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RESEARCH ARTICLE

Disclosing genetic risk for Alzheimer's dementia to individuals with mild cognitive impairment

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Abstract

Introduction: The safety of predicting conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia using apolipoprotein E (*APOE*) genotyping is unknown.

Methods: We randomized 114 individuals with MCI to receive estimates of 3-year risk of conversion to AD dementia informed by *APOE* genotyping (disclosure arm) or not (non-disclosure arm) in a non-inferiority clinical trial. Primary outcomes were anxiety and depression scores. Secondary outcomes included other psychological measures.

Results: Upper confidence limits for randomization arm differences were 2.3 on the State Trait Anxiety Index and 0.5 on the Geriatric Depression Scale, below non-inferiority margins of 3.3 and 1.0. Moreover, mean scores were lower in the disclosure arm than non-disclosure arm for test-related positive impact (difference: -1.9, indicating more positive feelings) and AD concern (difference: -0.3).

Discussion: Providing genetic information to individuals with MCI about imminent risk for AD does not increase risks of anxiety or depression and may provide psychological benefits.

KEYWORDS

Alzheimer's disease, anxiety, apolipoprotein E4, cognitive dysfunction, dementia, depression, emotions, genetic testing, health behavior, humans, random allocation, risk assessment, risk

1 | INTRODUCTION

Genomic testing is increasingly used to diagnose and treat disease,[1,2] but its use to estimate risks for developing dementia remains controversial,[3-6] particularly for conditions such as Alzheimer's disease (AD) for which proven strategies to prevent or delay disease onset are lacking. Consensus statements discourage genetic susceptibility testing for AD when individuals are asymptomatic for reasons that include its potential to cause psychological harm.[7,8] People with symptoms that may suggest subclinical levels of disease may be especially vulnerable to anxiety, depression, or even suicidality.[9]

Prior research has shown that disclosing apolipoprotein E (*APOE*) genotypes and communicating AD risk to asymptomatic individuals in clinical settings does not cause psychological harm for most individuals[1012] although questions remain about direct-to-consumer contexts.[13] But these studies enrolled participants who, if they were to develop AD, were often decades away from developing symptoms. Questions remain about whether genetic risk disclosure is safe for individuals who have memory problems and may progress to AD dementia in the near future.

To address this gap in knowledge, we conducted a randomized trial of individuals with amnestic mild cognitive impairment (MCI), a clinical syndrome characterized by memory problems without significant impairment in social or occupational functioning.[14] Approximately 10% to 15% of MCI patients progress to AD dementia annually,[15] depending on factors that include *APOE* genotype.[16] We compared participant outcomes when risk assessments for progressing to AD dementia within 3 years included or omitted disclosure of *APOE* genotypes. We hypothesized that participants who learned their *APOE* genotype would experience no greater anxiety or depression than participants who did not receive genotype disclosure. We hypothesized secondarily that participants who learned they were *APOE* ε4-positive would experience no greater anxiety or depression than participants who learned they were *APOE* ε4-negative.

2 | METHODS

2.1 | Design overview

As described in prior reports,[10-12] the multidisciplinary Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study group designed the protocol and risk disclosure procedures. Institutional review boards at each study site approved the protocol. *APOE* was genotyped at a Clinical Laboratory Improvement Amendments-certified facility (Athena Diagnostics). Methods for risk disclosure were reported previously.[17]

After verbal consent and a phone interview to assess eligibility (Figure 1), participants met with a study clinician (typically a genetic counselor) for screening and to provide written consent. Participants also learned more about MCI and AD, and reviewed the benefits, risks, and limitations of genetic risk assessment for AD. Risks and limitations included potential difficulties coping with test results and the lack of "proven ways to prevent Alzheimer's disease." If participants met inclusion criteria and wished to proceed, blood was drawn for *APOE* genotyping. Participants were randomized 2:1 in blocks of six to groups that received *APOE* genotype disclosure (disclosure arm) or did not receive genotype disclosure (non-disclosure arm). Randomization strata were defined by site and age.

Approximately 1 month after the blood draw, participants returned to the clinic to receive results in person. Participants in both randomization arms received education about MCI and AD and personalized estimates from a study clinician about the likelihood they would progress to AD dementia within 3 years. These estimates, provided as part of a semi-scripted protocol, ranged from 8% to 57% (see Appendix S2 in supporting information) and were created using data from the Memory Impairment Study.[18] Personalized estimates for progressing to AD dementia were based on participants' age stratum and their MCI diagnoses.[17] For participants in the disclosure arm, personalized estimates of conversion to AD were additionally based on the presence ("*APOE* ε4-positive") or absence ("*APOE* ε4-negative") of a copy of the *APOE* ε4 allele (*APOE* ε4 heterozygotes and homozygotes were provided the same AD risk estimates). All personalized risk estimates included written information, a pictogram, and a line graph (see Appendix S3 in supporting information). Participants were followed for 6 months after disclosure sessions, with assessments conducted in person at 6 weeks and via telephone and mail at 6 months.

A 1-year follow-up visit was originally planned, but was shortened to 6 months to reduce demands on participants and because prior studies[10] and anecdotal descriptions had suggested that there were no additional changes in psychosocial outcomes after 6 months. Participants in the genotype non-disclosure arm had the option to learn their *APOE* genotypes after completing their final follow-up survey.

2.2 | Study population

We recruited individuals with amnestic MCI who were ages 55 to 90 years from memory clinics, neurology and medicine departments, and AD centers. MCI was defined as having (1) a memory complaint, corroborated by an informant; (2) abnormal memory function, as documented by delayed recall on the Logical Memory II subtest of the Wechsler Memory Scale-Revised; and (3) adequate general cognitive function (Mini-Mental State Examination [MMSE] score ≥24[19] or approval from a clinician for scores below 24). To ensure participants' safety, we required participants to enroll and attend sessions with a companion. Exclusion criteria included severe anxiety or depression per a clinician's judgment and informed by scores on mood scales. Additional details about the recruitment and safety monitoring protocols are provided in Appendix S4 in supporting information.

2.3 | Outcome measures

Co-primary outcomes were time-averaged scores of anxiety, as assessed with a six-item version of the State-Trait Anxiety Inventory (STAI)[20]; and depression, assessed with the 15-item version of the Geriatric Depression Scale (GDS).[21,22] STAI scores were scaled to range from 20 to 80, and scores above 40 may warrant clinical concern.[29,30] GDS scores ranged from 0 to 15, with higher scores indicating greater depression and scores of 5 or above indicating clinical concern.[23,24] Secondary psychological measures included test-related distress, as measured by the Impact of Event Scale (IES)[25] (range: 0 to 75; higher scores indicate greater distress), and the individual subscales that comprised the Impact of Genetic Testing for Alzheimer's Disease scale (IGT-AD)[26]: test-specific distress (range: 0–60; higher scores indicate greater distress) and positive test impact (range: 0–20; lower scores indicate greater positive feelings). We also assessed hopelessness with the four-item Beck Hopelessness Scale (BHS; range: 0–4, higher scores indicate greater hopelessness),[27] and a 4-item AD concern scale (range: 1–5, higher scores indicate greater concern about AD).[28] Participants who scored above 8 on the 15-item GDS, above 56 on the 6-item STAI, or endorsed at least two out of four statements on the BHS received additional follow-up and monitoring. Test-related distress and positive impact scales were administered only after AD risk assessments. All other measures were assessed at baseline and again at 6 weeks and 6 months after AD risk assessments. As in prior REVEAL Study trials,[28-30] we also assessed participants' risk perceptions at all time points by asking them to estimate their chances of AD conversion within the next 3 years on a scale of 0% to 100%.

2.4 | Statistical analysis

We planned to enroll 180 participants and provide 151 risk assessments. We used a non-inferiority framework to test the primary hypothesis that participants in the genotype disclosure arm would report no greater anxiety or depression than participants in the non-disclosure arm.[31] We also used a non-inferiority framework to test the secondary hypothesis that, within the genotype disclosure arm, participants who received *APOE* ε4-positive results would report no greater symptoms of anxiety or depression than participants who received *APOE* ε4-negative results. In this paper therefore, the phrase "non-inferiority of genotype disclosure" means the comparison of scores of one group to another showed that genetic risk disclosure did not increase scores of psychological harm more than a margin of error from that of the comparison group.

We used *t* tests and chi-squared tests to compare demographics of the randomization arms and to analyze who dropped out after randomization. We used chi-squared tests to compare dropout of study arms after randomization, but before results were communicated to participants. For all other analyses, we used generalized linear models fit with generalized estimating equations to compare time-averaged and time-specific outcomes by randomization arm or by *APOE* status. Analyses of STAI, GDS, IES, test-related distress with the IGT-AD, and BHS used a log link and gamma distribution because the distributions of these outcomes were highly skewed. A value of one was added to each of these scales, except the STAI, to shift their distributions away from zero. Analyses of positive impact, AD concern, and perceived risk for AD conversion used an identity link and normal distribution. Models included interaction terms between time and randomization status because prior work has shown that, when observed, the psychological impact of genetic information typically fades over time.[32] All models included terms for randomization status, time as a categorical variable, and interaction between time and randomization arm. We included baseline scores, where applicable, age, sex, race, education, and, given imbalances by randomization status, marital status as covariates in

RESEARCH IN CONTEXT

1. Systematic review: Genetic risk assessments for Alzheimer's disease (AD) based on apolipoprotein E (*APOE*) genotyping do not increase risks for psychological harm when provided in clinical settings to volunteer populations who are asymptomatic. To date, however, studies have excluded individuals with mild memory problems who are at risk of AD in the more immediate future.
2. Interpretation: In a multisite randomized controlled non-inferiority trial of individuals with mild cognitive impairment, we showed that subjects with *APOE* genotyping to predict conversion to Alzheimer's dementia within 3 years showed no greater risk for depression or anxiety than those not disclosed.
3. Future directions: Results provide a foundation for follow-up studies of alternative strategies of predicting imminent risk for or diagnosing AD, such as biomarker analyses of cerebrospinal fluid and amyloid imaging.

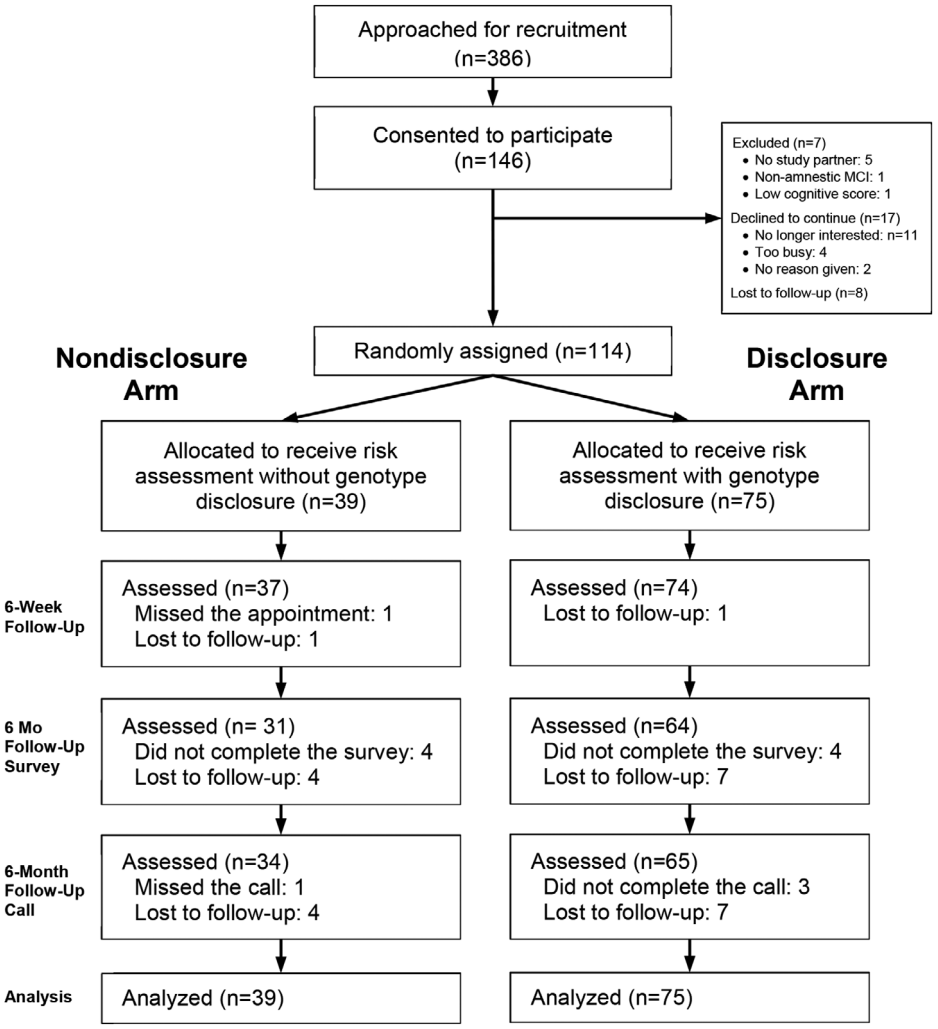

FIGURE 1 Study flow diagram

analyses of continuous outcomes. The analytic approach followed our initial statistical analysis plans (these covariates were omitted from analyses of dichotomous outcomes because statistical models that included them were unstable). We also included the clinician who disclosed results as a covariate in the analyses of continuous outcomes to account for potential confounding.[33] We included baseline scores where available (STAI, GDS, BHS, and AD concern) given their strong associations with scores at follow-up and best practices.[10,34] Analyses that compared participants by *APOE* status included a dichotomous variable to distinguish participants with no copies of the $\varepsilon 4$ allele and participants with at least one copy, as well as terms for interaction between *APOE* status and randomization status; *APOE* status and time; and *APOE* status, randomization status, and time.

For non-inferiority testing, we calculated 97.5% confidence limits (CL), using upper bounds of two-sided confidence intervals (Cis) of $(1 - 2\alpha) \times 100\%$, with α equal to 2.5% (0.05/2) to account for multiple testing across 2 primary outcomes.[35] We asserted non-inferiority (ie, no greater anxiety or depression) if 97.5% CL for the differences between randomization arms or *APOE* genotypes were below non-inferiority margins (because all scales indicated worse scores with higher values, we were able to focus on upper bounds). The same approach was used to examine all outcomes at specific time points and all secondary psychological outcomes. More details about the margins that defined non-inferiority and the statistical models are provided in Appendix S4.

Analyses included all randomized participants. Analyses were conducted using R version 3.5.1 or SAS, version 9.4 (SAS Institute). We assumed that data were missing at random (up to 19 participants were missing data on primary and secondary outcomes), and imputed missing data with fully conditional specification, running 100 iterations to create each of 20 imputed data sets.

3 | RESULTS

We enrolled 146 of the 386 participants that we recruited (37.8%), and ultimately provided results to 114 participants (Figure 1). Characteristics of participants who were provided risk assessments are summarized in Table 1. Participants were 74 years old, on average, and 75 (65.8%) had at least a bachelor's degree. MMSE scores ranged from 21 to 30, with most participants (91.7%) scoring 24 or

TABLE 1 Baseline characteristics of the 114 participants who attended risk disclosure sessions

Characteristic: n (%), unless noted	Disclosure arm (n = 75)	Non-disclosure arm (n = 39)
Age in years		
57–70	30 (40%)	14 (36%)
71–77	19 (25%)	10 (26%)
78–89	26 (35%)	15 (38%)
Sex		
Female	39 (52%)	18 (46%)
Male	36 (48%)	21 (54%)
Self-identified race		
Black	11 (15%)	9 (23%)
White	64 (85%)	30 (77%)
Years of education, mean (SD)	16.2 (2.7)	16.4 (2.9)
Median household income	$70–$99K	$50–69K
Currently married	57 (76%)	20 (51%)[a]
Has AD-affected family member	43 (59%)	17 (44%)
ε4-positive	39 (52%)	17 (44%)
MMSE score, mean (SD)	27.4 (1.9)	27.0 (2.4)
Mood scale scores, mean (SD)		
Anxiety (range: 20-80)	36.5 (10.9)	36.3 (12.0)
Depression (range: 0-15)	2.1 (2.0)	2.6 (2.6)
Hopelessness (range: 0-4)	0.3 (0.6)	0.5 (0.8)
AD concern (range: 1-5)	3.7 (0.9)	3.6 (0.7)
Perceived risk of AD conversion (range: 0%-100%), mean (SD)	34.9% (28.5%)	30.2% (24.2%)

[a]Difference between randomization arms at *P* value < .01
Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; SD, standard deviation

higher. A greater percentage of participants in the genotype disclosure arm were married compared to the non-disclosure arm (76.0% vs 51.3%, respectively, *P* value = .007). No other differences were observed by randomization status. Clinicians communicated results to between 4 and 47 participants each and did not differ in their likelihood of disclosing results to participants in either randomization arm (*P* value = .819).

3.1 | Randomization arm comparisons

Mean anxiety and depression scores in both randomization arms were below cutoffs for concern at all time points (Table 2), and non-inferiority of genotype disclosure was demonstrated in time-averaged analyses (Figure 2). Mean adjusted time-averaged anxiety scores were 1.4 points lower in the disclosure arm than the non-disclosure arm, and the 97.5% CL (2.3) was below the non-inferiority margin (3.3). Mean adjusted time-averaged depression scores were the same in the disclosure and non-disclosure arms, and the 97.5% CL (0.5) was below non-inferiority margin (1.0). Non-inferiority of genotype disclosure was also supported on time-averaged analyses of all secondary psychological outcomes. Similar patterns were observed at 6 weeks. Non-inferiority of genotype disclosure at 6 months was observed only for positive impact and AD concern. Notably, participants were more likely to score above our pre-established cutoffs for increased monitoring on scales of anxiety, depression, and hopelessness if they were randomized to genotype non-disclosure compared to genotype disclosure (28.9% vs 13.5%, respectively, *P* value = .050).

3.2 | Comparisons by APOE status

Mean anxiety and depression scores were still below cutoffs for concern regardless of *APOE ε4* status (Table 3). Preplanned secondary analyses of participants in the disclosure arm that compared disclosure of *APOE ε4*-positive status against disclosure of *APOE ε4*-negative status were inconclusive (Figure 3), as upper bounds of the 97.5% CL for both anxiety and depression (4.1 and 1.0, respectively) were equal to or above margins for non-inferiority (3.3 and 1.0, respectively). Furthermore, participants who received *APOE ε4*-positive results scored higher than those who received *APOE ε4*-negative results on time-averaged scales of test-related distress as measured by the IGT-AD (diff = 6.8, 95% CI: 2.7 to 10.9), as well as all time-point-specific analyses of the same scale.

3.3 | Comparisons of randomization arms by APOE status

We conducted exploratory analyses that compared genotype disclosure to genotype non-disclosure for participants with specific *APOE* genotypes (Appendix S5 in supporting information). Among individuals who were *APOE ε4*-negative, genotype disclosure was non-inferior on time-averaged analyses of all psychological outcomes except anxiety and hopelessness. Moreover, scores were lower in the genotype disclosure arm on time-averaged scores of test-related distress as measured by the IGT-AD (diff = −7.4, 97.5% CL: −2.1), positive impact (diff = −3.1, 97.5% CL: −0.7), and AD concern (diff = −0.6, 97.5% CL: -0.2). Similarly, analyses of 6-week outcomes among *APOE ε4*-negative participants showed non-inferiority of genotype disclosure on all measures except hopelessness, and lower scores in the genotype disclosure arm on measures of test-related distress, as measured by the IGT-AD, and AD concern. At 6 months, non-inferiority of genotype disclosure was observed only for test-related distress (both measures), positive impact, and AD concern.

Among individuals who were *APOE ε4*-positive, genotype disclosure was non-inferior to genotype non-disclosure on time-averaged measures of anxiety (diff = −2.3, 97.5% CL: 3.0 vs margin of 3.3), depression (diff = 0.3, 97.5% CL: .9 vs margin of 1.0), positive impact (diff = −0.6, 97.5% CL: 2.3 vs margin of 5.0), and hopelessness (diff = −0.1, 97.5% CL: 0.2 vs margin of 0.3). In time-point-specific analyses of *APOE ε4*-positive participants, disclosure was demonstrated to be non-inferior

TABLE 2 Mean psychological outcome scores and standard errors, by randomization arm and time after risk disclosure sessions[a]

	Disclosure arm (n = 75)			Non-disclosure arm (n = 39)		
	Time-averaged	6 week	6 months	Time-averaged	6 weeks	6 months
Anxiety	35.6 (1.0)	35.6 (1.0)	35.6 (1.5)	37.0 (1.6)	38.2 (1.9)	35.8 (2.0)
Depression	1.9 (0.2)	1.8 (0.1)	1.9 (0.2)	1.9 (0.2)	2.0 (0.2)	1.7 (0.3)
Test-related distress (IES)	11.8 (1.3)	11.4 (1.5)	12.1 (1.5)	11.3 (1.4)	11.7 (1.7)	11.0 (1.9)
Test-related distress (IGT-AD)	10.0 (1.0)	10.0 (1.1)	10.1 (1.2)	12.3 (1.6)	13.8 (1.8)	11.0 (1.8)
Positive impact	9.3 (0.5)	9.2 (0.6)	9.4 (0.6)	11.1 (0.7)	10.4 (0.8)	11.9 (0.9)
Hopelessness	0.3 (0.1)	0.3 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
AD concern	3.3 (0.1)	3.2 (0.1)	3.4 (0.1)	3.6 (0.1)	3.6 (0.1)	3.6 (0.2)

[a]Scores were estimated using generalized estimating equations, with adjustment for demographic characteristics, disclosing clinician, and baseline values. Models for all outcomes used a log link and gamma distribution.
Abbreviations: IES, Impact of Event Scale; IGT-AD, Impact of Genetic Testing for Alzheimer's Disease scale

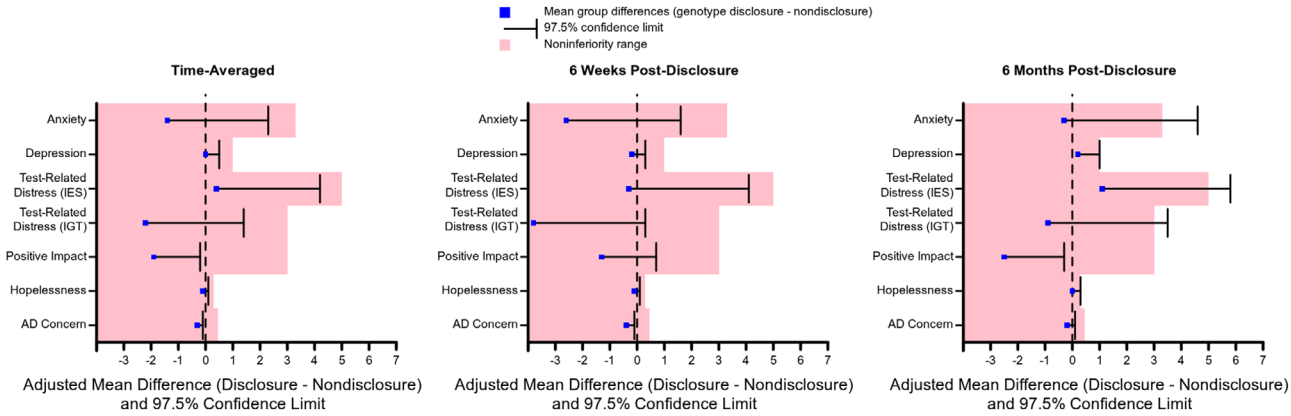

FIGURE 2 Noninferiority analyses comparing genotype disclosure to nondisclosure

to non-disclosure at 6 weeks only for depression, positive impact, hopelessness, and AD concern, and for no psychological outcomes at 6 months except positive impact.

3.4 | Perceptions of risk for converting to AD

Exploratory analyses also showed differences between randomization arms in perceived risk of progressing to AD within 3 years, contingent upon *APOE* status (Appendix S6 in supporting information). Among participants who were *APOE* ε4-negative, individuals in the genotype disclosure arm provided time-averaged estimates of their risk of progressing to AD that were an average of 11.3% lower in the disclosure arm than the non-disclosure arm (24.6% vs 36.0%, respectively, *P* value = .010), although differences were not significant at 6 weeks. No differences between randomization arms were observed at any time point or in time-averaged analyses among participants who were *APOE* ε4-positive (all *P* values ≥.165). Among participants in the disclosure arm, participants who were ε4-positive provided risk estimates for AD conversion that were 19.7% higher in time-averaged analyses than participants who were ε4-negative (44.3% vs 24.6%, respectively, *P* value < .001). Differences were also significant in time-point-specific analyses.

4 | DISCUSSION

This study showed that among individuals with MCI, disclosing genetic risk about progressing to AD dementia does not increase risks for clinically significant depression or anxiety, and overall reduced concern about AD. It also resulted in more positive feelings about the risk assessment experience. These findings are consistent with results from prior trials that demonstrated the safety of disclosing genetic risk information about AD when provided to volunteer populations by clinicians in a well-designed education and disclosure protocol[10-12,36] and that showed psychological benefits for participants who learned that they were *APOE* ε4-negative. In this trial, it is likely that psychological benefits accrued, in part, because participants were expecting bad news given their mild memory problems. Similar responses have been observed in studies of genetic testing for conditions such as Huntington's disease and Lynch syndrome, in which identification of genetic risk factors have not caused clinically significant distress but negative results have provided emotional relief.[37,38] Further supporting this rationale, we found participants estimated their likelihood of progressing to AD lower when their *APOE* ε4-negative status was disclosed rather than withheld, while no differences were observed when participants were *APOE* ε4-positive.

TABLE 3 Mean psychological outcome scores, by randomization arm, APOE status, and time after risk disclosure sessions[a]

	Time-averaged	6 weeks post-discl	6 months post-discl	Time-averaged	6 weeks post-discl	6 months post-discl
Disclosure arm	APOE ε4-positive (n = 39)			APOE ε4-negative (n = 36)		
Anxiety	35.6 (1.4)	36.0 (1.6)	35.1 (1.9)	35.7 (1.6)	35.3 (1.4)	36.1 (2.4)
Depression	2.1 (0.2)	2.1 (0.2)	2.1 (0.3)	1.7 (0.2)	1.5 (0.2)	1.8 (0.3)
Test-related distress (IES)	12.9 (1.8)	12.6 (1.9)	13.2 (2.0)	10.4 (1.9)	10.1 (2.3)	10.8 (2.1)
Test-related distress (IGT-AD)	13.5 (1.7)	13.1 (1.9)	13.8 (2.0)	6.7 (1.2)	7.0 (1.4)	6.4 (1.3)
Positive impact	10.0 (0.7)	10.0 (0.9)	10.0 (0.8)	8.5 (0.8)	8.3 (1.0)	8.7 (1.0)
Hopelessness	0.3 (0.1)	0.2 (0.1)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)
AD concern	3.4 (0.1)	3.3 (0.2)	3.6 (0.2)	3.1 (0.1)	3.0 (0.1)	3.1 (0.1)
Nondisclosure arm	*APOE* ε4-Positive (n = 17)			*APOE* ε4-Negative (n = 22)		
Anxiety	37.9 (2.3)	37.9 (2.3)	37.9 (2.8)	36.1 (2.1)	38.3 (2.9)	34.1 (2.6)
Depression	1.8 (0.2)	1.9 (0.3)	1.7 (0.4)	1.9 (0.3)	2.1 (0.4)	1.7 (0.4)
Test-related distress (IES)	9.2 (1.9)	11.3 (2.4)	7.5 (1.9)	13.0 (2.1)	12.2 (2.4)	13.8 (2.8)
Test-related distress (IGT-AD)	9.7 (2.0)	11.0 (2.2)	8.6 (2.3)	14.1 (2.4)	15.8 (2.8)	12.5 (2.7)
Positive impact	10.6 (1.3)	10.2 (1.4)	11.0 (1.6)	11.6 (1.0)	10.6 (1.1)	12.6 (1.3)
Hopelessness	0.5 (0.1)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)
AD concern	3.4 (0.1)	3.5 (0.2)	3.4 (0.2)	3.7 (0.2)	3.7 (0.2)	3.8 (0.2)

[a]Scores were estimated using generalized estimating equations, with adjustment for demographic factors, disclosing clinician, and baseline values. Models for all outcomes used a log link and gamma distribution.

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; IES, Impact of Event Scale; IGT-AD, Impact of Genetic Testing for Alzheimer's Disease scale.

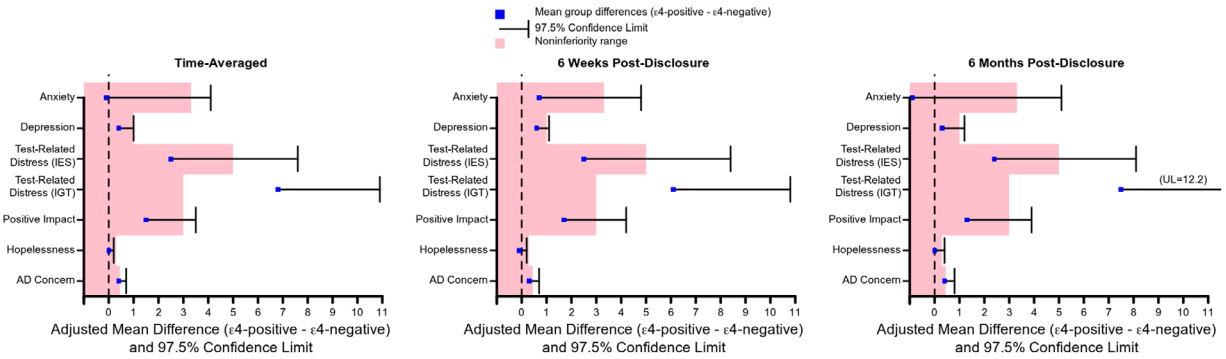

FIGURE 3 Noninferiority analyses of the disclosure arm that compared participants with *APOE* ε4-positive status to participants with *APOE* ε4-negative status

Findings from our study have grown in importance as *APOE* genotyping has become more available. Trials of investigational medications, such as the A4 Trial[44] and the bapineuzumab trial[39] have used *APOE* genotyping to enrich or stratify their study populations. In the Generation Program,[40] disclosure of APOE genotype is a mandatory part of determining trial eligibility. The design of these trials provide access to *APOE* genotyping results to their participants. In addition, some healthy individuals have obtained genetic risk information about AD through studies of precision medicine, physicians, or direct-to-consumer options.[13,41,42] Most notably, 23andMe has FDA approval to include *APOE* results in their direct-to-consumer personal genome service.[43] Given the strong public interest in genetic susceptibility testing about AD[44,45] it is likely that the number of individuals with mild memory problems—and healthy individuals—who pursue *APOE*-based risk information about AD will only continue to increase.

In this trial, participants' distress responses to risk disclosure appeared to be greater than in prior studies of asymptomatic, at-risk adults. Mean scores on both test-related distress scales were higher at all time points than previously observed.[10-12,36] Differences in responses between trials may be the result of differences by trial in eligibility criteria (eg, MCI in this trial, no MCI in prior trials), the magnitude of numeric risk estimates, or the proximity of AD conversion (ie, risk was conveyed for the next 3 years in this trial, as opposed to by age 85 in prior trials).[46] These findings highlight the heightened risk for distress in disclosing AD risk information to individuals with MCI, regardless of whether *APOE* genotypes are disclosed,[47] and the need

for carefully designed education, communication, and follow-up protocols when providing dementia information to individuals with MCI.

Strengths of this study include an ethnically diverse study population, with 18% of participants self-identifying as black or African American. Limitations include enrollment of a volunteer population of individuals who were generally more educated and may be better prepared to cope with higher-risk results than the population at large.[13] Our study also mandated that participants enroll with a study partner who provided social support and responded to risk disclosure in ways that may have influenced study outcomes,[17,48] so the findings may not be generalizable to individuals lacking such social support. The wait for disclosure in the non-disclosure arm may have induced anticipatory anxiety. Last, we did not achieve our study enrollment targets, and provided risk assessments to fewer participants than planned (151 planned vs 114 actual). Moreover, loss to follow-up and missing data at each time point also increased the width of confidence intervals. Nonetheless, sample sizes were sufficient to confirm non-inferiority of genetic risk disclosure in analyses that compared randomization arms on primary outcome measures. Tests of hypotheses that compared *APOE* ε4-positive and ε4-negative participants within the disclosure arm were inconclusive, however, possibly because these analyses were underpowered.

Importantly, our data suggest that including genetic information to estimate the likelihood that individuals with MCI will progress to AD dementia may reassure people who are ε4-negative. Although short-term test-related distress was clearly higher among participants who learned they were ε4-positive rather than ε4-negative, no differences were noted on general measures of anxiety or depression. Given the ever-increasing accessibility of genetic information, our findings provide encouraging data about the safety and personal utility of genetic risk disclosure via standardized education and counseling protocols among populations who are often considered to be most vulnerable to potential harms. These results provide reassurance that *APOE* genotypes, as well as common genotypes for other neurodegenerative diseases (such as *LRRK2* for Parkinson's disease), may be disclosed safely even in persons who have already begun to show clinical symptoms of the condition itself. Because enrollment for new experimental treatments may be increasingly genotype-specific in the future, our work suggests that even participants with MCI can receive information about their *APOE* status without increasing risks for depression or anxiety.

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CONFLICT OF INTEREST

Robert Green receives compensation for advising AIA, Applied Therapeutics, Biggs Institute, Helix, Humanity, Verily, and Veritas, and is a cofounder with equity in Genome Medical.

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SUPPORTING INFORMATION

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

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