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Predictive Testing for Alzheimer's Disease: Suicidal Ideation in Healthy Participants

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Introduction

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study[1] showed that disclosure of apolipoprotein E (APOE) genotype, the most prevalent genetic risk factor for Alzheimer's disease (AD)[2], can be done safely, but with the caveats that participants in this study were carefully screened for psychiatric problems and those with suicidal ideation were excluded. Further, participants had extensive education, counseling, and followup, all steps that characterize a best practice but which are unlikely to occur outside of the protective

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walls of a research trial. In an effort to explore the perspectives of unscreened and unsheltered individuals who are likely to seek presymptomatic testing for AD we administered a questionnaire through an online website and found that nearly 12% of more than 4000 respondents (who had not undergone genetic testing), when asked how they might react if found to be a "high risk" for AD endorsed "seriously consider suicide"[3]. With the advent of presymptomatic clinical trials, recruitment strategies include mass screening of individuals harboring genetic or biomarker evidence of high risk for Alzheimer's disease (AD)[4–6]. The present study explores possible demographic, cognitive, psychological, and personality characteristics that might identify a potential research participant as one at high risk of suicidal ideation by administering the same questionnaire to our longstanding research cohort, the Arizona APOE Cohort[7].

Methods

As previously described[3] this survey was developed from a 2 part interview with members of the Arizona APOE cohort to get a sense of what features of presymptomatic AD testing seemed most relevant to them (for example, whether they felt any form of predictive testing for AD was appropriate, and how they might handle such information if it was disclosed to them). The final questionnaire comprised of yes/no and multiple choice questions addressing demographics, genetic testing, biomarker testing, and possible reactions to such information was then mailed to the remaining cognitively normal members of the cohort.

Members of the Arizona APOE Cohort are cognitively normal residents of Maricopa County age 21 years and older recruited through local media ads, genotyped for APOE, and who undergo longitudinal neuropsychological assessment every two years[7]. The participants agreed to have the results of the APOE test withheld from them as a precondition to their participation in this study. Neuropsychological tests encompassed general intellect, memory, executive, language, and visuospatial skills. Behavioral measures included the Personality Assessment Inventory (PAI), Hamilton Depression Scale, Beck Depression Rating Scale, Geriatric Depression Scale, and the Neuropsychiatric Inventory Questionnaire (NPIQ). Also included were paired subjective cognition questionnaires, the Multidimensional Assessment of Neurodegenerative Symptoms (MANS), self and informant versions[8]. Personality was assessed with the Five Factor Neuroticism, Extraversion, and Openness (NEO) Inventory. Socioeconomic status was approximated in three ways. Income was estimated by zip code median income, major occupational background was quantified with the Dictionary of Occupational Titles General Educational Development (Reasoning, Mathematical, Language) (GED)[9], and subjective community and socioeconomic standing was self-assessed by patients using the subjective scale of social status indicated on a 10 rung ladder (1 lowest, 10 highest).

Members were asked two questions pertaining to consideration of suicide based on the following two scenarios. The first question addressed risk of Alzheimer's disease based on genetic test results and a second question asked about presymptomatic Alzheimer's disease based on biomarker test results. Members were eligible for analysis related to consideration of suicide if they answered both the genetic test and biomarker risk questions. Members not answering both questions were excluded from this analysis. Univariate analysis of responses

to questions regarding reactions to presymptomatic testing including consideration of suicide was performed for each demographic and behavioral variable. Variables that were statistically significant on univariate analysis were considered for inclusion in multivariable logistic regression models from which odds ratios (OR), 95% confidence intervals (CI) and corresponding p-values were calculated. In the logistic regression model, suicide endorsement was the dependent variable. Currently married, WAIS-R information, WAIS-R similarities, vegetable fluency and PAI-NON T score were considered for inclusion. All p-values were two sided and a p-value of ≤.05 was considered to be statistically significant. SAS statistical software version 9.3 (Cary, NC) was used for analysis.

Results

Surveys were sent to all 476 active APOE Cohort members who did not participate in the focus groups that led to development of the survey, and returned by 316 (66.4%). Compared to nonresponders, those returning the survey were slightly older (66.1 ± 10.4 vs 63.3 ± 13.6 years, p=.01) with more years of education (16.0 ± 2.4 vs 15.5 ± 2.4 years, p=.03), lower depression scores (e.g., Ham-D 2.1 ± 2.2 vs 2.8 ± 3.0, p=.004), and higher conscientiousness scores on the NEO (52.1 ± 10.0 vs. 47.1 ± 9.7, p=.001), but with similar gender makeup, family history of dementia, marital status, number of children, months in the study, and neuropsychological test performance.

256/316 (81.0%) were interested in obtaining genetic test results: 61 wanted results only if testing was free (covered by insurance), 28 only within the context of research, and 167 were willing to personally pay at least $100. 287 of the 316 (90.8%) APOE Cohort members answered both questions related to consideration of suicide; 29 were excluded from this analysis. 19/287 (6.6%) endorsed that they would seriously consider suicide if found to be at high risk for AD whether based on genetic or biomarker test results; 13 responded yes to both questions, 3 responded yes to genetic test risk only, and 3 responded yes to biomarker risk only. 268/287 (93.4%) responded no to both questions. 16/19 (84.2%) of those endorsing suicide indicated that they wanted genetic testing compared with 222/268 (82.8%) of those not endorsing suicide (p=.88), and similarly the proportion wanting biomarker testing was 13/18 (72.2%) and 190/264 (72.0%) respectively (p=.98).

Demographics are summarized in Tables 1, and a representative subset of the cognitive, behavioral and personality data in table 2 for those endorsing and not endorsing suicide. The NEO Inventory was added at a later date to our battery, thus only 121 respondents completed it, including nine who endorsed suicide and 112 who did not. Those endorsing suicide were more likely to be unmarried (52.6% vs. 25.0%, p=.009); performed better on WAIS-R information (age scaled score 13.9 ± 2.3 vs. 12.4 ± 2.3, p=.01), WAIS-R similarities (age scaled score 13.9 ± 2.2 vs. 12.9 ± 2.0, p=.04), vegetable fluency (items in 1 minute, 18.1 ± 5.4 vs. 15.5 ± 4.1, p=.01) and endorsed greater feelings of nonsupport (PAI-NON T score 52.1 ± 9.7 vs. 46.3 ± 8.5, p=.01). Those endorsing suicide did not have significantly different cognitive or depression measure scores. In a multivariable logistic regression model, vegetable fluency (OR=1.21, 95% CI 1.06 to 1.37, p=.004) and PAI-NON T nonsupport score (OR=1.07, 95% CI 1.01 to 1.14, p=.02) were significantly associated with suicide endorsement.

Discussion

Perhaps the most remarkable finding from our relatively small study is the relative lack of anything extraordinary about those endorsing suicidal ideation. Consistent with previous research, we found feelings of nonsupport to be a predictor, but more remarkably, there was no evidence that these individuals were depressed, neurotic, or in the early stages of cognitive decline. A second and potentially important observation is that the rate of endorsement was substantially lower in this research cohort than in our previously reported[4] website cohort (19/287 [6.6%] vs 427/3706 [11.6%], p=.01). (A comparison of the website and research cohorts is summarized on the supplementary eTable One). While this does not constitute a controlled trial, it raises the hope (and testable hypothesis) that inclusion within the context of a research trial may itself provide that sense of belonging that Durkheim identified as protective against suicidal ideation[10]. This has practical implications for those prevention trials that are performing genetic and biomarker screening of asymptomatic people as part of their recruitment strategies. Participants accepted into the trials will be able to share in the group identity of the trial, but those who are found to be at high risk yet not qualified for inclusion for other reasons will be at increased risk for suicidal ideation which might be mitigated by enrollment into an alternate research study, some other form of group inclusion, or clinical followup to monitor for suicidal ideation.

A significant limitation of our study is the relatively small number of individuals endorsing suicidal ideation. Further, while we had complete responses for most of our data sets, we had a smaller subset that completed the NEO personality measure. There are, however, few other such studies and none with a similar breadth and depth of behavioral data. Also, the results of our study should not be confused with the observed impact of actual disclosure of results such as in the REVEAL study.

The findings of this study are important to consider in the recruitment and disclosure strategies of research trials. It is our further intention that the results of this study inspire further discussion and consideration of the unintended potential adverse psychological consequences of predictive testing for AD in the absence of disease modifying therapy, and most importantly, offer an initial guide to mitigating their impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic Features of APOE Cohort Members Answering Suicide Questions (n=287)

	Suicide-yes [1]	Suicide-no [1]	*p*
N	19 (6.6%)	268 (93.4%)	
Age	69.0 (7.8)	64.9 (10.6)	0.10
Women	13 (68.4%)	187 (69.8%)	0.90
Caucasian	17 (89.5%)	225 (84.0%)	0.52
Education	16.8 (2.0)	16.0 (2.4)	0.12
First Degree Relative With Dementia	13 (68.4%)	191 (71.8%)	0.75
Family History # relatives	1.1 (1.1)	1.7 (1.9)	0.83
APOE e4 carriers	9 (47.4%)	114 (42.5%)	0.22
Married currently	9 (47.4%)	201 (75.0%)	0.009
With Any Children	12 (63.2%)	200 (74.6%)	0.27
Zip code median income	$46,371	$50,000	0.09
GED (Dictionary of Occupational Titles)	13.2 (2.2)	12.9 (2.5)	0.62
Ladder-community	6.4 (1.5)	7.2 (1.5)	0.11
Ladder- socioeconomic status	6.3 (1.6)	6.5 (1.6)	0.64

Values are expressed as mean ± SD or as No. (%).

[1]Members were eligible for analysis if they answered both AD risk and biomarker risk questions related to suicide. 13 responded yes to both questions, 3 responded yes to AD risk and no to biomarker risk, and 3 responded no to AD risk and yes to biomarker risk. Members not answering both questions were excluded (n=29).

GED = General Educational Development

Table 2

	Suicide-yes (n=19, 6.6%)	Suicide-No (n=268, 93.4%)	*p*
Minimental Status Exam	29.9 (.3)	29.7 (.7)	0.17
AVLT-Long Term Memory	9.3 (3.7)	9.4 (3.5)	0.94
Rey-O Complex Figure Test Recall	20.2 (6.0)	20.2 (7.1)	0.97
Controlled Oral Word Association Test	50.3 (11.7)	48.5 (11.3)	0.50
Hamilton Depression Scale	1.8 (1.8)	2.0 (2.2)	0.73
Beck Depression Inventory	4.0 (3.6)	4.8 (4.4)	0.49
Geriatric Depression Scale	2.4 (2.4)	3.0 (3.5)	0.50
PAI-Somatization	45.4 (5.3)	47.8 (7.6)	0.25
PAI-Anxiety	42.6 (6.6)	45.3 (6.6)	0.15
PAI-Depression	46.4 (6.1)	46.9 (7.5)	0.81
PAI-Suicide	49.8 (8.0)	46.8 (5.7)	0.06
PAI-Nonsupport	52.1 (9.7)	46.3 (8.5)	0.01
NEO Neuroticism Factor	42.9 (9.9)	43.7 (9.2)	0.80
NEO Extraversion Factor	47.4 (10.3)	48.9 (9.6)	0.67
NEO Openness Factor	56.3 (11.6)	52.4 (10.3)	0.28
NEO Agreeableness Factor	52.7 (13.6)	54.5 (8.7)	0.57
NEO Conscientiousness Factor	56.0 (7.2)	51.8 (8.9)	0.18

Values are expressed as mean ± SD.

AVLT-Auditory Verbal Learning Test; PAI-Personality Assessment Inventory; NEO-Neuroticism, Openness, Extraversion Five Factor Personality Inventory