disease dementia"), whereas only those with not elevated amyloid demonstrated increased scores in Item 2 ("To put my mind at ease if I found out I do not have elevated amyloid on my PET scan"), while those with elevated amyloid saw an average decrease in score for this item. Previously published results agree with this finding:

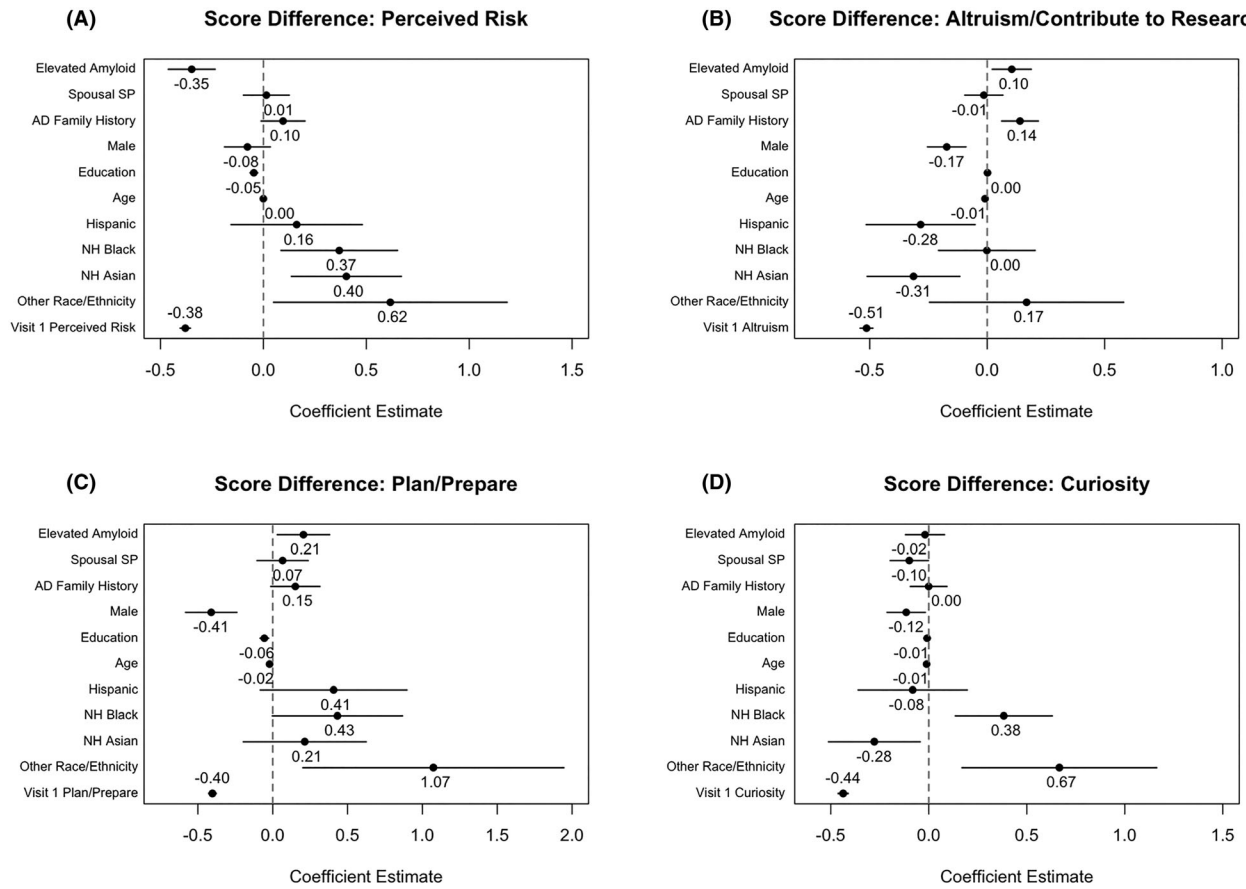


Figure 4. Estimated associations for regression models assessing the relationship of amyloid status with change in perceived risk (A), altruism/contribute to research (B), plan/prepare (C), and curiosity (D) category visit scores. Points represent estimated score change and solid lines represent estimated 95% confidence interval.

participants with elevated amyloid similarly demonstrated no change on the FTP scale after biomarker disclosure.⁶ In the SOKRATES study, participants learning an elevated amyloid result felt that the result validated their memory concerns, compared to participants with not elevated amyloid who reinterpreted memory concerns as normal aging.⁹ These observations serve to endorse the continued need for consistent and sensitive delivery of biomarker results in future preclinical AD trials, especially to participants with elevated amyloid.²⁵

We note some limitations to this work. While the prescreening sample from the A4 Study was large, sample sizes for diverse racial and ethnic groups were smaller, limiting precision. Paired with the high education levels observed across the sample, it is likely that the A4 Study participants are a unique cohort, potentially impacting the generalizability of our results to more diverse populations. In addition, there are likely many factors that affect a person's reasoning to undergo amyloid imaging that are not captured by the questionnaire

used in this study. We attempted to mitigate this by controlling for plausible confounding factors found in the available data, but it remains possible that some factors may not have been observed or adjusted for. There may have also been additional motivations not covered in the main nine items but addressed in the tenth free-response item of the questionnaire that was not included in this analysis. Future studies should investigate the themes presented in the free-response item. We a priori assigned questionnaire items to categories. We assigned Item 4 ("To be able to participate in anti-amyloid clinical trials [such as the A4 trial]") to an altruism category since there was no guarantee that one would receive active treatment nor that one would experience benefits if they did receive active treatment in the A4 Study. This, combined with our previous work²⁶ support the role of altruism and a desire to contribute to research as a main motivation for participation in prevention trials like the A4 Study. We acknowledge that the desire to benefit personally also motivates participation²⁶ and that

this and other alternate assignments of items could have altered results.

Conclusions

Participants in the A4 Study considered altruism and contribution to research the strongest motivations for undergoing amyloid imaging. Prior to disclosure, elevated amyloid participants more strongly endorsed a need to confirm or assuage concerns of AD risk compared to their not elevated counterparts, likely due to their concerns about cognitive impairment. Disclosure of amyloid status produced unique changes on the scale between the amyloid groups, which may be notable for investigators performing future trial disclosures.

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Conflict of Interest

Authors M. M. Ryan and D. L. Gillen declare no conflict of interest. J. D. Grill has received consultancy fees from

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Supporting Information

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

Table S1. Estimated associations for pre-disclosure regression model assessing the relationship of amyloid status with Perceptions of Amyloid Imaging category score, with CFI scores included as a mediator. Model results are reported as coefficient point estimates (95% confidence interval).