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Effect of Alzheimer disease genetic risk disclosure on dietary supplement use[1–4]

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ABSTRACT

Background: Genetic susceptibility testing for Alzheimer disease (AD) with *APOE* genotype disclosure is not recommended for clinical use but is available through direct-to-consumer (DTC) genetic testing companies. Little is known about whether *APOE* genotype disclosure would actually prompt changes in nutrition behaviors among at-risk individuals.

Objective: We studied the effect of *APOE* genotype disclosure for AD risk assessment on dietary supplement use in adults with a family history of AD.

Design: As part of a secondary analysis of data from the second Risk Evaluation and Education for Alzheimer's Disease Study, we examined the effect of genotype disclosure on health-behavior changes among 272 unaffected first-degree relatives of persons with AD.

Results: Overall, 16% of all participants reported a change in dietary supplement use after AD risk assessment. Participants who learned that they had at least one copy of the risk-increasing *ε4* allele (*ε4*+) had 4.75 times the odds of reporting a change in dietary supplement use than did their counterparts who had an absence of the risk-increasing *ε4* allele (*ε4*−) (95% CI: 2.23, 10.10; $P < 0.0001$) after adjustment for age, sex, race, baseline supplement use, randomization arm, and educational level. There were no significant differences between *APOE ε4*+ and *ε4*− participants in changes in overall diet, exercise, or medications.

Conclusions: In this sample of first-degree relatives receiving genetic susceptibility testing for AD, an *APOE ε4*+ genotype status was positively associated with dietary supplement use after risk disclosure. Such changes occurred despite the absence of evidence that supplement use reduces the risk of AD. Given the expansion of DTC genetic tests, this study highlights the need for future studies in disease risk communication. *Am J Clin Nutr* 2010;91:1402–7.

INTRODUCTION

In recent years, the sequencing of the human genome has identified several susceptibility genes or genes with incomplete penetrance. Mutations in these genes may increase disease susceptibility but are not causative for disease. Genetic susceptibility testing allows unaffected individuals to obtain risk information for a variety of common complex diseases and health conditions including Alzheimer disease (AD), cancer, and diabetes (1, 2). The development of these complex diseases is dependent on genetic and nongenetic factors; therefore, genetic susceptibility tests can vary in predictability and validity. Individuals can directly purchase these genetic tests over the Internet through a growing number of direct-to-consumer (DTC) genetic testing companies (3, 4). This DTC initiative has been on the rise in recent years and remains controversial because of the lack of overall regulation, the wide variability in tests used, and the interpretation of results (5). Despite the recent rise in the popularity of personalized medicine, including DTC genetic testing, research regarding the effect of genetic testing on health behaviors is very limited. Examining dietary behaviors, especially dietary supplement consumption in particular, is of interest given the growing number of companies that use genetic risk information to market nutrigenetic-based products (including supplements and other nutraceuticals) that supposedly provide health benefits and/or disease risk reduction that are personalized for one's genetic makeup. The Government Accountability Office has issued a statement expressing concern about the quality of these products and showed that the majority of companies provided "personalized" advice that was either ambiguous or misleading (6).

According to data from a recent national survey (7), ≈20% of Americans consume some form of herbal supplement, a number that has dramatically increased in recent years. Supplements are marketed for everything from alleviating back pain to improving memory, despite the relative lack of evidence for these claims. For example, *Ginkgo biloba* is a botanic supplement commonly

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taken to improve memory and prevent dementia, but a recent clinical trial (8) reported that the administration of *G. biloba* supplements had no effect on the rate of progression of dementia and did not affect the overall incidence rate of dementia or AD. An emerging area for the marketing of dietary supplements is in partnership with DTC genetic testing. This marketing, combined with the limited regulation of the supplement industry, may lead to questionable choices being made by individuals looking to improve their quality of life or prevent future disease.

AD provides an instructive context in which to examine health-behavior changes, including dietary supplement use, after genetic risk assessment. Like many complex diseases, the development of AD depends on many genetic and nongenetic factors. Several susceptibility genes for AD were identified (9–11). The most well-studied susceptibility gene is *APOE*. The *APOE* gene has 3 allelic variations: *ε2*, *ε3*, and *ε4*, with the *ε4* allele conferring an increased risk of AD. The presence of 1 or 2 copies of the apolipoprotein *ε4* allele increases the risk of developing AD 5- to 15-fold, depending on the number of copies present (12) and was recently shown to impair cognition as early as childhood (13). The exact biological role that the *ε4* variant plays in the development of AD is not fully understood, but it was shown to vary on the basis of age, sex, and race (11, 12). Our previous work (14) suggested that individuals with a family history of AD who also have the *APOE ε4* allele, and therefore are at a higher risk of developing the disease, are nearly 3 times as likely to report making an AD-related health-behavior change than those who are *APOE ε4−* (14). This finding was based on a composite variable that encompassed changes in diet, exercise, supplements, and medications. The current study seeks to determine the effect of genotype risk disclosure on the use of dietary supplements.

SUBJECTS AND METHODS

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study is a series of multicenter randomized clinical trials that examine the effect of genetic risk assessment, including *APOE* genotype disclosure, in cognitively normal adults with a family history of AD. Details of the REVEAL Study, including the clinical trial rationale, study design, and other results, were described elsewhere (15–17). The current study uses data collected during the second REVEAL trial (REVEAL II), in which participants were enrolled between February 2003 and May 2005. Eligible participants were cognitively intact adult subjects with a first-degree relative who had been diagnosed with AD. All participants were randomly assigned to receive information about AD and genetic risk assessment in 1 of 2 ways: in an extended protocol involving an in-person education session with a PowerPoint presentation (Microsoft, Redmond, WA) and a pamphlet that participants could take home (the control group) or in a condensed protocol in which subjects were mailed identical information in the form of an educational brochure and participated in a general question-and-answer session (the intervention group). Participants were informed that AD is a complex condition, and disease development is dependent on several genetic and nongenetic factors. The primary outcomes of that trial will be reported elsewhere. The risk assessment involved disclosure of genotype by either genetic counselors or study physicians and individualized risk estimates for developing AD. These estimates were based on age-, sex-, race-, and *APOE* genotype–specific risk curves (18, 19). Participants were provided with their lifetime risk of developing AD (range: 13–77%; **Table 1**) and an age-adjusted remaining risk estimate. Graphical representations of these estimates were shown to subjects during the disclosure session. In addition to these risk curves, participants were reminded that a positive test result did not mean that they would develop AD, as there are genetic factors other than *APOE* that may increase risk. Participants in both protocol arms were specifically told, "There are many other factors that determine risk of AD, both genetic and environmental, that we are still learning about. Therefore, your risk estimate is an interpretation of your known risk factors and is based on our current knowledge."

For data-analysis purposes, participant data were grouped into 2 categories: participants who had an absence of the risk-increasing *ε4* allele (*ε4−*) and participants who had at least one copy of the risk-increasing *ε4* allele (*ε4+*). Participants who were *ε4+* received a lifetime AD risk estimate between 25% and 77%; participants who were *ε4−* received lifetime AD risk estimates from 13% to 41%, as shown in Table 1. Participants in the study were not given any information about current therapies under investigation for AD treatment or prevention. The effect of the information was tracked during 3 follow-up visits after disclosure at 6 wk and 6 and 12 mo. The development and administration of this protocol were overseen and approved by institutional review boards at each study site and an external advisory board.

In this study, participants received genetic risk assessment and *APO* genotype disclosure. Six weeks after disclosure, participants were asked yes/no questions on 8 items related to health-behavior changes made since learning their genotype status. For each item that was checked yes, participants were required to provide details in a free-text field. Specific questions focused on dietary changes, including changes in overall diet, and changes in the use of vitamins and botanicals. Participant responses were

TABLE 1
Alzheimer disease risk estimates on the basis of *APOE* genotype[1]

APOE genotype	Sex	Ethnicity	Lifetime risk
			%
ε2ε3	F	White	19
		African American	36
	M	White	13
		African American	33
ε3ε3	F	White	29
		African American	49
	M	White	18
		African American	41
ε2ε4	F	White	49
		African American	69
	M	White	25
		African American	48
ε3ε4	F	White	52
		African American	73
	M	White	29
		African American	56
ε4ε4	F	White	57
		African American	74
	M	White	56
		African American	77

evaluated and coded by using both check-box and open-ended questions. For analysis purposes, collected dietary data were collapsed into 2 categories: changes in overall diet (food-specific changes) and changes in dietary supplement use (all nonfood herbal supplements, vitamins, minerals, and antioxidants). JAV and CAC independently coded participant responses to open-ended questions into these categories where appropriate. Responses to the open-ended question regarding dietary supplements were further categorized as either vitamin (ie, vitamin E, vitamin C, and folate), nonvitamin (eg, fish oil), or botanical (eg, curcumin or green tea).

Data were analyzed with SAS software (SAS 9.1; SAS Institute, Cary, NC). Univariate chi-square tests were used to determine the relation between genotype and postdisclosure health-behavior changes. All significant relations determined by chi-square testing were included as covariates in the model. Logistic regression models were used to evaluate the effect of genetic disclosure on dietary choices, specifically regarding the initiation of dietary supplements. Endpoints were adjusted for age, sex, race randomization arm, baseline health behaviors, number of affected relatives, and education. Results are presented as adjusted odds ratios with 95% CIs, with significance determined at $P < 0.05$.

RESULTS

A total of 272 participants (97.5% of trial subjects) completed the 6-wk follow-up and answered the questions necessary for analysis. A description of subject characteristics is provided in **Table 2**. Overall, 26% ($n = 59$) of all participants reported changes in diet- and exercise-related health behaviors after AD risk assessment and genotype disclosure during their 6-wk follow-up visit, with 16% ($n = 45$) of the participants reporting a change in dietary supplement use. Among participants who reported postdisclosure changes in dietary supplement use, 71% ($n = 32$) of the participants were *ε4+* ($P < 0.0001$). The results of changes in diet and exercise behaviors are presented in **Table 3**. The *ε4+* participants had a 4.75 times higher odds of taking dietary supplements than those participants who were *ε4−* (95% CI: 2.23, 10.10; $P < 0.0001$) after adjustment for age, sex, baseline supplement use, randomization arm, race, and education. When exploring which specific supplements were consumed, it was noted that >50% of the subjects reported consuming only vitamin supplements (including multivitamins and single-vitamin supplements), and 25% of subjects reported consuming a combination of vitamins and botanical supplements. The most commonly reported supplement changes were in vitamin E (47%), vitamin C (29%), botanicals (including gingko biloba, curcumin, and green tea; 22%), multivitamins (18%), vitamin B (16%), and fish oil/omega (16%). On average, subjects who consumed supplements were younger than subjects who did not consume supplements and were slightly more likely to be women, although this sex difference was not significant (Table 2). There was a significant difference between participants randomly assigned to the extended protocol and participants randomly assigned to the condensed protocol, with condensed-protocol participants nearly twice as likely to report supplement consumption after genotype disclosure (Table 2). This difference was accounted for during the logistic regression analysis presented in Table 3.

TABLE 2
Subject characteristics at baseline and at 6-wk follow-up[1]

		6-wk Follow-up		
	Baseline (total $n = 272$)	Reported change in supplement use ($n = 45$)	Did not report change in supplement use ($n = 227$)	*P*
Age (y)	58.1 ± 10.6[2]	54.2 ± 8.9	58.9 ± 10.7	0.006
Sex [*n* (%)]				0.07
Women	193 (71.0)	37 (80.4)	156 (68.4)	
Men	79 (29.0)	8 (19.6)	71 (31.6)	
Race [*n* (%)]				0.85
White	221 (81.3)	37 (82.2)	184 (81.1)	
African American	51 (18.8)	8 (17.8)	43 (18.9)	
Educational level [*n* (%)]				0.53
<4 y of college	86 (31.6)	16 (35.6)	70 (30.7)	
≥4 y of college	186 (68.4)	29 (64.4)	157 (69.3)	
APOE status [*n* (%)]				<0.0001
ε4−	161 (59.2)	13 (28.9)	148 (65.1)	
ε4+	111 (40.8)	32 (71.1)	79 (34.8)	
Baseline supplement consumption [*n* (%)]				0.02
Yes	138 (50.7)	30 (66.7)	108 (47.6)	
No	134 (49.3)	15 (33.3)	119 (52.4)	
Randomization arm [*n* (%)]				0.006
Condensed	182 (66.9)	38 (84.4)	144 (20.9)	
Extended	90 (33.1)	7 (15.5)	83 (79.1)	
Number of affected relatives [*n* (%)]				0.13
1	155 (57.0)	21 (53.3)	134 (59.0)	
>1	117 (43.0)	24 (46.7)	93 (41.0)	

[1] *ε4−*, absence of the risk-increasing *ε4* allele; *ε4+*, having at least one copy of the risk-increasing *ε4* allele.
[2] Mean ± SD (all such values).

TABLE 3
Association of *APOE ε4*+ genotype and diet- and exercise-related changes at 6-wk follow-up (n = 272)[1]

Health-behavior change	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)[2]	P
Any dietary change	1.98 (1.14, 3.45)	0.01	2.32 (1.29, 4.36)	0.01
Diet	1.37 (0.75, 2.50)	0.31	1.56 (0.80, 3.02)	0.19
Exercise	1.52 (0.82, 2.80)	0.18	1.85 (0.96, 3.57)	0.07
Dietary supplements	4.61 (2.29, 9.29)	<0.0001	4.75 (2.23, 10.10)	<0.0001

[1] OR, odds ratio. Univariate and multivariate logistic regression analyses were used to identify diet- and exercise-related changes made 6 wk after genotype disclosure. For each health-behavior change, the reference genotype was *ε4−*.

[2] Endpoints were adjusted for age, sex, race, randomization arm, baseline prevention, number of affected relatives, and education (<4 or ≥4 y of college).

Additional analysis determined that some participants who reported engaging in preventative measures for AD at baseline were significantly more likely to report additional changes after genotype disclosure, regardless of genotype (Table 2). In the domain of diet, participants who reported using diet to prevent AD at baseline had 3.4 times the odds of reporting future changes after genotype disclosure (P = 0.0004; 95% CI: 1.73, 6.86). This relation was not seen in the domain of exercise (P = 0.53; odds ratio = 1.23; 95% CI: 0.64, 2.36).

DISCUSSION

After *APOE* genotype disclosure, participants who learned that they were at an increased risk of AD were significantly more likely to make health-behavior changes. The findings from this study suggest that the disclosure of *ε4* status to individuals with a family history of AD may influence nutritional behaviors, specifically regarding supplement use. At the time of the REVAL study, *APOE* was the only gene definitively shown to increase AD risk; other genes may independently contribute to AD risk beyond *APOE* mutations, and recently, it was shown that there are possible gene-gene interactions between *APOE* and surrounding genes (9, 10, 20, 21).

National health-surveillance monitoring surveys have tracked supplement use in the United States and indicated a significant increase in the use of dietary supplements during the early part of the millennium, but more recent data suggest that the consumption of complementary and alternative medicine has stabilized between 2002 and 2007 (22–24). In 2002, the US Department of Agriculture Health and Diet Survey (25) showed that 73% of participants had consumed some sort of dietary supplement during the past 12 mo, a statistic that had increased from data reported 8 y earlier in the Third National Health and Nutrition Examination Survey (NHANES III), in which only 40% of participants reported consuming dietary supplements.

The finding of patients taking supplements to reduce their personal risk of a disease after genetic risk assessment was illustrated by several authors. One large New Zealand study (26) reported that several participants felt that vitamin and mineral supplements could provide a protective measure against cancer. Another risk-assessment study, which included genetic susceptibility testing for breast and ovarian cancer, reported this trend in supplement use (27). One anthropologic study conducted by Nichter and Thompson (28) described several interviews with supplement consumers, including a 40-y-old woman with a family history of breast cancer who regularly took 6 different nutritional supplements to reduce her risk—without ever confirming her genetic risk. The authors point out a current societal belief that supplementing the diet may help aid in the promotion of wellness as well as the prevention of illness in our modern society. In our study sample, ≈50% (n = 138) of the study participants reported taking some form of supplement to prevent the onset of AD at baseline. Given this high percentage using supplements at baseline, it is especially interesting to find that a positive genetic test result led to a subsequent change in supplement use. This finding is of particular interest given the growing number of DTC genetic testing companies that promote the use of specific supplements to reduce disease risk or promote general health without providing substantial scientific data to document the risks and benefits of supplement intake and use (7). Nationally, public awareness of DTC testing is ≈14% (29), and as marketing of such services increases, we can expect to see increased public knowledge. As the field of personalized medicine expands, our study highlights one potential outcome of DTC genetic testing, suggesting that individuals who pursue genetic-based risk assessments for conditions that do not have established recommendations for risk management may be more likely to engage in nontraditional treatments.

AD is a progressive neurodegenerative disease that lacks effective prevention and treatment options and currently has no proven treatments that offer prevention or cure (30). Despite this, our data suggest that people with a family history of AD disease are significantly more likely to make a change in dietary supplement use after learning that they are at an increased genetic risk of developing AD. The 2 most commonly consumed supplements among our study participants were vitamins E and C, perhaps due in part to the "Maintain Your Brain" campaign of the Alzheimer's Association (31), a lay-media educational initiative that summarizes current research findings as the basis for general recommendations for maintaining brain health. This public health campaign focused on 4 components, one of which was eating a "brain-healthy diet" (31). The campaign specifically mentioned vitamins E and C as potentially helpful components of the diet. Although both of these vitamins are relatively well tolerated, a few studies (32–34) have indicated that there are negative health consequences when either vitamin is taken in very high doses. In addition to changes in vitamin use, other participants reported use of botanical supplements to prevent the onset of AD, such as gingko balboa, which was popular at the time but has since been shown to be ineffective in improving memory scores in cognitively intact and cognitively impaired adults (8, 35). Because all participants in our study had at least one first-degree relative with AD, it is likely that study participants represent a population that is highly motivated to seek out any

information regarding the prevention of AD. Unfortunately, there are many nonreliable sources describing possible disease-prevention strategies, especially on the Internet. A survey conducted during the same years as REVEAL II was conducted showed that >50% of Americans used the Internet to find health information (36). Considering that a recent article (37) in *The Journal of the American Medical Association* indicated that Wikipedia is a top Internet source for health information, it is possible that the rate of misinformation obtained by participants is high. During our data analysis, it was noted that there was a significant difference in postdisclosure supplement use between randomization arms. Because participants in both arms received the exact same educational information, the only difference in protocols was the ability for participants in the extended protocol arm to ask questions during the educational session. It is possible that participants may have inquired about strategies to prevent the onset of AD during these sessions, in which case the presenter would simply state that there are no effective methods of treatment or prevention to date. Participants in the condensed protocol arm would not have had the opportunity to specifically ask about treatment/prevention options in an in-person setting and, like many Americans, turned to the Internet for information. This finding may be especially applicable in the field of DTC genetic testing, in which consumers do not have the option of in-person consultation. Because many DTC companies combine genetic information with nutraceutical suggestions, it is possible that DTC genetic test consumers will be even more likely to make health-behavior changes after learning the test results.

To our knowledge, the findings from this study present an interesting first look at the influence of genetic susceptibility testing on dietary supplement use. However, the generalizability of this finding is limited by 2 important factors. The first factor concerns the study population. The REVAL II trial included only healthy adults with a first-degree relative who had been diagnosed with AD. The presence of a family history of AD alone puts all participants at an increased risk of developing the disease compared with the general population and may influence health behaviors. As noted in Table 2, our study sample was predominately white, female, and highly educated. In addition, as with all studies using survey data, the self-reported consumption of supplements does not represent a quantitative measure of supplement use. Because many supplements preparations in the United States include vitamins and minerals, information collected about vitamin use may possibly reflect use of vitamins and minerals. Because of the nature of the data collection, it is impossible to determine the exact preparations of supplements consumed, which is a limitation. These findings highlight the need for future studies that include a more objective measure of health-behavior changes, including quantitative measures of dietary change and supplement use. Follow-up studies may also pursue questions regarding the motivations and expectations behind health-behavior changes, in particular those concerning supplement use, to assess the public health effect of such testing.

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