Health Behavior Changes After Genetic Risk Assessment for Alzheimer Disease: The REVEAL Study

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Abstract: Risk information for Alzheimer disease (AD) may be communicated through susceptibility gene disclosure, even though this is not currently in clinical use. The REVEAL Study is the first randomized clinical trial of risk assessment for AD with apolipoprotein E (APOE) genotype and numerical risk estimate disclosure. We examined whether APOE genotype and numerical risk disclosure to asymptomatic individuals at high risk for AD alters health behaviors. One hundred sixty-two participants were randomized to either intervention (APOE disclosure) or control (no genotype disclosure) groups. Subjects in both groups received numerical lifetime risk estimates of future AD development based on sex and family history of AD. The intervention group received their APOE genotype. Subjects were informed that no proven preventive measures for AD existed and given an information sheet on preventative therapies under investigation. Participants who learned they were ε4 positive were significantly more likely than ε4 negative participants to report AD-specific health behavior change 1 year after disclosure (adjusted odds ratio: 2.73; 95% confidence interval: 1.14, 6.54; $P = 0.02$). Post hoc analyses revealed similar significant associations between numerical lifetime risk estimates and self-report of AD-specific health behavior change. Despite lack of preventive measures for AD, knowledge of APOE genotype, numerical lifetime risk, or both, influences health behavior.

Key Words: Alzheimer, memory, health behavior change, risk assessment

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Gene markers are rapidly being identified that can provide presymptomatic estimates of risk to individuals for the eventual development of complex late-onset diseases. Many recently discovered genes are not deterministic genes but rather susceptibility genes that provide probabilistic information about risk, and there is considerable controversy about the benefits of disclosing such information to those who seek it.

Alzheimer disease (AD) is a common progressive disease affecting cognition and behavior in which a susceptibility polymorphism [apolipoprotein E (APOE)] has been identified. First-degree family members and those carrying 1 or 2 copies of the APOE ε4 allele are at increased risk of developing AD.[1,2] APOE genotyping is not currently recommended for clinical use as a predictive test given its limited predictive value and the lack of treatment options for AD,[3] but ongoing research experience suggests that many asymptomatic family members of patients with AD are interested in genetic risk assessment.[4–6]

In surveys, 1 reason that family members commonly endorsed for genetic risk assessment was the hope that such information would help in seeking treatments to delay or prevent AD.[6] This was intriguing because there are currently no accepted treatment modalities to delay or prevent AD. We hypothesized that participants receiving APOE ε4 positive (ε4+) disclosure would make more AD-related health behavior changes than those receiving APOE ε4 negative (ε4−) disclosure or those receiving risk assessment without genotype disclosure.

METHODS

The Risk Evaluation and Education for Alzheimer's disease (REVEAL) Study is a multicenter randomized, controlled trial examining the impact of genetic susceptibility testing and disclosure on asymptomatic adult children of patients with AD. Details of the study rationale, design, and other results have been published elsewhere.[6–11] Eligible participants had only 1 living or deceased affected parent who developed AD after the age of 60. The diagnosis of AD in the affected parent was determined by obtaining written documentation from medical records or a letter from the diagnosing physician. In the minority of cases where written documentation was unavailable, the diagnosis of AD was determined using a detailed interview with the participant regarding the parent's history. Individuals were excluded if they exhibited clinically significant cognitive impairment, depression, and anxiety.

Two hundred eighty-nine individuals were initially eligible for the study, dropping to 162 by the randomization phase (Fig. 1). At each phase before randomization (education session, blood draw to test for genotype status, neuropsychologic and psychiatric screening), participants were allowed to drop out if they did not want to receive clinical information offered in that phase. Before randomization, participants attended an education session where they were informed about the difference between deterministic and susceptibility genetic testing. The session emphasized that although the APOE ε4 allele is an important risk factor for AD, it is neither necessary nor sufficient to cause the disease. Participants were also told that there are no proven preventive measures for AD; they received a handout outlining therapies under investigation but not currently recommended for their protective effects against AD such as vitamin E, anti-inflammatory medications, hormone replacement therapies, cholesterol-lowering drugs, and mental stimulation. Participants who proceeded to randomization did not differ significantly from those who declined participation earlier in the protocol with regard to age, sex, race, income, or number of affected relatives; details of this analysis have been published elsewhere.[5,6]

A blocking technique was used to generate the random allocation sequence, and the allocation was concealed from the investigators, and the participants until interventions were assigned. Participants were randomized in a 2:1 ratio to the intervention and control arms of the study, respectively, to have sufficient power to examine response to risk assessment by APOE genotype (ie, ε4+ vs. ε4−). Subjects who were randomized to the control arm received an individualized numerical risk assessment on the basis of family history and sex alone. Subjects in the intervention arm received APOE genotype disclosure and an individualized numerical risk assessment on the basis of family history, sex, and APOE genotype. In both arms, risk estimates were illustrated to

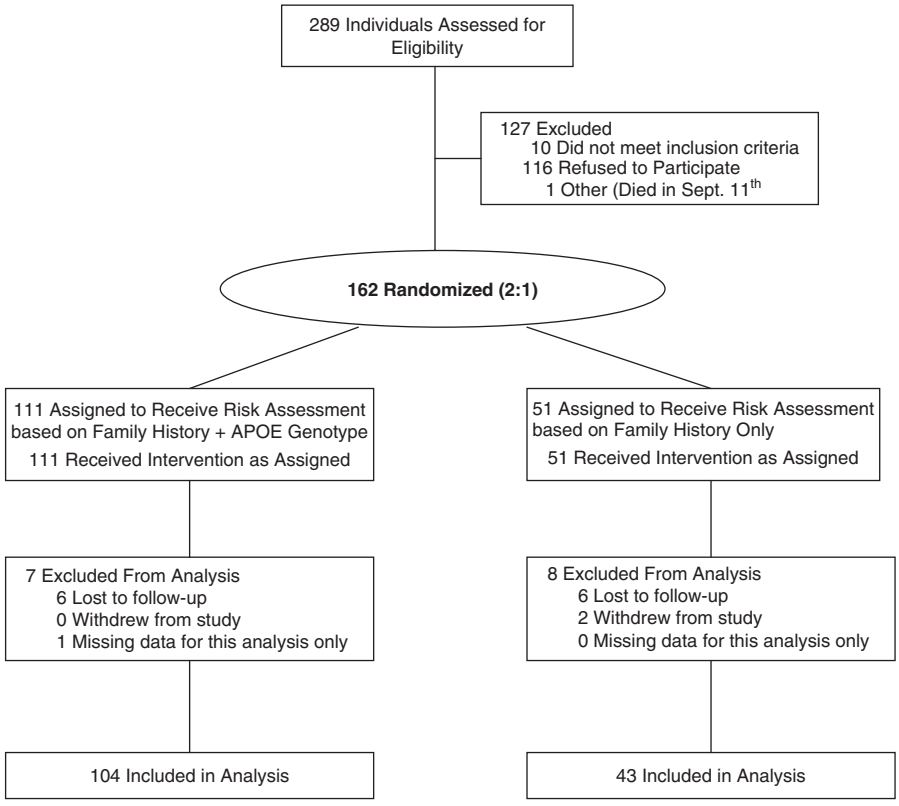

FIGURE 1. Participants' progression through the REVEAL Study.

participants with cumulative risk curves constructed from epidemiologic data, details of which are described in a separate paper.[8] Control participants were given lifetime risk estimates through age 85 ranging between 18% and 29%, whereas intervention participants received estimates between 13% and 57%.

One year after disclosure, participants were asked 3 questions related to health behavior changes made specifically for the purpose of AD prevention. These questions focused on: (1) changes in diet, (2) changes in exercise, or (3) changes in medications and/or vitamins (participants were also allowed to describe these changes in an open-ended format). The primary outcome variable for this analysis was a composite variable gauging whether or not participants answered at least one of these questions affirmatively.

Rather than comparing controls with the disclosure group as a whole, logistic regression analyses using SAS 8.2 were used to test the preplanned dual hypotheses that participants who learned that they were ε4+ were more likely to make changes in AD-specific health behaviors than participants who learned that they were ε4− and than controls. Covariates included demographic data (age, sex, and education) and a composite comorbidity variable that was considered positive if the participant had a history of diabetes mellitus, heart disease, hypertension, hypercholesterolemia, thyroid disease, cancer, or osteoporosis (all conditions where behavioral modifications have potentially preventive effects). Post hoc analyses included a term for the numerical lifetime risk estimate that was also given to each participant as part of the disclosure protocol.

RESULTS

One hundred sixty-two participants were randomized. Fifteen participants dropped out over the 1-year follow-up period, yielding an analysis of 147 individuals (Fig. 1). Table 1 shows demographic characteristics of the participants contributing to this analysis. The ε4+ participants were more likely to be female than the ε4− participants ($P = 0.02$), and slightly younger than the controls ($P = 0.01$).

Table 2 shows unadjusted data on the frequency of health behavior changes specific to AD prevention. At 12 months, ε4+ participants were significantly more likely than both ε4− participants (52% vs. 24%, $P = 0.003$) and control participants (52% vs. 30%, $P = 0.03$) to endorse any AD-specific health behavior change. Of the 3 health behaviors surveyed, ε4+ participants most commonly endorsed changing their medications or vitamins for the purpose of preventing AD. An analysis of open-ended responses to this questionnaire item indicated that adding vitamin E was the most common change in this area.

After adjustment for age, sex, education, and comorbidities, ε4+ participants had 2.73 times the odds of endorsing AD-specific health behavior change compared with ε4− participants (95% confidence interval CI: 1.14, 6.54; $P = 0.02$; Table 3). ε4+ participants showed a trend toward increased endorsement of behavior change compared with controls in the regression model (adjusted odds ratio: 1.5; 95% CI: 0.94, 2.37). Because 26 participants had another family member in the study, we ran a logistic regression model including only 1 unique family member, picked randomly, adjusted for the covariates listed above. We also ran an ordinal logistic regression model to take into account the 14 participants who endorsed 2 or 3 of the AD-specific health behavior changes. In both of these models, APOE ε4+ participants remained significantly more likely to endorse behavior change compared with APOE ε4− participants.

In addition to APOE disclosure, participants in the intervention arm received a numerical risk estimate. To assess whether the provision of a numerical lifetime risk

TABLE 1. Sample Demographics (n = 145)

	All	ε4+	ε4−	Controls
Total number (n)	147	50	54	43
Mean age (range)	52.8 (30-78)	50.3* (34-72)	53.3 (30-76)	55.2 (37-78)
% Female (n)	73% (108)	82% (41)†	61% (33)	79% (34)
Mean years of education (range)	16.7 (12-22)	16.8 (12-21)	16.6 (12-22)	16.7 (12-21)
% With modifiable comorbidity (n)	54% (80)	54% (27)	48% (26)	63% (27)

*ε4+ vs. controls, $P = 0.01$.
†ε4+ vs. ε4−, $P = 0.02$.

TABLE 2. Responses to Health Behavior Questions by Study Group

	All (n = 147)	ε4+ (n = 50)	ε4− (n = 54)	Controls (n = 43)
Any behavior change specific to AD prevention (% endorsing, n)	52% (52)	52%*† (26)	24% (13)	30% (13)
Medications/vitamins (% endorsing, n)	29% (43)	40% (20)	20% (11)	28% (12)
Diet (% endorsing, n)	13% (19)	20% (10)	11% (6)	7% (3)
Exercise (% endorsing, n)	5% (8)	8% (4)	4% (2)	5% (2)

*ε4+ vs. ε4−, $P = 0.003$.
†ε4+ vs. controls, $P = 0.03$.

TABLE 3. Logistic Regression Analysis Predicting any Health Behavior Change for AD Prevention

Variable	Adjusted Odds Ratios	95% CI	P
Test result (ε4+ vs. ε4−)	2.73	1.14, 6.54	0.02
Age	0.97	0.93, 1.01	0.18
Sex	0.39	0.14, 1.11	0.08
Years of education	0.98	0.80, 1.20	0.83
Modifiable comorbidity? (yes/no)	1.17	0.49, 2.80	0.73

estimate of AD development confounded the association between APOE genotype knowledge and endorsement of behavior change,[9,12] we conducted a post hoc logistic regression analysis using the numerical lifetime risk estimate in place of APOE genotype. For each 1% of increase in lifetime risk, there was a 5% increased odds that participants endorsed AD-specific behavior changes (adjusted odds ratio: 1.05; 95% CI: 1.01, 1.09, $P < 0.005$). However, in a logistic regression model including both APOE genotype status and lifetime risk estimate, neither variable was an independent predictor of AD-specific health behavior change, suggesting collinearity between these 2 measures. We confirmed collinearity using tolerance statistics. Furthermore, the fit of models with APOE genotype only, lifetime risk estimate only, and both variables was equivalent as indicated by Receiver Operating Characteristics (ROC) statistics (ROC = 0.729 for model with APOE genotype; ROC = 0.728 for model with lifetime risk estimate; and ROC = 0.727 for model with both variables).

DISCUSSION

In this study, persons who learned they were ε4+ were significantly more likely to report the adoption of AD-specific health behavior changes 1 year after disclosure in comparison with ε4− participants. It is interesting to note that participants endorsed health behavior changes after explicitly being informed that none were proven to prevent AD. Our findings add to the growing literature on genetic risk and behavior change.[12] Although these results seem counterintuitive, one possible explanation is the persistence of lay press information that some dietary measures, leisure time activities, vitamins, and medications may decrease AD risk. Our results are consistent with other REVEAL results, suggesting that genotype and AD risk disclosure influence behavioral changes. In a study of insurance changes endorsed 1 year after risk disclosure, APOE ε4+ participants were 5.76 times more likely to have changed long-term insurance than APOE ε4− participants.[11] Further research is required to help understand why people may be more motivated to engage in putative preventive behaviors for AD versus other disease contexts where provision of genetic risk information has had seemingly little impact on behavior change (eg, screening behavior after genetic risk assessment for breast cancer).

Our study was limited by the fact that the health behavior questions were nonspecific, and that we measured responses to questions about health behavior changes, rather than directly measuring the changes themselves. The study design also did not allow us to fully disentangle the effects of genetic information from more general lifetime risk information. The REVEAL Study participants were predominantly female, white, and college-educated; therefore, the results may not be generalizable to all populations who might qualify for APOE genotype testing in the future. However, study participants may reflect the population of high-risk individuals who would voluntarily seek APOE genotype information.

Our results suggest that people who learn they are at high risk for AD are motivated to engage in behaviors to reduce risk, even if the effectiveness of activities is uncertain. When preventative treatments for AD are developed, studies such as REVEAL may provide insights into how risk disclosure may be more effectively presented to motivate adherence to these treatments.

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