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Disclosing Pleiotropic Effects During Genetic Risk Assessment for Alzheimer Disease

A Randomized Trial

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Background: Increasing use of genetic testing raises questions about disclosing secondary findings, including pleiotropic information.

Objective: To determine the safety and behavioral effect of disclosing modest associations between apolipoprotein E (*APOE*) genotype and coronary artery disease (CAD) risk during *APOE*-based genetic risk assessments for Alzheimer disease (AD).

Design: Randomized, multicenter equivalence clinical trial. (ClinicalTrials.gov: NCT00462917)

Setting: 4 teaching hospitals.

Participants: 257 asymptomatic adults were enrolled, 69% of whom had 1 AD-affected first-degree relative.

Intervention: Disclosure of genetic risk information about AD and CAD (AD+CAD) or AD only (AD-only).

Measurements: Primary outcomes were Beck Anxiety Inventory (BAI) and Center for Epidemiologic Studies Depression Scale (CES-D) scores at 12 months. Secondary outcomes were all measures at 6 weeks and 6 months and test-related distress and health behavior changes at 12 months.

Results: At 12 months, mean BAI scores were 3.5 in both the AD-only and AD+CAD groups (difference, 0.0 [95% CI, −1.0 to 1.0]), and mean CES-D scores were 6.4 and 7.1 in the AD-only and AD+CAD groups, respectively (difference, 0.7 [CI, −1.0 to 2.4]). Both confidence bounds fell within the equivalence margin of ±5 points. Among carriers of the *APOE* ε4 allele, distress was lower in the AD+CAD groups (difference, −4.8 [CI, −8.6 to −1.0]) ($P = 0.031$ for the interaction between group and *APOE* genotype). Participants in the AD+CAD groups also reported more health behavior changes, regardless of *APOE* genotype.

Limitations: Outcomes were self-reported by volunteers without severe anxiety, severe depression, or cognitive problems. Analyses omitted 33 randomly assigned participants.

Conclusion: Disclosure of pleiotropic information did not increase anxiety or depression and may have decreased distress among persons at increased risk for 2 conditions. Providing risk modification information about CAD improved health behaviors. Findings highlight the potential benefits of disclosure of secondary genetic findings when options exist for decreasing risk.

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* For a list of the members of the REVEAL Study Group, see **Appendix 1** (available at www.annals.org).

Physicians in all specialties are increasingly using genomic tools, including whole-genome and whole-exome sequencing (1–3) and genotyping for risk variants and pharmacogenomics variants (4, 5). These tools often identify incidental or secondary findings that have important implications for disease but are unrelated to the original purposes of testing. Although recommendations exist for the reporting of secondary findings in genome sequencing (6, 7), this topic remains controversial (8–10). In particular, experts are concerned that disclosing such information to patients may increase psychological risks while providing minimal clinical benefits (11–15). Despite these concerns, few studies have empirically examined the benefits and harms of disclosure of secondary genomic findings.

Pleiotropy, the association between genetic variants and multiple disease traits, provides a useful model for examining this issue. An estimated 17% of genes have pleiotropic effects (16). Pleiotropy poses challenges to communicating genetic test results because disclosing a genetic variant associated with a disease may unexpectedly confer knowledge of a separate disease risk (17–19). The ε4 allele of the apolipoprotein E (*APOE*) gene, which is present in more than 20% of most populations (20), is robustly associated with risk for Alzheimer disease (AD) (21) and has a weaker and less well-known association with risk for coronary artery disease (CAD) (22, 23). We previously conducted 2 randomized trials of *APOE* genotype disclosure during AD risk assessment, which showed that such disclosure did not increase psychological risks to volunteer populations (24, 25) and motivated at-risk participants to change potential AD risk–

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EDITORS' NOTES

Context

Genetic information may be used to inform persons about their risk for a specific disease. It is unknown whether providing information on risks for conditions about which the persons were not specifically seeking information is beneficial or harmful.

Contribution

This trial, in which participants were provided information on their risk for Alzheimer disease, found that also providing information on risk for coronary artery disease did not increase anxiety or depression but did improve health behaviors.

Implication

Disclosure of secondary findings of genetic tests may be safe in some conditions and may benefit some patients.

reducing behaviors (26, 27). Neither trial addressed associations between *APOE* genotype and CAD.

In this article, we describe an independent trial in which we randomly assigned participants seeking a genetic risk assessment for AD to receive risk information on AD only (AD-only) or on AD and CAD (AD+CAD). We hypothesized that both groups would show equivalent levels of anxiety and depression 1 year after disclosure. We also conducted secondary analyses examining test-related distress and health behaviors.

METHODS

Design

The multidisciplinary REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Study Group designed the study and risk disclosure procedures (24, 25, 28, 29), including ethnicity-specific risk estimates (30, 31). An independent Ethics and Safety Board (ESB) and institutional review boards at each study site approved the protocol. Participants provided informed consent for initial steps during study enrollment and again before having blood drawn for genotyping. Genotyping of *APOE* was done at a Clinical Laboratory Improvement Amendments–certified facility.

Figure 1 shows the design and flow of the study. After a telephone interview and completion of a written questionnaire, participants received brochures that summarized known benefits, risks, and limitations of *APOE* testing, including potential difficulties coping with test results and the lack of "proven ways to prevent Alzheimer's disease" (24, 29) (**Supplement**, available at www.annals.org). They then met with genetic counselors, who answered questions, and had blood drawn for genotyping. Approximately 1 month after the blood draw, participants received scripted information on genetic risk either in person or by telephone (depending on randomization) from 1 of 7 genetic counselors who also addressed any participant concerns. Participants were then followed for 1 year, with measurements at 6 weeks, 6 months, and 12 months.

Setting and Participants

We recruited cognitively healthy adults from Boston, Massachusetts; Cleveland, Ohio; Washington, DC; and Ann Arbor, Michigan, by using mailings to research registries, referrals from neurologists, and advertisements in local newspapers. To achieve greater sample diversity, we enrolled equal numbers of adults older and younger than 60 years and equal numbers of men and women. We also tried to enroll a sample in which 75% of participants had a single AD-affected first-degree relative and 25% had no family history. We excluded persons with 2 or more AD-affected first-degree relatives or family members with average AD onset before age 60 years; those with scores less than 87 (after adjustment for education) on the Modified Mini-Mental State Examination (32); and those with severe anxiety and depression, as defined in the Outcomes and Follow-up section.

Randomization and Intervention

The primary goals of the trial focused on the effect of pleiotropic disclosure, but the opportunity to address a key question about service delivery led to the addition of a second randomization to compare telephone and in-person disclosure of genotyping results (these results will be reported in a separate manuscript). Participants were randomly assigned equally within strata, in blocks of 4, into "AD-only, in-person disclosure," "AD-only, telephone disclosure," "AD+CAD, in-person disclosure," and "AD+CAD, telephone disclosure" groups. Randomization strata were defined by site, age (<60 vs. ≥60 years), family history of AD, and sex. Randomization status was concealed in a serially numbered envelope until needed. Before randomization, participants were informed only that they would receive "different types of genetic risk information." Participants in the AD-only groups were not informed about associations between *APOE* genotype and CAD; those in the AD+CAD groups were told during a second consent step that they would receive information about CAD. Participants learned whether they would receive results in person or via telephone during their blood draw appointment.

During disclosure of genetic risk, all participants received scripted information about their *APOE* genotype, cumulative lifetime risk (range, 6% to 73%), and remaining risk for AD to age 85 years, along with AD risk curves (25, 30, 31). Participants randomly assigned to the AD+CAD groups were also provided with the following statement orally and in writing, regardless of genotype: "In addition to Alzheimer's disease, *APOE* has been found to be connected to heart disease. Some studies have shown that people who carry e4 also have a higher risk of developing heart disease. Potential strategies to reduce the risk of coronary artery disease include smoking cessation, a healthy diet, weight loss, treatment of elevated cholesterol, and exercise (with your doctor's permission)." This information

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was reiterated after each follow-up session. The statement was crafted to be appropriate for disclosure of secondary findings during AD risk assessment by a study cardiologist (D.L.B.) who conferred with cardiologists unrelated to the REVEAL Study.

Outcomes and Follow-up

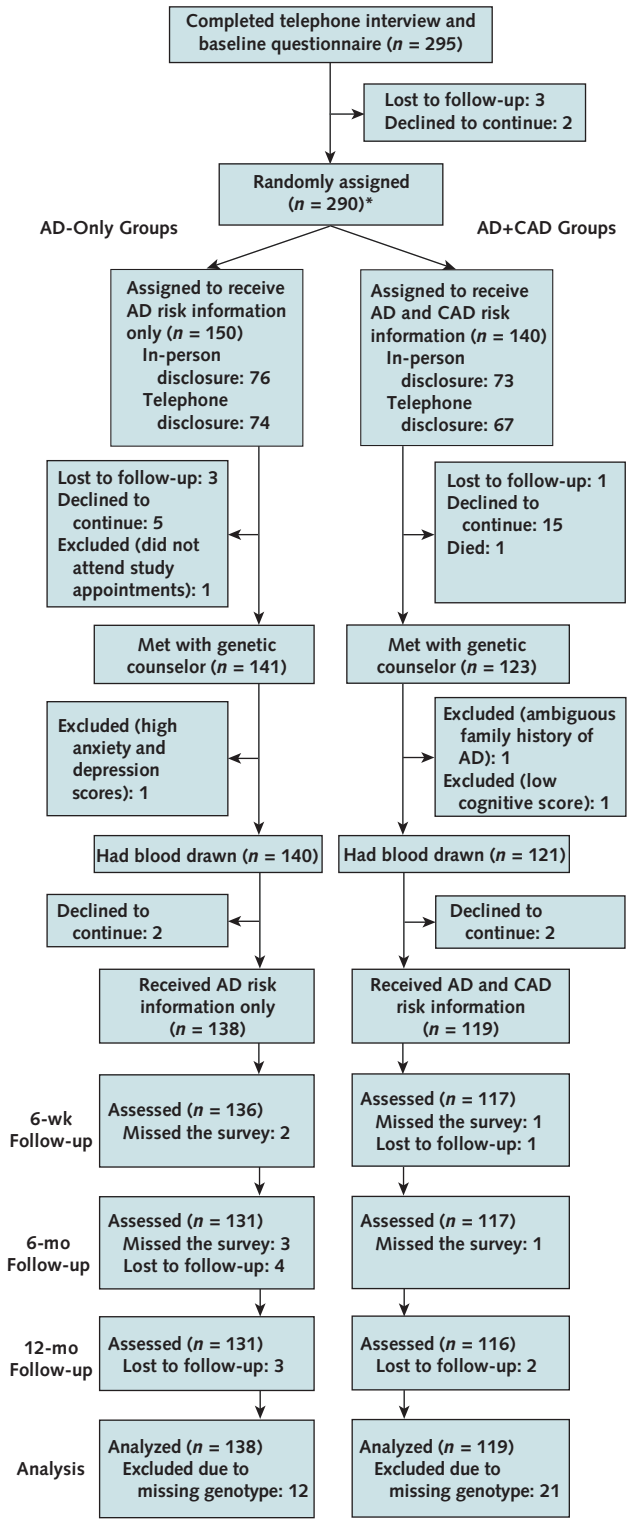
Outcomes were assessed at 6 weeks, 6 months, and 12 months after disclosure, as summarized in Appendix Table 1 (available at www.annals.org). Primary outcomes were scores at 12 months on the Beck Anxiety Inventory (BAI) (33) and the Center for Epidemiologic Studies Depression Scale (CES-D) (34), which are validated scales for measuring anxiety and depression. Scores on the BAI range from 0 to 63 (9 to 15 = mild, 16 to 25 = moderate, and >25 = severe), and CES-D scores range from 0 to 60 (11 to 16 = mild, 17 to 26 = moderate, and >26 = severe) (35). Secondary outcomes included 6-week, 6-month, and time-averaged anxiety and depression scores, as well as test-related distress specific to the genetic risk assessment at all time points, which was measured with the Impact of Event Scale (IES) (36, 37), with scores ranging from 0 to 75 (≥20 = significant distress). For safety purposes, an ESB-approved plan required immediate interview of participants whose BAI or CES-D scores exceeded 25 or 26, respectively, or increased by more than 15 points from baseline.

Secondary outcomes also included changes to health behaviors (diet, exercise, medications, dietary supplements, stress reduction, and mental activities) at 12 months. At 6 weeks, participants were asked, "Since you learned your *APOE* test results, have you made any health or wellness changes?" Participants who responded affirmatively answered additional questions about the types of behavior change they had initiated. At 12 months, participants were asked whether they had continued the changes reported at 6 weeks and were asked about additional changes initiated since the 6-week survey. Participants were coded as having made a health behavior change at 12 months if they continued a behavior reported at 6 weeks or if they initiated a behavior between the 6-week and 12-month surveys. Physical activity was assessed using the Rapid Assessment of Physical Activity (38), which scored participants on a scale of 1 to 7 for aerobic activity and 0 to 3 for strength and flexibility training. Smoking status was assessed at baseline and 12 months by asking participants whether they had smoked within the prior 7 days. To assess recall of pleiotropic information, each follow-up survey asked participants in the AD+CAD groups, "What other disease did we tell you is associated with the *APOE* gene?"

Statistical Analysis

We estimated that 32 participants in each group would need to receive genetic risk disclosure to achieve 80% power to detect 5-point differences between the AD+CAD and AD-only groups (39). We set enrollment targets of 70 participants at each study site to enroll 280 total participants and to achieve 256 total disclosures (assuming dropout of approximately 10%).

Figure 1. Study flow diagram.



AD = Alzheimer disease; CAD = coronary artery disease.
* Second randomization occurred at this point to determine whether participants would receive in-person or telephone disclosure.

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The sample size was expanded to allow for subanalyses by *APOE* genotypes and demographic factors.

We used *t* tests and chi-square tests to compare demographic features and discontinuation rates in the AD-only and AD+CAD groups and participant variables associated with discontinuation. We initially designed the protocol using a superiority framework, but before seeing data and conducting analyses, we concluded that our scientific aims would be best served by the use of equivalence comparisons. Data for the telephone and in-person disclosure groups were pooled in analyses presented here because interactions between AD-only versus AD+CAD randomization status and in-person versus telephone disclosure randomization status were not observed (*P* values for tests of interactions were 0.18 for the BAI, 0.34 for the CES-D, and 0.68 for the IES; *P* values for tests of 3-way interactions between the treatment groups and time were all ≥0.40). Two participants who did not receive disclosure of genotype and AD risk and whose randomization status was mistakenly entered into the study database as AD-only were recoded as AD+CAD for analyses of study dropout.

We used longitudinal analyses for psychological outcomes, including all observed data and imputed data for the few missing observations from participants who received genetic risk disclosure. Because the distribution of these outcomes was skewed, we used generalized linear models fit with generalized estimating equations with a log link and a γ distribution to compare outcomes by AD-only versus AD+CAD randomization status. We used an autoregressive working correlation structure with robust SEs to account for repeated measures within participant. A value of 1 was added to all measures to shift the distribution away from zero. Models included terms for AD-only versus AD+CAD randomization status; time as a categorical variable; the interaction between time and randomization group; the corresponding baseline psychological measure, when applicable; and the genetic counselor providing disclosure. Additional analyses were further adjusted for age, sex, education, race, family history of AD, telephone or in-person disclosure, and *APOE* genotype. We used contrasts to compare randomization groups at specific time points and overall for a time-averaged comparison. Equivalence was defined using a margin of 5 points, per prior REVEAL Study trials (24, 25). We used 95% CIs based on recommendations to use CIs of $(1 - 2\alpha) \times 100\%$ for equivalence testing, with α equal to 2.5% (0.05/2) to account for multiple testing across 2 primary outcomes (40, 41). To be conservative and consistent across psychological outcomes, we also used 95% CIs for all secondary analyses. We evaluated whether interaction effects existed between AD-only versus AD+CAD randomization status and *APOE* genotype because pleiotropic information might concern participants only if they are at increased risk for both diseases. We used the model described earlier and added variables for the *APOE* ε4 allele, its interaction with time, its interaction with pleiotropy randomization group, and the interaction among all three. From these analyses, we also obtained results for each *APOE* stratum for secondary analyses comparing pleiotropy groups. In addition, we used contrasts from these models to estimate the differences between carriers and noncarriers of the *APOE* ε4 allele within randomization groups.

Secondary analyses tested for differences in rates of change in health behaviors and physical activity levels between the AD-only and AD+CAD groups and by *APOE* status. We compared rates of changes in health behaviors between groups by using logistic regression, allowing for the interaction with *APOE* genotype and adjusting for the genetic counselor providing disclosure. We compared changes in physical activity levels between groups by using multiple linear regression, with adjustment for *APOE* genotype and the genetic counselor providing disclosure. Changes to smoking status were assessed but are not reported because only 13 current smokers were enrolled.

Because *APOE* genotypes could not be reliably imputed, analyses included only participants receiving genetic risk information. Genotype data for participants who provided blood but dropped out of the study before the disclosure session were destroyed, per the protocol approved by the institutional review board. Two participants in the AD-only groups and 2 in the AD+CAD groups were excluded from the analysis for this reason. Twenty of the remaining 257 participants were missing BAI, CES-D, and IES scores. We assumed data were missing at random and imputed missing values for these outcomes by using multiple imputation

Table 1. Characteristics of Participants Who Received Genetic Risk Disclosure

Characteristic	Randomization Group	
	AD-Only (*n* = 138)	AD+CAD (*n* = 119)
Age, *y*		
Mean (SD)	58.2 (12.4)	58.2 (13.6)
Range	27–82	21–83
Female, *n (%)*	76 (55)	65 (55)
African American, *n (%)**	29 (21)†	9 (8)†
Education, *y*		
Mean (SD)	16.8 (2.2)	16.8 (2.4)
Range	12–20	10–20
Currently married, *n (%)*	81 (59)	72 (61)
Mean BAI score (SD)	3.8 (3.6)	3.2 (3.3)
Mean CES-D score (SD)	6.0 (5.3)	5.3 (4.8)
Site, *n (%)*		
Boston, Massachusetts	42 (30)	36 (30)
Cleveland, Ohio	34 (25)	30 (25)
Ann Arbor, Michigan	33 (24)	35 (29)
Washington, DC	29 (21)	18 (15)
Parent or sibling with AD, *n (%)*	93 (67)	85 (71)
APOE ε4 carrier, *n (%)*	51 (37)	32 (27)
Current heart disease/previous myocardial infarction, *n (%)*	9 (7)	13 (11)
Current smoker, *n (%)*	8 (6)	5 (4)

AD = Alzheimer disease; *APOE* = apolipoprotein E; BAI = Beck Anxiety Inventory; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression Scale.
* Self-reported.
† $P < 0.01$.

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(Markov-chain Monte Carlo procedures with 40 imputed data sets [Appendix 2, available at www.annals.org]). All analyses were conducted using SAS, version 9.3 (SAS Institute).

Role of the Funding Source

This study was funded by the National Human Genome Research Institute of the National Institutes of Health, which had no role in the design of the study; collection, analysis, or interpretation of the data; writing, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Of 290 participants randomly assigned, 257 (89%) received genetic risk disclosure (Figure 1). Four participants were screened out (1 had a cognitive score below the eligibility criterion, 1 had a high depression score, 1 had an ambiguous family history of AD, and 1 did not attend study appointments). Other than race, demographic characteristics did not vary between the AD-only and AD+CAD groups (Table 1) and were similar to those in our previous trials (24, 29), except for the deliberate inclusion of participants without an affected first-degree relative. Genetic counselors communicated results to between 9 and 82 participants each and did not differ statistically in their likelihood of being randomly assigned to disclose AD-only or AD+CAD information ($P = 0.58$). Dropout before disclosure occurred in 8% of AD-only participants and 15% of AD+CAD participants ($P = 0.061$). Participants were more likely to drop out if they were younger ($P = 0.003$), female ($P = 0.009$), unmarried ($P = 0.028$), and less educated ($P < 0.001$), independent of randomization status (Appendix Table 2, available at www.annals.org). At all time points, a high proportion of AD+CAD participants (81.3% at 6 weeks, 86.4% at 6 months, and 84.4% at 12 months) recalled receiving risk information about the association between *APOE* genotype and CAD.

Anxiety, Depression, and Test-Related Distress

Mean anxiety, depression, and test-related distress scores were below cutoffs for mood disorders regardless of disclosure protocol, at all time points, and when time-averaged (Table 2). All 95% confidence bounds for between-group differences were within a margin of ±5 points. Equivalence was also supported in adjusted analyses (Appendix Table 3, available at www.annals.org). Interactions between randomization status and time were not observed ($P \geq 0.57$ for BAI; $P \geq 0.07$ for CES-D; $P \geq 0.26$ for IES).

Results on psychological scales by *APOE* group are presented in Table 3. Anxiety and depression scores remained well below cutoffs for concern regardless of *APOE* ε4 status, and 95% confidence bounds for mean differences between the AD-only and AD+CAD groups for each *APOE* genotype were within a margin of ± 5 points at all time points. However, among carriers of the *APOE* ε4 allele, mean IES scores were lower at 12 months in the AD+CAD groups than in the AD-only groups, whereas mean IES scores did not differ among noncarriers (mean difference, −4.8 [95% CI, −8.6 to −1.0] for carriers and 0.6 [CI, −1.1 to 2.2] for noncarriers; $P = 0.031$ for interaction). Differences by *APOE* status were also observed at 6 months, when anxiety was modestly lower after receipt of AD+CAD information among *APOE* ε4 carriers and modestly higher among noncarriers (mean difference, −1.8 [CI, −3.2 to −0.4] for carriers and 1.1 [CI, 0.1 to 2.0] for noncarriers; $P = 0.004$ for interaction). Findings from analyses stratified by *APOE* status were supported in adjusted analyses (Appendix Table 4, available at www.annals.org).

Table 2. Mean Anxiety, Depression, and Test-Related Distress Scores, by Randomization Group and Time After *APOE* Genotype Disclosure*

Variable	AD-Only ($n = 138$)	AD+CAD ($n = 119$)	Difference (95% CI)
12-mo outcomes			
BAI†	3.5	3.5	0.0 (−1.0 to 1.0)
CES-D‡	6.4	7.1	0.7 (−1.0 to 2.4)
IES§	4.0	2.6	−1.4 (−3.3 to 0.5)
6-mo outcomes			
BAI†	2.9	3.0	0.1 (−0.7 to 1.0)
CES-D‡	6.0	5.2	−0.8 (−2.3 to 0.7)
IES§	4.1	3.5	−0.6 (−2.5 to 1.4)
6-wk outcomes			
BAI†	3.0	3.0	0.0 (−0.8 to 0.7)
CES-D‡	5.7	5.3	−0.4 (−1.8 to 1.0)
IES§	4.4	3.8	−0.6 (−2.6 to 1.4)
Time-averaged outcomes			
BAI†	3.1	3.2	0.0 (−0.7 to 0.7)
CES-D‡	6.0	5.8	−0.2 (−1.4 to 1.0)
IES§	4.2	3.3	−0.9 (−2.6 to 0.8)

AD = Alzheimer disease; *APOE* = apolipoprotein E; BAI = Beck Anxiety Inventory; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; IES = Impact of Event Scale.
* Scores were estimated using generalized estimating equations with log link and γ distribution, with adjustment for corresponding baseline values and the genetic counselor providing disclosure.
† Scores range from 0 to 63; higher scores indicate greater anxiety.
‡ Scores range from 0 to 60; higher scores indicate greater depression.
§ Scores range from 0 to 75; higher scores indicate greater distress.

Overall, 24% of study participants reported moderate anxiety, depression, or test-related distress at one or more follow-up time points, with no differences between the AD-only and AD+CAD groups over time ($P = 0.53$). As in prior REVEAL Study trials (24, 25), mean IES scores were greater among *APOE* ε4 carriers than among noncarriers in the AD-only groups (12-month mean difference, 3.8 [CI, 0.7 to 6.9]), whereas differences in mean depression scores by ε4 status within AD-only groups were not observed (12-month mean difference, 1.6 [CI, −0.9 to 4.0]). Anxiety scores were higher among *APOE* ε4 carriers than among noncarriers in the AD-only groups (12-month mean difference, 1.9 [CI, 0.1 to 3.7]). No differences were noted by ε4 status in the AD+CAD groups.

Health Behavior Responses

Among all participants, 57% reported changing at least 1 health behavior at 12 months in response to

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Table 3. Mean Anxiety, Depression, and Test-Related Distress Scores, by Randomization Group, *APOE* Status, and Time After *APOE* Genotype Disclosure*

Variable	*APOE* ε4 Noncarriers			*APOE* ε4 Carriers			*P* Value for Interaction
	AD-Only (*n* = 87)	AD+CAD (*n* = 87)	Difference (95% CI)†	AD-Only (*n* = 51)	AD+CAD (*n* = 32)	Difference (95% CI)†	
12-mo outcomes							
BAI‡	2.8	3.6	0.9 (−0.2 to 2.0)	4.8	3.1	−1.7 (−3.5 to 0.1)	0.048
CES-D§	5.5	6.8	1.3 (−0.5 to 3.1)	7.8	7.7	−0.1 (−3.6 to 3.4)	0.137
IES‖	2.1	2.7	0.6 (−1.1 to 2.2)	7.1	2.3	−4.8 (−8.6 to −1.0)	0.031
6-mo outcomes							
BAI‡	2.3	3.4	1.1 (0.1 to 2.0)	3.8	2.0	−1.8 (−3.2 to −0.4)	0.004
CES-D§	5.5	5.5	0.0 (−1.7 to 1.7)	6.9	4.6	−2.3 (−4.8 to 0.2)	0.29
IES‖	2.4	3.0	0.7 (−1.3 to 2.6)	7.0	4.7	−2.3 (−5.9 to 1.4)	<0.001
6-wk outcomes							
BAI‡	2.8	2.9	0.2 (−0.8 to 1.1)	3.4	3.1	−0.3 (−1.6 to 1.0)	0.67
CES-D§	5.9	5.6	−0.3 (−2.1 to 1.5)	5.3	4.6	−0.7 (−2.7 to 1.3)	0.60
IES‖	2.5	3.6	1.1 (−0.7 to 2.9)	7.7	4.3	−3.4 (−7.2 to 0.5)	0.002
Time-averaged outcomes							
BAI‡	2.6	3.3	0.7 (−0.1 to 1.5)	4.0	2.7	−1.3 (−2.3 to −0.2)	0.006
CES-D§	5.6	5.9	0.3 (−1.0 to 1.7)	6.6	5.5	−1.1 (−3.1 to 0.9)	0.23
IES‖	2.3	3.1	0.8 (−0.7 to 2.3)	7.2	3.6	−3.6 (−7.0 to −0.2)	0.005

AD = Alzheimer disease; *APOE* = apolipoprotein E; BAI = Beck Anxiety Inventory; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; IES = Impact of Event Scale.
* Scores were estimated using generalized estimating equations with log link, γ distribution, and robust SEs, with adjustment for baseline values and the genetic counselor providing disclosure.
† Mean scores among participants in AD+CAD groups minus mean scores among those in AD-only groups.
‡ Scores range from 0 to 63; higher scores indicate greater anxiety.
§ Scores range from 0 to 60; higher scores indicate greater depression.
‖ Scores range from 0 to 75; higher scores indicate greater distress.

genetic risk disclosure. The proportions reporting specific health behavior changes are shown in **Appendix Table 5** (available at www.annals.org). Participants in the AD+CAD groups were more likely than those in the AD-only groups to report changes to most queried health behaviors, and differences were independent of *APOE* genotype (**Figure 2**). Among the 36 participants who reported a medication change, 9 (25%) made a change related to CAD (such as blood pressure or cholesterol medications or fiber supplements). Secondary analyses also showed that *APOE* ε4 carriers were more likely than noncarriers to report changes in all health behavior outcomes (**Appendix Table 5**). Differences were not observed between the AD+CAD and AD-only groups on 12-month aerobic activity scores (mean difference, 0.34 [CI, −0.09 to 0.76]) or strength and flexibility scores (mean difference, −0.01 [CI, −0.35 to 0.33]). Of note, 33% of participants in the AD+CAD groups reported sharing results with a health professional compared with 22% of those in the AD-only groups ($P = 0.063$).

DISCUSSION

We report a randomized trial of disclosure of pleiotropic risk information during genetic risk assessment for AD. Responses on the primary outcomes of anxiety and depression were equivalent between participants receiving information on AD risk plus secondary information on CAD risk and those receiving information on AD risk only, with no differences in mean scores at any time point and CIs within conservative margins for clinical significance. However, participants at increased risk for disease (*APOE* ε4 carriers) seemed to experience less test-related distress at 12 months if they also received CAD information. Most other studies on the subject have shown no effect of genetic risk disclosure on general measures of mood but occasional short-term increases in test-related distress among persons at increased risk for disease (42). Our results build on those findings by suggesting that "positive pleiotropic disclosure" (the disclosure of unsolicited risk information about a modifiable condition, such as CAD) may reduce distress in patients receiving risk information about a less readily modifiable condition, such as AD. These findings prompt the interesting speculation that worry about medically nonactionable genetic risk results may be mitigated by simultaneous receipt of actionable genetic risk results. Our study did not address "negative pleiotropic disclosure," such as choosing to learn *APOE* genotype for CAD risk and incidentally discovering its implications for AD risk, which could have yielded different results.

Nearly every health behavior we assessed improved in response to the AD+CAD information, regardless of *APOE* status. The statement about strategies to reduce CAD risk, which was given to all participants in the AD+CAD groups, may explain differences in reported changes in health behavior. However, participants receiving AD+CAD information were more likely to report sharing results with a health pro-

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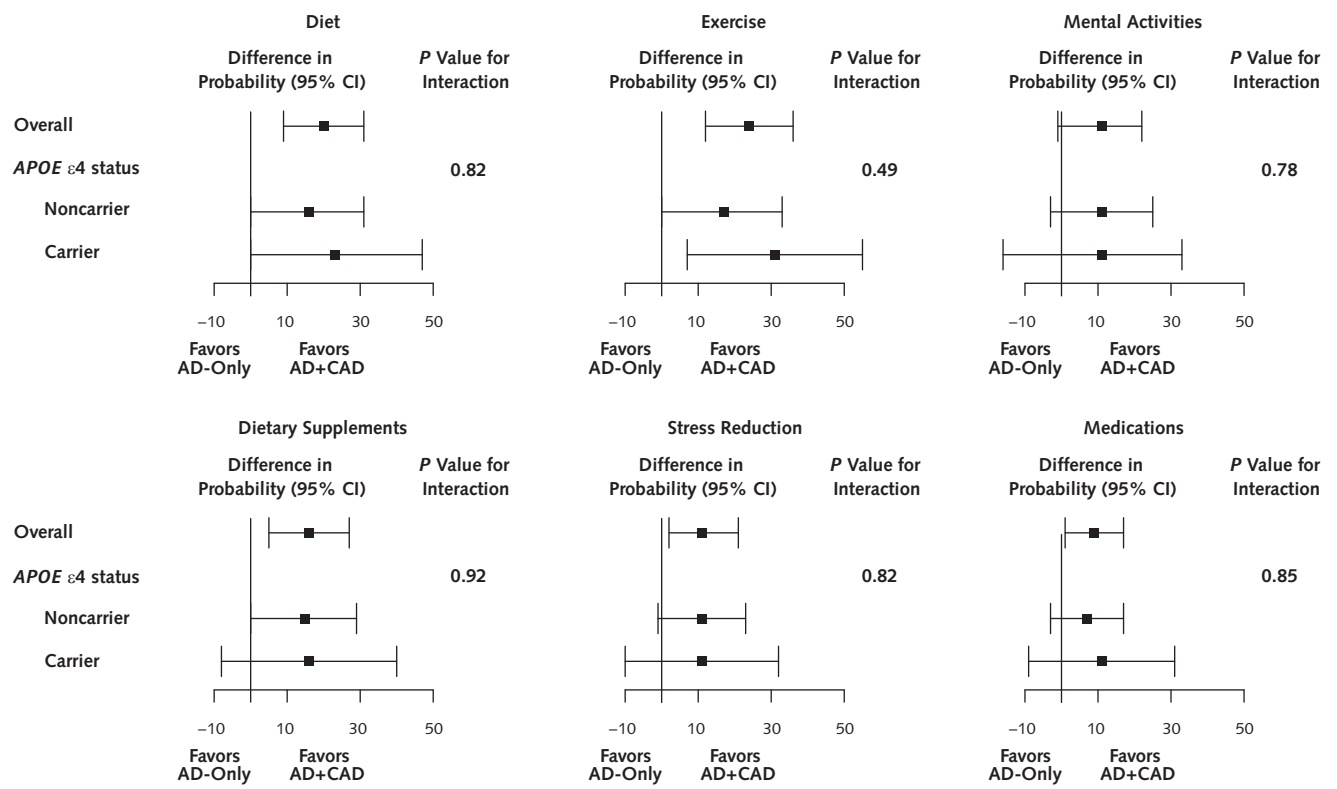
fessional, who may have in turn encouraged health behavior changes. Pleiotropic disclosure may also have prompted persons who had been focused on AD to attend to CAD, a more modifiable and prevalent condition. Carriers of the *APOE* ε4 allele in both randomization groups were more likely than noncarriers to report changes to all health behaviors despite receiving education that highlighted a lack of proven options to reduce AD risk. Learning about an increased risk for AD and addressing pleiotropic outcomes may motivate persons to be healthier in general rather than motivating them to take steps to reduce risk for a specific disease.

Our participants were generally well-educated persons who volunteered for genetic risk assessment for AD, were not representative of the general population, and were more likely to have known about associations between *APOE* genotype and CAD independent of our study. This study focused on disclosure of pleiotropic information during single-gene testing for AD, and the results may not be generalizable to other conditions or to methods that can explore broader sets of genetic variants and diseases, such as genomic sequencing. Our study excluded one person with a low cognitive score and one with severe depression, raising the possibility that results could differ among more vulnerable populations. We also omitted 33 randomly assigned participants who dropped out of the study before being genotyped. Self-reported outcomes, particularly those measuring health behaviors, are subject to bias due to participants responding in ways they believe investigators want them to (43). Some of our health behavior measures have not been validated and do not provide insight about whether changes were clinically meaningful, although our physical activity measure has demonstrated validity for older adults (38). Finally, clinical outcomes associated with health behavior measures (such as weight loss) were not assessed.

Our study examined only one strategy for communicating associations between *APOE* status and CAD. Because of questions about the strength of the relationship between *APOE* genotype and CAD at the time of our study, we deliberately omitted quantified risk estimates for CAD from our disclosure statement that may have made pleiotropic disclosure more impactful. Indeed, meta-analyses published during our study sug-

Figure 2. Between-group differences (AD+CAD minus AD-only) in the proportion of participants reporting health behavior changes 12 mo after genetic risk disclosure.



Estimates are from an analysis using logistic regression and accounting for *APOE* status, its interaction with pleiotropy randomization group, and the genetic counselor providing disclosure (except for stress reduction, for which genetic counselor was omitted because some combinations of randomization status, *APOE* status, and genetic counselor had no events). Adjusted percentages are conditional probabilities estimated from the logistic model with all covariates set to their mean values (lsmeans statement in SAS). *P* values for interactions correspond to the *P* values from the interaction terms for randomization group by *APOE* status. The unadjusted numbers of participants reporting changes were 86 for diet, 91 for exercise, 76 for mental activities, 71 for dietary supplements, 57 for stress reduction, and 37 for medications. AD = Alzheimer disease; *APOE* = apolipoprotein E; CAD = coronary artery disease.

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gest that increased CAD risk among *APOE* ε4 carriers may be modest (23). In addition, *APOE* genotype may be associated with other neurologic and ocular disorders (44), further complicating the issue. As the field transitions to technologies that identify a wider array of secondary and incidental genomic findings, laboratories and clinicians will need to make difficult decisions about what kinds of findings merit disclosure and how to provide it.

Nevertheless, our data support the safety of disclosing secondary pleiotropic information about a modifiable condition, such as CAD, during genetic risk assessment for AD and counterintuitively suggest that such disclosure may mitigate test-related distress among persons who learn that they are at increased risk for not 1, but 2 life-threatening conditions.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Green (e-mail, rcgreen@genetics.med.harvard.edu).

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Appendix 1: Additional REVEAL Study Group Members

All persons named in the byline were authors and were members of the REVEAL Study team at one point during the preparation of the manuscript. The following persons are additional members of the REVEAL Study team and were nonauthor contributors to the manuscript: Deborah Blacker, Massachusetts General Hospital/Harvard Medical School and Harvard School of Public Health, Boston, Massachusetts; Clara Chen, Boston University School of Public Health, Boston, Massachusetts; Elana Cox, Weill Cornell Medical College, New York, New York; Jessica Davis, Weill Cornell Medical College, New York, New York; Lindsay Farrer, Boston University School of Medicine and Boston University School of Public Health, Boston, Massachusetts; Patrick Griffith, Morehouse School of Medicine, Atlanta, Georgia; Kristin Harkins, Perelman School of Medicine, Philadelphia, Pennsylvania; Megan Johnson, Howard University, Washington, DC; Stephanie Johnson, Howard University, Washington, DC; Eric Juengst, University of North Carolina School of Medicine, Chapel Hill, North Carolina; Jason Karlawish, Perelman School of Medicine, Philadelphia, Pennsylvania; Denise Perry, Brigham and Women's Hospital, Boston, Massachusetts; Lan Le, University of Michigan School of Public Health, Ann Arbor, Michigan; Elana Levison, Division of Genetics, New York Presbyterian Hospital, New York, New York; Elisabeth McCarty Wood, Perelman School of Medicine, Philadelphia, Pennsylvania; Stephen Post, Stony Brook University, Stony Brook, New York; Kimberly Quaid, Indiana University School of Medicine, Indianapolis, Indiana; Lisa Ravdin, Weill Cornell Medical College, New York, New York; Norman Relkin, Weill Medical College of Cornell University, New York, New York; Debra Roter, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Robert Stern, Boston University School of Medicine, Boston, Massachusetts; A. Dessa Sadovnick, University of British Columbia, Vancouver, British Columbia, Canada; Susan Sami, Case Western Reserve University, Cleveland, Ohio; Pamela Sankar, Perelman School of Medicine, Philadelphia, Pennsylvania; Leo Waterston, Brigham and Women's Hospital, Boston, Massachusetts; and Lori Wright, Medical College of Georgia, Athens, Georgia.

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Appendix 2: Methods for Imputation

We assumed data were missing at random and imputed missing values for these outcomes into 40 data sets using Markov-chain Monte Carlo procedures that assumed data were sampled from a multivariate normal distribution, generated the initial parameter estimate from the expectation maximum algorithm, and used different chains for each imputation. For dichotomous health behavior outcomes (13 participants had missing responses), we used fully conditional specification procedures that implemented a logistic regression model to impute missing values (45). The Markov-chain Monte Carlo and fully conditional specification procedures were implemented in PROC MI in SAS, version 9.3. For imputation of missing variables, 40 imputed data sets were created and the following variables were included in the imputation process: observed outcomes, AD-only versus AD+CAD randomization status, race, *APOE* status, age, sex, education, AD family history, genetic counselor, and telephone versus in-person disclosure randomization status.

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Appendix Table 1. Study Outcomes and Analytic Overview

Outcome	Comparison	Time Point	Instrument	Range	Test
Primary analyses: psychological outcomes					
Anxiety	Randomization	12 mo	BAI	0–63	Equivalence (±5 points)
Depression	Randomization	12 mo	CES-D	0–60	Equivalence (±5 points)
Secondary analyses: psychological outcomes					
Anxiety	Randomization	6 wk, 6 mo, time-averaged	BAI	0–63	Equivalence (±5 points)
Depression	Randomization	6 wk, 6 mo, time-averaged	CES-D	0–60	Equivalence (±5 points)
Test-related distress	Randomization	All	IES	0–75	Equivalence (±5 points)
Anxiety	*APOE* status	All	BAI	0–63	Superiority
Depression	*APOE* status	All	CES-D	0–60	Superiority
Test-related distress	*APOE* status	All	IES	0–75	Superiority
Secondary analyses: behavioral outcomes					
Health behavior change	Randomization	12 mo	Created	Yes/no	Superiority
Health behavior change	*APOE* status	12 mo	Created	Yes/no	Superiority
Aerobic activity	Randomization	12 mo	RAPA	1–7	Superiority
Strength and flexibility	Randomization	12 mo	RAPA	0–3	Superiority

APOE = apolipoprotein E; BAI = Beck Anxiety Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; IES = Impact of Event Scale; RAPA = Rapid Assessment of Physical Activity.

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Appendix Table 2. Characteristics of Randomly Assigned Participants Who Did and Did Not Receive Genetic Risk Disclosure

Characteristic	Randomly Assigned, No Disclosure			Randomly Assigned, Disclosure			*P* Value*
	AD-Only (*n* = 12)	AD+CAD (*n* = 21)	Total (*n* = 33)	AD-Only (*n* = 138)	AD+CAD (*n* = 119)	Total (*n* = 257)	
Age, *y*							
Mean (SD)	47.9 (11.3)	52.9 (13.2)	51.1 (12.6)	58.2 (12.4)	58.2 (13.6)	58.2 (12.9)	0.003
Range	21–67	29–77	21–77	27–82	21–83	21–83	
Female, *n (%)*	9 (75)	17 (81)	26 (79)	76 (55)	65 (55)	141 (55)	0.009
African American, *n (%)*	3 (25)	6 (29)	9 (27)	29 (21)	9 (8)	38 (15)	0.067
Education, *y*							
Mean (SD)	14.2 (2.0)	15.5 (2.7)	15.0 (2.5)	16.8 (2.2)	16.8 (2.4)	16.8 (2.3)	<0.001
Range	11–18	12–20	11–20	12–20	10–20	10–20	
Currently married, *n (%)*	4 (33)	9 (43)	13 (39)	81 (59)	72 (61)	153 (60)	0.028
Site, *n (%)*							0.215
Boston, Massachusetts	3 (25)	5 (24)	8 (24)	42 (30)	36 (30)	78 (30)	
Cleveland, Ohio	2 (17)	6 (29)	8 (24)	34 (25)	30 (25)	64 (25)	
Ann Arbor, Michigan	4 (33)	2 (10)	6 (18)	33 (24)	35 (29)	68 (26)	
Washington, DC	3 (25)	8 (38)	11 (33)	29 (21)	18 (15)	47 (18)	
Current smoker, *n (%)*	3 (25)	1 (5)	4 (12)	8 (6)	5 (4)	13 (5)	0.104

AD = Alzheimer disease; CAD = coronary artery disease.
* Comparison of all randomly assigned, no-disclosure participants with all randomly assigned participants who received disclosure. Within-group analyses of randomly assigned, no-disclosure participants showed no differences by randomization group. Within-group analyses of randomly assigned participants who received disclosure showed no differences by randomization group, except by race ($P = 0.002$).

Appendix Table 3. Mean Adjusted Anxiety, Depression, and Test-Related Distress Scores, by Randomization Group, Stratified by Outcome and Time After *APOE* Genotype Disclosure*

Variable	AD-Only (*n* = 138)	AD+CAD (*n* = 119)	Difference (95% CI)
12-mo outcomes			
BAI†	3.5	3.4	−0.1 (−1.1 to 0.8)
CES-D‡	6.3	6.9	0.6 (−0.9 to 2.2)
IES§	4.1	2.6	−1.5 (−3.2 to 0.2)
6-mo outcomes			
BAI†	2.9	3.0	0.1 (−0.7 to 0.9)
CES-D‡	6.0	5.2	−0.8 (−2.3 to 0.7)
IES§	4.1	3.4	−0.7 (−2.3 to 0.9)
6-wk outcomes			
BAI†	3.0	3.0	−0.1 (−0.9 to 0.7)
CES-D‡	5.7	5.2	−0.4 (−1.7 to 0.9)
IES§	4.3	3.6	−0.7 (−2.4 to 1.0)
Time-averaged outcomes			
BAI†	3.1	3.1	0.0 (−0.7 to 0.7)
CES-D‡	6.0	5.7	−0.2 (−1.4 to 0.9)
IES§	4.2	3.2	−1.0 (−2.4 to 0.5)

AD = Alzheimer disease; *APOE* = apolipoprotein E; BAI = Beck Anxiety Inventory; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; IES = Impact of Event Scale.
* Scores were estimated using generalized estimating equations with log link, γ distribution, and robust SEs, with adjustment for corresponding baseline values, *APOE* status, age, education, sex, race, family history of AD, telephone vs. in-person disclosure randomization status, and the genetic counselor providing disclosure.
† Scores range from 0 to 63; higher scores indicate greater anxiety.
‡ Scores range from 0 to 60; higher scores indicate greater depression.
§ Scores range from 0 to 75; higher scores indicate greater distress.

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Appendix Table 4. Mean Anxiety, Depression, and Test-Related Distress Scores, by Randomization Group, *APOE* Status, and Time After *APOE* Genotype Disclosure*

Variable	*APOE* ε4 Noncarriers			*APOE* ε4 Carriers		
	AD-Only (*n* = 87)	AD+CAD (*n* = 87)	Difference† (95% CI)	AD-Only (*n* = 51)	AD+CAD (*n* = 32)	Difference† (95% CI)
12-mo outcomes						
BAI‡	2.8	3.5	0.7 (−0.3 to 1.7)	4.7	3.0	−1.7 (−3.6 to 0.1)
CES-D§	5.7	6.5	0.8 (−0.8 to 2.4)	7.2	8.0	0.8 (−2.6 to 4.1)
IES‖	2.7	2.7	0.0 (−1.7 to 1.8)	6.5	2.1	−4.4 (−7.5 to −1.3)
6-mo outcomes						
BAI‡	2.4	3.3	0.9 (0.0 to 1.9)	3.7	2.0	−1.7 (−3.0 to −0.5)
CES-D§	5.7	5.4	−0.3 (−2.0 to 1.4)	6.6	4.8	−1.8 (−4.3 to 0.8)
IES‖	2.7	2.9	0.3 (−1.3 to 1.9)	6.5	4.3	−2.2 (−5.4 to 1.0)
6-wk outcomes						
BAI‡	2.8	2.9	0.1 (−0.9 to 1.0)	3.3	3.0	−0.3 (−1.5 to 1.0)
CES-D§	6.0	5.5	−0.6 (−2.2 to 1.1)	4.9	4.5	−0.4 (−2.2 to 1.5)
IES‖	2.7	3.4	0.7 (−1.0 to 2.3)	6.9	3.8	−3.1 (−6.5 to 0.4)
Time-averaged outcomes						
BAI‡	2.7	3.2	0.6 (−0.2 to 1.4)	3.8	2.6	−1.2 (−2.3 to −0.2)
CES-D§	5.8	5.8	0.0 (−1.3 to 1.3)	6.2	5.6	−0.6 (−2.5 to 1.4)
IES‖	2.7	3.0	0.3 (−1.1 to 1.7)	6.6	3.3	−3.3 (−6.1 to −0.5)

AD = Alzheimer disease; *APOE* = apolipoprotein E; BAI = Beck Anxiety Inventory; CAD = coronary artery disease; CES-D = Center for Epidemiologic Studies Depression Scale; IES = Impact of Event Scale.
* Scores were estimated using generalized estimating equations with log link and γ distribution, with adjustment for baseline values (where applicable), *APOE* status, age, education, sex, race, family history of AD, telephone vs. in-person disclosure randomization status, and the genetic counselor providing disclosure.
† Mean scores among participants in AD+CAD groups minus mean scores among those in AD-only groups.
‡ Scores range from 0 to 63; higher scores indicate greater anxiety.
§ Scores range from 0 to 60; higher scores indicate greater depression.
‖ Scores range from 0 to 75; higher scores indicate greater distress.

Appendix Table 5. Participants Self-Reporting Health Behavior Changes 12 mo After Genetic Risk Disclosure, by Randomization Group and *APOE* Status*

Variable	*APOE* ε4 Noncarriers		*APOE* ε4 Carriers		Difference	
	AD-Only (*n* = 87)	AD+CAD (*n* = 87)	AD-Only (*n* = 51)	AD+CAD (*n* = 32)	AD+CAD vs. AD-Only†	Carriers vs. Noncarriers‡
Diet	21 (12 to 31)	37 (25 to 49)	38 (23 to 79)	61 (43 to 79)	20 (9 to 31)	21 (10 to 32)
Exercise	22 (11 to 32)	38 (25 to 51)	29 (14 to 43)	59 (40 to 79)	24 (12 to 36)	14 (2 to 26)
Mental activities	18 (9 to 28)	29 (18 to 41)	42 (27 to 57)	51 (32 to 70)	11 (−1 to 22)	23 (13 to 33)
Dietary supplements	17 (8 to 26)	31 (20 to 43)	35 (21 to 50)	51 (32 to 70)	16 (5 to 27)	20 (9 to 30)
Stress reduction	14 (6 to 21)	25 (16 to 34)	24 (11 to 36)	35 (18 to 51)	11 (2 to 21)	10 (1 to 19)
Medications	6 (1 to 12)	13 (5 to 21)	14 (4 to 25)	26 (9 to 43)	9 (1 to 17)	10 (2 to 19)

AD = Alzheimer disease; *APOE* = apolipoprotein E; CAD = coronary artery disease.
* Values are percentages (95% CIs). Percentages were estimated using logistic regression models, with adjustment for the genetic counselor providing disclosure (except for stress reduction, where genetic counselor was omitted because some combinations of randomization status, *APOE* status, and genetic counselor had no events).
† Estimated percentages among participants in AD+CAD groups minus estimated percentages among those in AD-only groups.
‡ Estimated percentages among *APOE* ε4 carriers minus estimated percentages among noncarriers.

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