

**Explaining behaviour change after genetic testing: the problem of collinearity  
between test results and risk estimates**

Running Head: Genetic testing and behaviour change

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**ABSTRACT**

This study explores whether and how the behavioural impact of genotype disclosure can be disentangled from the impact of the associated numerical risk estimates.

Secondary data analyses are presented from a randomised controlled trial of 162 first degree relatives of patients with Alzheimer's disease given lifetime risk estimate of Alzheimer's disease (AD). Those in the Control Group received estimates based on age, gender and family history while those in the Intervention Group received estimates based upon these factors and their apolipoprotein E (APOE) genotype, which was disclosed to them. AD-specific self-reported behaviour change (diet, exercise and/or medication use) was assessed at 12 months.

Behaviour change was more likely with increasing lifetime risk estimates. Behaviour change was also more likely, but not significantly so, in those in the Intervention Group who were  $\epsilon 4$  positive compared with those in the Control group. The collinearity between lifetime risk estimates and genotype prevented assessment of their independent effects in these two groups. Behaviour change in the Intervention Group for those who were  $\epsilon 4$  negative was similar to that observed for those in the Control Group, two groups with similar lifetime risk estimates thereby allowing an assessment of their independent effects.

Novel study designs are proposed to determine whether genotype disclosure has an impact upon behaviour beyond that of the associated numerical risk estimates.

Key words: Alzheimer's disease, behaviour change, collinearity, genetic testing, risk estimates, APOE.

## **INTRODUCTION**

There are high expectations that using genotype to estimate the risk of common complex conditions will motivate health-related behaviour change more strongly than other types of risk information (Collins et al 2003, Gramling et al 2003). Conversely, the detection of a genotype associated with a lowered risk of disease may lessen motivation to change behaviour beyond the impact on motivation of the risk estimate associated with this genotype. Such expectations are consistent with the observations that the results of risk assessments that include genotype analyses are perceived as more accurate when a diagnosis is being confirmed (Marteau et al 2004) and more reassuring when a risk conferring mutation is not found (La Russe et al 2005). Such expectations are also consistent with theories of attitude change which predict that the greater the personal salience of information, the greater the impact (Chen and Chaiken 1999).

In assessing risks of common complex conditions, a numerical risk estimate is often provided together with information about the presence or absence of a risk conferring mutation. So, for example, those undergoing a risk assessment for Crohn's disease that includes a genetic test may be informed of their mutation status for CARD15 and of the likelihood that they will develop the disease (Lewis et al 2007). Providing risk estimates of disease has a small, but significant, impact on risk perceptions (Slovic, Fishhoff and Lichtenstein 1980) which in turn have a small effect upon behaviour to reduce the identified risk (Milne, Sheeran and Orbell 2000). It is therefore germane to consider the extent to which any motivating impact of genetic risk information is attributable to learning about the presence or absence of a risk conferring mutation or being given a

numerical risk estimate of disease.

The few studies conducted in this area suggest that disclosure of genotypes indicating increased risk of disease are sometimes associated with an increased motivation to engage in behaviour change (Lerman et al 1997, Sanderson et al, in press) but not always (Ito et al 2006, McBride et al 2002). Disclosure of the decreased risks associated with lower risk genotypes did not occur in two of the four trials designed to evaluate the motivational impact of DNA predictive testing for lung cancer in smokers (Lerman et al 1997, McBride et al 2002). There is, however, limited evidence to suggest that disclosure of such a genotype might reduce motivation beyond that following a lowered risk estimate (Sanderson and Wardle 2005, Marteau et al 2005). In each of these studies, in addition to genotype disclosure, participants were given a numerical risk estimate of the likelihood of developing lung cancer. The design of the studies was such that it was not possible to disentangle the effects of the numerical risk information from genotype disclosure. We report here secondary analysis from a randomised controlled trial in which we attempted to disentangle these effects, statistically.

The Risk Evaluation and Education for Alzheimer's disease (REVEAL) Study is a randomized controlled trial assessing the impact of genetic susceptibility testing and APOE disclosure on asymptomatic adult children of patients with AD. Details of the study rationale, design and main results have been published elsewhere (Roberts et al 2004, Green 2002, Cupples et al 2004, Marteau et al 2005, Roberts et al 2005). While there is no conclusive evidence that the risk of developing AD can be reduced by

behaviour change, diet, physical activity and vitamin supplementation are under investigation for their potential to prevent or reduce risk of cognitive decline and dementias (Hendrie et al 2006). One part of the trial assessed self-reported behaviour change undertaken with the hope of reducing AD risk.

We have reported elsewhere the main analysis examining whether APOE disclosure motivates behaviour change intended to reduce the risk of the disease (Chao et al, in press) Adjusting for important baseline confounding variables (age, gender, years of education and presence of a modifiable comorbidity), there was no effect on behaviour change of the intervention group (all those whose genotype was disclosed whether positive or negative) compared with the control group (those whose genotype was not disclosed) (38% vs 31%: adjusted OR 1.45, 95% CI [0.65, 3.21],  $p=0.36$ ). Subgroup analyses showed that behaviour change was more likely in those who were APOE  $\epsilon 4$  positive than those who were APOE  $\epsilon 4$  negative (53% vs 24%: adjusted OR 2.9, 95% CI [1.19,6.86],  $p=0.002$ ). Behaviour change was also more likely as lifetime risk estimates increased (per 1% increase in lifetime risk estimate: adjusted OR 1.05, 95% CI [1.01, 1.10],  $p=0.007$ ). The aim of the secondary analyses reported in this paper is to explore whether and how the behavioural impact of DNA testing can be disentangled from the impact of the risk estimates generated by such tests.

We report here additional analyses of the REVEAL Study data in order to test two hypotheses:

- I Given equivalent lifetime risk estimates, behaviour change is more likely following the communication of DNA test results indicating the presence of a genotype associated with increased risk than following risk communication when DNA testing is not performed.
- II Given equivalent lifetime risk estimates, behaviour change is less likely following the communication of DNA test results indicating the presence of a genotype associated with lowered risk than following risk communication when DNA testing is not performed.

## **MATERIALS AND METHODS**

### **Risk estimates**

The methodology of the REVEAL clinical trial is described in detail elsewhere (Roberts et al 2004, Green 2002). We report here on details specifically relevant to this analysis. Prior to randomization, all participants attended an education session where they were informed about genetic susceptibility testing and told there was no proven preventive measure for AD. They were informed that while a number of interventions to prevent AD were under investigation, such as vitamin E, cholesterol lowering drugs and mental stimulation, none was currently recommended. Eligible participants were randomized to either the Intervention or the Control groups in the ratio of 2:1 to achieve similarly sized groups for those testing positive, negative and for the Control group (see Box 1 for REVEAL study design). Both groups received lifetime (up to age 85) risk estimates of AD based on gender, family history and genotype, presented as a percentage (Cupples et al 2004, Roberts et al 2005). . In addition, the Intervention group had disclosed to them

their APOE genotype. The Intervention and Control groups received their risk estimates during individual counselling sessions followed by a letter detailing the information presented.

FIGURE ONE ABOUT HERE

### **Intervention Group**

Lifetime risk assessments to the age of 85 were based upon age, gender, family history and APOE genotype. Risk estimates were based on numerous sources, including a large-scale (N ~ 13,000 families) study of the genetic epidemiology of AD; the generation of risk estimates used in the clinical trial are described in detail elsewhere (Cupples et al 2004). In addition to being given their lifetime risk assessments, participants' APOE genotype was disclosed.

### **Control Group**

Lifetime risk assessments to the age of 85 were based upon age, gender, family history and an assumed  $\epsilon 4$  negative genotype. As the most common genotype, APOE  $\epsilon 3/3$ , occurs in over 60% of the population (Farrer et al 1997), the lifetime risk estimates given in the Control group therefore resembled those given to participants who were tested and found to carry the APOE  $\epsilon 3/3$  genotype.

### **Measures**

The primary outcome in the analysis of behavioural change was a binary indicator of self-reported behaviour change undertaken with the hope of preventing AD. Three questions were asked in which respondents were asked to indicate whether they had made changes in (a) their diet (b) level of exercise and (c) use of medication or vitamins, with the specific aim of preventing AD. Those reporting change at 12 months in one or more of diet, exercise level, use of medication or vitamins, were classified as having engaged in AD-specific behaviour change. Those reporting no change in any of these were classified as not having engaged in AD-specific behaviour change. Self-reported behaviour change was relatively uncommon: 64% reported no change, 30% reported taking medication or vitamins with the aim of reducing their risks of AD, 13% reported changes to their diet and 6% reported changes in exercise levels. As few participants reported two or more changes, responses were combined to produce a binary variable of behaviour change (*ie* No or Yes).

### **Analysis**

Multiple logistic regression was carried out to compare those receiving  $\epsilon 4$  positive and  $\epsilon 4$  negative test results with the Control group, as appropriate, to test the two stated hypotheses. In an attempt to disentangle the effect upon behaviour change of numerical lifetime risk estimate and APOE genotype, logistic regression models were fitted including either of these as independent variables. A combined model that included both APOE genotype and numerical lifetime risk estimates as independent variables was fitted subsequently in order to try to assess their independent effects, controlling for each other. All models were adjusted for age, gender, presence of a modifiable comorbidity and

number of years of education. Collinearity between genotype and risk estimate was assessed by Pearson's correlation coefficient, Principal Components Analysis of these two variables was used in order to attempt to address the effect of collinearity on the model.

All analyses were conducted using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

## **RESULTS**

One hundred and sixty-two participants were randomised. Seventeen participants were excluded due to drop out (n=14) or incomplete data at one year (n=3). The characteristics of the 145 participants included in the subsequent analyses are shown in Table 1.

Lifetime risk estimates in the different study groups are shown in Table 1 and Figure 1.

Lifetime risks are similar in the  $\epsilon 4$  negative and control groups, but higher for those who were tested and found to be  $\epsilon 4$  positive.

### **Hypothesis I**

The rate of self-reported behaviour change was higher, but not statistically significantly so, in the  $\epsilon 4$  positive than in the Control group (53% vs 31%; adjusted OR=2.20, 95% CI [0.87,5.56], p=0.10). Correspondingly, higher lifetime risk estimates were associated with significantly higher rates of self-reported behaviour change (for an increase in lifetime risk estimate of 1%, adjusted OR=1.05, 95% CI [1.01, 1.09], p=0.02). There was

high collinearity between group ( $\epsilon 4$  positive or Control) and lifetime risk estimate ( $r=0.84$ , 95% CI [0.77, 0.89]), and very little overlap in the distributions of lifetime risk in these two groups (mean 48% in the  $\epsilon 4$  positive group, 27% in Control group, and 84% and 0% of participants in the respective groups having risk above 30%, Table 1, Figure 1). The odds ratio for the former, adjusting for the latter, is required in order to test Hypothesis I. Because of the collinearity between the two, the least squares estimate of this odds ratio was unstable, having opposite sign and considerably inflated standard error relative to that in the single-variable model; hence it has not proved possible to test Hypothesis I. An attempt to re-fit the model by first conducting a principal components analysis on the two correlated variables, and then using the resulting orthogonal principal components as covariates, did not alter the result. If the collinearity were less marked, analysis of deviance could be used to compare models containing both variables with those containing only one.

## **Hypothesis II**

Given lifetime risk estimates were similar in the  $\epsilon 4$  negative and Control groups (Table 1), this Hypothesis could be tested by direct comparison between the proportions of participants reporting behaviour change in these two groups. The rates of self-reported behaviour change were similar in the  $\epsilon 4$  negative and Control groups (24% vs 31%; adjusted OR=0.82, 95% CI [0.32, 2.11],  $p=0.68$ ). We are unable to reject the null hypothesis: there is no evidence that behaviour change is less likely following the communication of risk that incorporates analysis of DNA that is negative for a risk conferring mutation.

## DISCUSSION

Behaviour change following risk assessment of AD was more likely the greater the numerical lifetime risk estimate and following disclosure of a genotype associated with increased risk of AD. We were not able to assess the effect of disclosing an  $\epsilon 4$  genotype (relative to the Control group) after controlling for numerical risk estimate. When numerical risk estimates were similar, as they were for those in the Control Group and for those in the Intervention Group informed they were  $\epsilon 4$  negative, there was no difference in self-reported behaviour change. This suggests that, contrary to predictions (Chen & Chaiken, 1999; Marteau et al 2004; LaRusse et al 2005) disclosure of genotype status associated with lower disease risk has no impact upon behaviour beyond the impact of any associated numerical risk estimate.

The findings from these analyses illustrate a general problem in trying to isolate the motivational impact of genotype disclosure and indeed other biomarker risk information. The estimates derived from genotype disclosure differ from those derived from other sources both in provenance and the range of magnitudes of the risk estimated. So, for example, randomising groups to undergo any additional biomarker test, in this case an analysis of APOE genotype, will result in a greater segregation of risk in those subjected to the additional biomarker, leading to the generation of both lower and higher risk magnitudes although overall the risk in the population tested remains the same. The interest, however, is in being able to disentangle the effects of type of test from numerical risk estimates in order to test the hypothesis that the salience of genotype has an impact

on motivation beyond that produced by feedback of the risk estimates generated from genotype. Communicating the results of predictive genetic testing for common complex conditions is difficult, involving the communication of genotype and numerical risk estimates. If communicating genotype status has no motivating effect upon risk-reducing behaviour beyond the motivating effect of disclosing the associated numerical risk estimate or if it has a de-motivating effect (for example, if it instils a sense of fatalism) then it may be more effective and efficient to not disclose genotype but only the resultant numerical risk.

A further, more general problem with randomised trials designed to assess the behavioural impact of DNA predictive testing (Sanderson et al, in press, Ito et al 2006, McBride et al 2002), is that the main comparison between the intervention and the control group is most often not informative. This is because the intervention group contains two subgroups, one of individuals receiving genotype positive test results, and one of individuals receiving genotype negative test results. These different test results lead to higher and lower risk estimates which lead to higher and lower risk perceptions (Marteau et al 2005). There is, therefore, an expectation that genotype positive and genotype negative test results will have opposite effects on behaviour and thus when the two subgroups are pooled to form a genotype feedback intervention group, there is unlikely to be any difference between this and a control group. The solution most often applied to this problem is to conduct subgroup analyses (Sanderson et al, in press, Ito et al 2006, McBride et al 2002, Chao et al, in press) However, given that subgroup allocation is not randomly determined, such comparisons are at risk of confounding

(Pocock 1983). They may also lack the statistical power to detect differences between subgroups.

The role of gender in explaining behaviour change represents a further complexity in interpreting the results of the analyses presented in the current study. There is an association between gender and lifetime risk of AD (females tend to have higher risks than males) and, in this sample, between gender and genotype (a greater proportion of females were mutation positive). If behaviour change is more likely in women undergoing AD risk assessment, then this may explain the higher rates of behaviour change in those receiving higher lifetime risk estimates of AD and those who are mutation positive. While the effects of gender were controlled for in the analyses, the strengths of the gender variable's associations with genotype and lifetime risk are such that we cannot be sure that some of the apparent effect of the latter pair of variables is not in part due to gender.

The solution to the problems of collinearity and subgroup analyses outlined above may be to consider alternative designs for studies of this type in preference to using increasingly complex methods of statistical analysis. We propose two possible designs. The first is to use explanatory as opposed to pragmatic trials (MacRae 1989) in which the risk estimates given in the two trial arms are equivalent, but in only one arm is the provenance of the test revealed as emanating from genotypes. In the other arm the test could be described as an unspecified biomarker test or a test of protein. This would mean that both groups received comparable risk estimates allowing the variable of interest,

namely the provision of risks that stem from an analysis of genotype, to be assessed. While conceptually neat, this design raises questions concerning acceptability and feasibility. The acceptability would critically depend upon the views of clinical ethics committees reviewing such a study. The feasibility would be influenced by how plausible an unspecified biomarker test would be for study participants. This would require piloting. In addition, further clinical studies assessing the behavioural impact of genotype feedback will provide stronger evidence if they include measures of actual behaviour change.

The second type of design for addressing the problems of collinearity involves the use of analogue studies, *ie* those in which individuals are asked to respond as though they were in a particular situation. This allows variables of interest to be experimentally manipulated either prior to a clinical study or instead of one. While the internal validity of such studies is high, there is also evidence that their external validity can be acceptable provided the study mirrors closely the situation it is intended to mimic (Lanza et al 1997, Holt and Mazzuca 1992) with greater validity likely with the use of video-based technologies (Lievens and Sackett 2006). In the current context an analogue study might involve asking participants to imagine being given a lifetime risk for AD or indeed any other common complex disease. The risk estimate provided would then vary independently of the type of test and test result. So, for example, those given lifetime risk estimates of AD which were 35% would be randomly assigned to be told that this was based on their genotypes, or not. The outcome variables might include risk perceptions and intentions to engage in risk reducing behaviours. Results from such studies provide

an estimate of the extent to which cognitive and behavioural responses to risk information are predicted by risk estimations and type of test. The impact of describing test results as emanating from genotype positive or genotype negative test results could also be assessed by comparing the impact of presenting the risk estimate either with the genotype described as positive or negative, with the impact of leaving the genotype undisclosed. It should be noted however that even responses to hypothetical scenarios, however richly drawn, require validation in studies in which individuals respond to actual risk information, with behaviour being measured objectively and not by self-report.

We are experimenting with both these designs in a series of studies investigating the motivational impact of DNA testing for common complex conditions (eg Wright et al, in press).

If neither of these design options is possible, we would advocate opting for a design tailored to allow a test of the hypothesis in a subset of participants who have similar enough risk distributions in each study group to avoid collinearity. Pilot work could be used to assess the frequency distribution of risk in study groups and therefore the extent of collinearity, and through repeated simulation of the pilot data to identify a range of risk within which choices in study sample size and in optimal allocation ratio to trial arms provide reasonable power for an answer to the question in the restricted risk range. In the REVEAL Study, the subset of  $\epsilon 4$  positive participants with risk less than 30% was small (eight participants), the collinearity was very high, and the event rate was zero in this subset; this did not affect the ability to answer the primary trial questions but did

prohibit reliable estimation required to address one of the current hypotheses. Design options in future trials could be modified further to allow an assessment of both sets of hypotheses.

### **Concluding Comment**

The collinearity between genotype and numerical lifetime risk estimates did not allow their independent effects to be assessed in those with a genotype associated with increased susceptibility. Novel study designs are needed to determine whether disclosure of genotype status has an impact upon behaviour beyond that of the numerical risk estimates associated with them.

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**Table 1 Patient Characteristics**

	All	Control	Intervention	ε4+	ε4-
Total number included in analysis	145	42	103	49	54
Age (years: mean(range))	53 (30-78)	55 (37-78)	52 (30-76)	51 (34-72)	53 (30-76)
Female gender	107 (74%)	34 (81%)	73 (71%)	40 (82%)	33 (61%)
Years of education (mean(range))	17 (12-22)	17 (12-21)	17 (12-22)	17 (12-21)	17 (12-22)
Any modifiable comorbidity? % yes	61 (42%)	20 (48%)	41 (40%)	22 (45%)	19 (35%)
Modelled % lifetime AD risk (mean(SD))	33 (13)	27 (4)	35 (14)	48 (9)	24 (5)
Behaviour change at 12M specific to AD prevention: % yes	52 (36%)	13 (31%)	39 (38%)	26 (53%)	13 (24%)

17 patients excluded as follows:

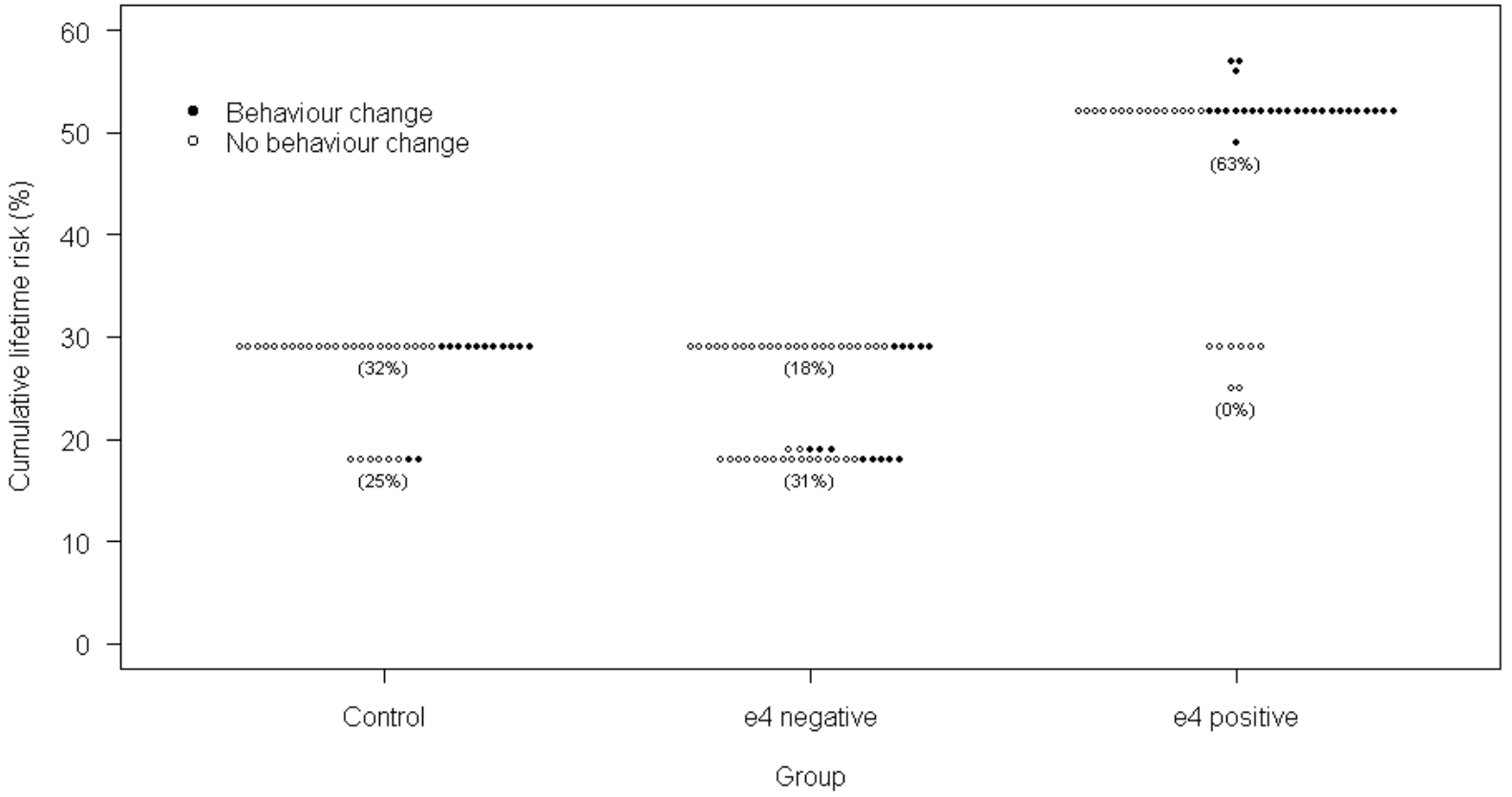
15 no 1-year follow-up (8 control, 3 ε4+, 4 ε4-)

2 missing data (1 control, 1 ε4+)

**Box 1 Summary of design of REVEAL study**

Group	Calculation of lifetime risk	Information made available to participants	
		Lifetime risk	APOE genotype
Intervention (n=103)	Based on gender, family history and true APOE genotype ( $\epsilon$ 4 negative or $\epsilon$ 4 positive)	Yes	Yes
Control (n=42)	Based on gender, family history and assumed $\epsilon$ 4 negative APOE genotype	Yes	No

Figure 1 Cumulative lifetime risk estimates for Alzheimer disease by Study Group



(values in brackets indicate percentages undergoing behaviour change for given group/lifetime risk cross-classifications)