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#### SHORT REPORT

# Disclosure of elevated amyloid status is not associated with long-term suicidality in a preclinical AD trial

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#### https://www.actcinfo.org/a4-study-teamlists/

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#### Abstract

**INTRODUCTION:** The long-term implications of disclosing Alzheimer's disease (AD) biomarker information to cognitively unimpaired individuals are unknown.

**METHODS:** We compared participants who disclosed their elevated amyloid imaging result in a preclinical AD trial to those who disclosed a not elevated result and enrolled in an observational cohort that underwent parallel assessments. Our primary outcome was a score > 0 on the Columbia Suicidality Severity Rating Scale (CSSRS) at any visit; we also considered suicidal behaviors (CSSRS > 5).

**RESULTS:** Among 1707 total participants (68% elevated amyloid, mean [standard deviation] age 71.5 [4.7], 60% female, 90% non-Hispanic White), followed for a mean 218 (74.1) weeks, there were no suicides and few indications of suicidal thoughts (n = 124[7%]) or behaviors (n = 13 [<1%]). In a generalized estimating equation model controlling for covariates, we observed no effect of amyloid status on the primary outcome of CSSRS > 0 (odds ratio = 1.6, 95% confidence interval = 0.76, 3.37).

**DISCUSSION:** With a structured approach, brain amyloid results can be returned safely.

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#### KEYWORDS

biomarker, disclosure, suicide, preclinical

#### Highlights

- The Anti-Amyloid Treatment in Asymptomatic Alzheimer's study was among the first and largest studies to include biomarker disclosure in a population without cognitive impairment.
- Routine psychological assessment provided a novel assessment of the impact of disclosure in this sample.
- Learning an elevated brain amyloid result through a protocolized approach was not associated with suicidal thoughts or behaviors compared to a matched cohort who learned they did not have elevated brain amyloid.
- Future research will be needed to ensure similar safety in more real-world settings.

#### 1 INTRODUCTION

Alzheimer's disease (AD) is among the most common causes of mild cognitive impairment (MCI) and dementia and among the most feared medical conditions.<sup>1</sup> Large-scale analyses of health systems data identified recent diagnosis as a risk factor for suicidal thoughts and behaviors among people with MCI<sup>2</sup> and dementia.<sup>2,3</sup>

Preclinical AD is a construct operationalized to represent a stage of disease before MCI or dementia. At this stage, disease-modifying treatments may be effective to prevent or delay the onset of MCI or dementia.<sup>4</sup> Preclinical AD trials enroll individuals with no cognitive impairment who are willing to undergo biomarker testing. If the biomarker test indicates AD pathophysiology is present, an individual is potentially eligible for randomization to treatment or placebo. By necessity, preclinical AD trials disclose individual biomarker results to participants.<sup>5</sup> One concern with this practice is that amyloid biomarker disclosure could produce negative emotions including suicidal thoughts or behaviors.<sup>6-8</sup>

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study was among the first preclinical AD trials.<sup>9</sup> Individuals who learned they had elevated brain amyloid, compared to those who learned they did not have elevated brain amyloid, did not experience short-term increases in suicidal thoughts or behaviors.<sup>10</sup> Here, we report whether learning an elevated brain amyloid result was associated with suicidal thoughts and behaviors over the duration of the study.

#### 2 | METHODS

The A4 study (NCT0200835) was a preclinical AD trial for which the primary results showed no benefit of treatment.<sup>9</sup> We compared participants with elevated amyloid who were eligible and randomized in A4 to a subset of individuals who were ineligible due to having not ele-

vated amyloid but who were enrolled in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN, NCT02488720) cohort study. Additional eligibility criteria and descriptive summaries of these two populations have been provided previously.<sup>10</sup>

Our primary outcome was the Columbia Suicide Severity Rating Scale (CSSRS).<sup>11</sup> We considered CSSRS scores during the blinded study phase (at any visit) for each participant. We examined dichotomized data using the CSSRS and scored 0 versus > 0 to assess for any suicidality including suicidal thoughts or behaviors and scored  $\leq$  5 versus > 5 to assess for suicidal behaviors.

To assess the association between disclosed amyloid status (elevated [A4] vs. not elevated [LEARN]) and longitudinal binary CSSRS, we used a generalized estimating equation (GEE) model (n = 1667[40 participants were excluded from the model due to missing CSSRS or Impact of Event Scale (IES) data]). In this model, we adjusted for age; sex; history of depression or anxiety; lifetime history of suicidal thoughts (collected as part of the baseline CSSRS); baseline Geriatric Depression Scale (GDS) score; baseline State–Trait Anxiety Scale (STAI) score; baseline score on the Cognitive Function Index (CFI), a measure of subjective cognitive concerns; and score on the IES, a measure of intrusive thoughts collected by telephone 24 to 72 hours after initial biomarker disclosure in all participants.<sup>10</sup>

#### 3 | RESULTS

Table 1 describes the participants included in this study and the distribution of CSSRS score categories. The mean duration of follow-up was 218.3 weeks (standard deviation = 74.1 weeks, range 0–348.9 weeks). One A4 participant had a reported aborted suicide attempt. There were no completed suicides. CSSRS scores > 0 were observed for 88 (7.5%) A4 and 36 (6.7%) LEARN participants. Suicidal behaviors (CSSRS > 5) were observed for 10 (0.8%) A4 and 3 (0.6%) LEARN participants. Compared to those with no CSSRS score > 0, those with higher

#### **RESEARCH IN CONTEXT**

- 1. **Systematic review**: The authors used traditional tools to assess the literature. To our knowledge, longitudinal data after biomarker disclosure in cognitively unimpaired individuals is limited to a few single-site studies.
- Interpretation: In this cohort study of cognitively unimpaired participants, learning an elevated brain amyloid result through a protocolized approach that included education and counseling was not associated with suicidal thoughts or behaviors compared to a matched cohort who learned they did not have elevated brain amyloid.
- Future directions: Future research will be needed to ensure similar safety in more real-world settings.

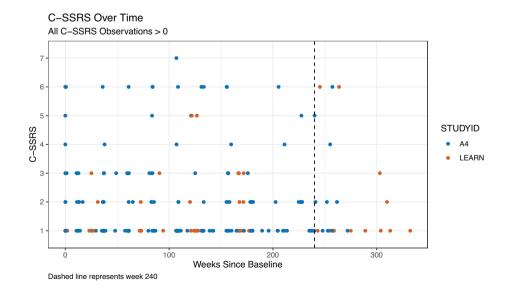
scores were similar in age, family history of dementia, and cognitive performance at baseline. Those with higher scores more frequently had lifetime reporting of suicidal thoughts, medical history of anxiety or depression, and higher IES scores (Table 1). Figure 1 illustrates each CSSRS score > 0 in the A4 and LEARN groups over the duration of the study.

In a GEE model for the outcome of CSSRS > 0 that adjusted for covariates, there was no effect of the disclosed amyloid status group (odds ratio [OR] = 1.6, 95% confidence interval [CI] = 0.76, 3.37; Table 2). Among covariates, age (OR = 1.09, 95% CI = 1.05, 1.14), time on study (OR = 1.01, 95% CI = 1.0, 1.1), and an interaction between time and disclosed amyloid status group, with A4 demonstrating lower risk of CSSRS > 0 over time (OR = 0.99, 95% CI = 0.99, 0.997), were observed to be significantly associated with the outcome of CSSRS

> 0. Baseline GDS score (OR = 1.27, 95% CI = 1.13, 1.43), but not STAI, IES, or CFI baseline scores, was associated with CSSRS > 0. Medical history of anxiety or depression (OR = 2.58, 95% CI = 1.68, 3.97) and lifetime history of suicidal thoughts (OR = 3.6, 95% CI = 2.39, 5.45) demonstrated the strongest associations with CSSRS > 0. Data were too sparse to run models for the outcome of CSSRS > 5 (n = 13, total).

#### 4 DISCUSSION

Individuals disclosed an elevated amyloid result were no more likely to experience suicidal thoughts than their counterparts who were disclosed a not elevated result and enrolled in a parallel observational cohort study. We believe these are among the first and largest scale results for long-term follow-up of cognitively unimpaired individuals undergoing AD biomarker testing and disclosure, which could soon represent a new clinical model for treating AD.<sup>12</sup> In this study, we were unable to separate effects of learning an elevated amyloid result from effects of having elevated amyloid. The lack of effect of amyloid status on suicidal thoughts, however, suggests that individuals enrolled in preclinical AD trials are not at increased risk for suicidal thoughts or behaviors, either resulting from the biological presence of amyloid or the psychological reactions to learning biomarker status. Instead, a lifetime history of suicidal thoughts or depression or anxiety, and higher scores on a depression scale at the time of enrollment were associated with CSSRS > 0. These results suggest that attention to current and previous depression, anxiety, or suicidality is valuable when considering the psychological impact of amyloid disclosure. The results also emphasize an inherent tension in trials like A4, which did not explicitly exclude participants based on depression or anxiety scale scores, but



**FIGURE 1** CSSRS over time in A4 (blue) and LEARN (orange) participants. Each CSSRS score > 0 is plotted for all participants included in the longitudinal study phase. In total, 124 participants experienced 210 events. CSSRS scores reflect greater severity with higher scores (CSSRS 1-5 = suicidal thoughts; CCSRS > 5 = suicidal behaviors). A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; CSSRS, Columbia Suicidality Severity Rating Scale; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration.

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#### **TABLE 1**Description of the sample at baseline.

Characteristic	Total (N = 1707)	CSSRS = 0 at every time point (N = 1579)	CSSRS > 0 at any time point (N = 124)	$CSSRS \leq 5$ at every time point (N = 1690)	CSSRS > 5 at any time point (N = 13)
Amyloid group					
A4, n (%)	1169 (68.5)	1077 (68.2)	88 (71.0)	1155 (68.3)	10 (76.9)
LEARN, n (%)	538 (31.5)	502 (31.8)	36 (29.0)	535 (31.7)	3 (23.1)
Female sex, n (%)	1024 (60)	941 (59.6)	82 (66.1)	1013 (59.9)	10 (76.9)
Age, mean (SD)	71.5 (4.7)	71.4 (4.7)	72.2 (4.8)	71.5 (4.7)	71.7 (4.4)
Race					
American Indian/Alaska Native, n (%)	7 (0.4)	7 (0.4)	0 (0)	7 (0.4)	0 (0)
Asian, n (%)	36 (2.1)	33 (2.1)	3 (2.4)	36 (2.1)	0 (0)
Black or African American, n (%)	42 (2.5)	41 (2.6)	1 (0.8)	41 (2.4)	1 (7.7)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	O (O)	0 (0)
White, <i>n</i> (%)	1601 (93.8)	1480 (93.7)	117 (94.4)	1585 (93.8)	12 (92.3)
More than one race, n (%)	13 (0.8)	13 (0.8)	0 (0)	13 (0.8)	0 (0)
Unknown or not reported, n (%)	8 (0.5)	5 (0.3)	3 (2.4)	8 (0.5)	0 (0)
Hispanic ethnicity, n (%)	52 (3.1)	50 (3.2)	2 (1.6)	52 (3.1)	0 (0)
Married, n (%)	1222 (71.6)	1143 (72.4)	75 (60.5)	1211 (71.7)	7 (53.8)
Retired, n (%)	1288 (75.5)	1190 (75.4)	95 (76.6)	1276 (75.5)	9 (69.2)
Family history dementia, n (%)	1233 (72.2)	1142 (72.3)	89 (71.8)	1221 (72.2)	10 (76.9)
MMSE, mean (SD)	28.9 (1.2)	28.9 (1.3)	28.9 (1.2)	28.9 (1.3)	29.3 (0.8)
GDS, mean (SD)	1.0 (1.4)	1.0 (1.3)	2.0 (2.1)	1.0 (1.4)	1.6 (1.6)
STAI, mean (SD)	9.9 (3.1)	9.8 (3.0)	11.8 (3.6)	9.9 (3.1)	10.8 (3.5)
CSSRS (lifetime)>0, n (%)	298 (17.5)	238 (15.1)	60 (48.4)	293 (17.3)	5 (38.5)
History of anxiety or depression <sup>a</sup> , n (%)	400 (23.4)	337 (21.3)	63 (50.8)	393 (23.3)	7 (53.8)
IES, mean (SD) <sup>b</sup>	8.9 (10.1)	8.6 (9.7)	13.1 (13.4)	8.9 (10.1)	9.4 (12.0)
CFI participant, mean (SD)	2.2 (2.1)	2.1 (2.1)	2.7 (2.3)	2.2 (2.1)	3.0 (1.7)

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; CFI, Cognitive Function Index; CSSRS, Columbia Suicidality Severity Rating Scale; GDS, Geriatric Depression Scale; IES, Impact of Event Scale; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration; SD, standard deviation; STAI, State–Trait Anxiety Scale.

<sup>a</sup>History of anxiety or depression is classified by participants reporting a history of anxiety, anxiety disorder, general anxiety disorder, depression, major depression, or persistent depressive disorder.

<sup>b</sup>Collected 24 to 72 hours after amyloid result disclosure by telephone.

did strongly encourage site investigators to consider the suitability of all participants for receiving this potentially distressing information.

Our study has important limitations. Because it was novel, the A4 Study may be associated with important sample bias. Few participants were from historically underrepresented racial and ethnic groups and culture could affect reactions to biomarker information.<sup>13</sup> The study implemented a protocolized approach to education, consent, counseling, and disclosure and included a sample with low levels of depression and anxiety; these elements may limit generalizability to other research or clinical approaches. Importantly, monthly study visits and routine assessments of suicidality, depression, and anxiety provided careful monitoring that is unlikely to be replicated in clinical practice. In fact, study visits may have provided engagement, support, a sense of purpose, and hope related to potential trial outcomes that all may have limited feelings of dysphoria or hopelessness. These results indicate that after structured education and disclosure and with careful longitudinal monitoring, biomarker results can be safely delivered. Future research into whether safety is similar to reduced disclosure practices (e.g., remote disclosure) or fewer follow-up assessments will be essential to instructing clinical practice.

#### ACKNOWLEDGMENTS

We would like to thank the participants and study partners of the A4 study. The complete list of A4 site investigators and the A4 study team is available at https://www.actcinfo.org/a4-study-team-lists/. The A4 study was funded by a public-private partnership between the National Institute on Aging (U19AG010483; R01AG063689; U24AG057437) and Eli Lilly, the Alzheimer's Association (LEARN, NIRG-12-243012), GHR Foundation, as well through other philan-thropic support. J.D.G. and D.S. are supported by NIA P30-AG066519.

#### TABLE 2 Model outcomes.

Covariate (referent)	CSSRS > 0 Odds ratio (95% CI)
Intercept	0 (0, 0) <sup>a</sup>
CSSRS, lifetime	3.605 (2.386, 5.446) <sup>a</sup>
Hx of anxiety/depression	2.585 (1.683, 3.969) <sup>a</sup>
Amyloid group (A4)	1.601 (0.761, 3.367)
Baseline GDS	1.27 (1.131, 1.426) <sup>a</sup>
Baseline STAI	1.047 (0.976, 1.124)
Age	1.093 (1.046, 1.142) <sup>a</sup>
CFI participant	1.044 (0.939, 1.161)
Sex (Female)	1.029 (0.645, 1.641)
IES	1.02 (0.998, 1.041)
Time	1.007 (1.003, 1.01) <sup>a</sup>
Time <sup>a</sup> -amyloid group (A4)	0.993 (0.99, 0.997) <sup>a</sup>
Family history dementia	0.877 (0.545, 1.41)

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; CFI, Cognitive Function Index; CI, confidence interval; CSSRS, Columbia Suicidality Severity Rating Scale; GDS, Geriatric Depression Scale; Hx, history; IES, Impact of Event Scale; STAI, State–Trait Anxiety Scale. <sup>a</sup>Significant at  $\alpha$  = 0.05

#### CONFLICT OF INTEREST STATEMENT

Dr. Grill reports research support from NIA, Alzheimer's Association, BrightFocus Foundation, Biogen, Eli Lilly, Genentech, and Eisai. He has consulted for SiteRx. He receives personal income for editorial service to Alzheimer's & Dementia and has received travel support from the Alzheimer's Association. Dr. Raman has received research support from the National Institutes of Health (NIH), the Alzheimer's Association, the American Heart Association, Eli Lilly, and Eisai. Ms. Flournoy has received research support from the National Institutes of Health (NIH), the Alzheimer's Association, and Eisai. Ms. Ernstrom has received research support from the National Institutes of Health (NIH), the Alzheimer's Association, the American Heart Association, and Eisai. Dr. Pierce reports research support from NIA, Alector, Eisai, Eli Lilly, and Vivoryon. She has consulted for Medscape. Dr. Smith reports research support from the National Institutes of Health (NIH), the Alzheimer's Association, the Alzheimer's Clinical Trial Consortium, Eli Lilly, Biogen, Eisai, Janssen, Vivoryon, Cassava, Bristol Myers Squibb, and the American College of Radiology. Dr. Rosenberg has received research grants from the National Institute on Aging, Alzheimer's Clinical Trials Consortium, Richman Family Precision Medicine Center of Excellence on Alzheimer's Disease, Eisai, Functional Neuromodulation, and Lilly; honoraria from Lilly, GLG, Leerink, Cerevel, Cerevance, Bioxcel, Sunovion, Acadia, Medalink, Novo Nordisk, Noble Insights, TwoLabs, Otsuka, Lundbeck, Acadia, MedaCorp, ExpertConnect, HMP Global, Sinaptica, Synaptogenix, and Neurology Week. PBR has received grant support from the National Institute on Aging including AGRO1054771 (CRD), AGRO1050515 (dronabinol), and AGRO1046543 (ADMET II). Dr. Burns reports research support from the NIH and conducts clinical trials (paid to institution) from Eli Lilly,

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Amylyx, Biogen, Eisai, AbbVie, Astra-Zeneca, and Roche. He has provided consulting to Renew Research, Eisai, Eli Lilly, Labcorp, and Renew Biotechnologies. Dr. Karlawish is on the advisory board of Linus Health. Dr. Aisen has research grants from NIH, the Alzheimer's Association, Lilly, and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint, AltPep, and Neurimmune. Ms. Holdridge is a full-time employee and minor shareholder of Eli Lilly and Company. Dr. Mancini is a full-time employee and minor shareholder of Eli Lilly and Company. Dr. Sperling has received research funding from the National Institute on Aging of the National Institutes of Health, Alzheimer's Association, and GHR Foundation, and funding for publicprivate partnership clinical trials from Eli Lilly and Eisai and Co. She has received consulting fees from Abbvie, AC Immune, Acumen, Alector, Biohaven, Bristol-Myers Squibb, Genentech, Ionis, Janssen, Merck, Prothena, Roche, Shionogi, and Vaxxinity. Her spouse has received consulting fees from Janssen, Merck, and Novartis. Dr. Sultzer has received research support from the National Institute on Aging, Alzheimer's Clinical Trials Consortium, Eisai, Vivoryon, Lilly, and Cognition Therapeutics; support for case adjudication or data monitoring from Otsuka and Janssen; and consulting fees from Novo Nordisk, AbbVie, and Ono Pharmaceuticals. Author disclosures are available in the supporting information.

#### DATA AVAILABILITY STATEMENT

Ms. Flournoy and Dr. Raman had full access to all data and completed all analyses. The longitudinal dataset for the A4 study is publicly available at A4STUDYDATA.org.

#### CONSENT STATEMENT

The current analyses did not access identifying information and are therefore not considered human subjects research.

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#### SUPPORTING INFORMATION

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

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