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SEP 81 T ROBERTSON, G WARRACK N00014-80-C-0321
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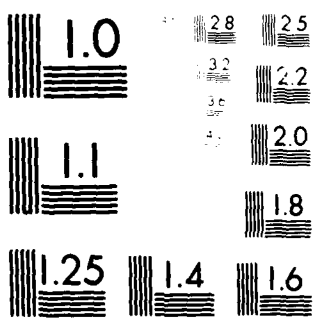

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ON TESTING TWO THEORIES REGARDING THE GENETIC MAKEUP OF PATIENTS SUFFERING FROM UNIPOLAR AFFECTIVE DISORDER

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Technical Report #76

September 1981

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ON TESTING TWO THEORIES REGARDING THE GENETIC MAKEUP OF PATIENTS SUFFERING FROM UNIPOLAR AFFECTIVE DISORDER*

Tim Robertson and Giles Warrack

SUMMARY

In an article in the Journal of Psychiatric Research, Cadoret, Woolson and Winokur (1977) consider two theories regarding the genetic makeup of patients suffering from unipolar affective disorder. Using likelihood ratio techniques from order restricted inference we analyze their data and compare the two analyses.

*This research was sponsored by the Office of Naval Research under Contract N00014-80-C-0321.

INTRODUCTION. In an article in the Journal of Psychiatric Research, Cadoret, Woolson and Winokur (1977) consider the genetic factors contributing to the risk of unipolar affective disorders (u.a.d.). They consider two theories accounting for the age of onset of u.a.d.: (1) the "qualitative" theory, which postulates that the genetic makeup of those afflicted early in life (under 40 years old), and those who are afflicted later (over 40) is somehow different, and 2) the "quantitative" theory which maintains that there is a particular type of gene causing u.a.d., and that those who succumb earlier do so because they possess the gene in greater numbers.

In their investigation Cadoret et al. consider samples of 767 women and 398 men suffering from u.a.d. Each sample is divided into 6 age groupings (3 less than 40 and 3 greater than 40) according to the age at which the patient first suffered from the disorder. For each age group they have obtained (a) the proportion of patients having alcoholic fathers, and (b) the proportion of fathers and mothers of patients within the group who suffered from depression.

These data reflect on the genetic makeup of the families in question and the two above-mentioned theories are modeled in terms of the shapes of the functions relating the probability of alcoholism or depression in parents to the age of onset of the patients' illness. If the "qualitative" theory holds then the risk function should be constant until age 40, drop at age 40, and be constant thereafter. If the "quantitative" theory holds then the risk function should simply be nonincreasing. The shapes of the risk function under the two theories are shown in Figure 1.

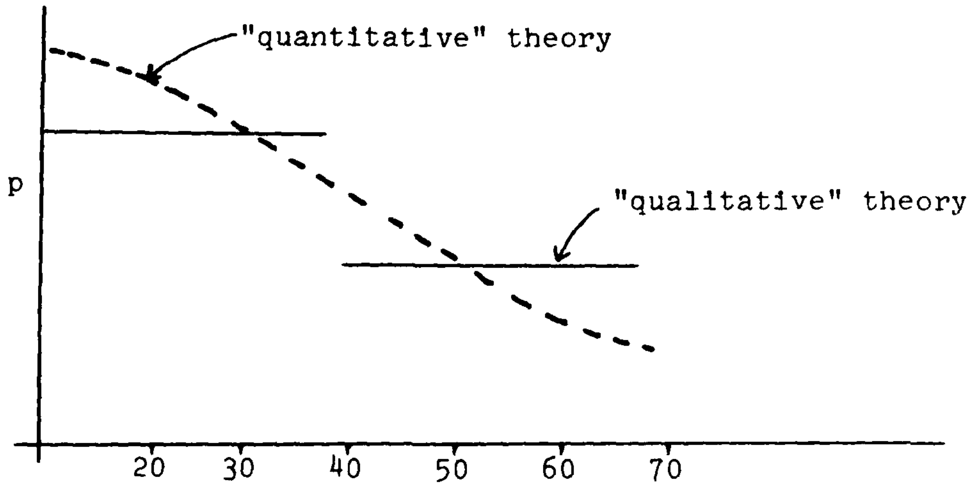

Figure 1. Shapes of the risk function under the two theories explaining the age of onset of u.a.d.

The six age groupings are 0-20 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, and over 60 years. Let p_i, $i = 1,2,\cdots,6$ be the respective risks for these age groups (probability of an alcoholic father is one case and the probability of a parent suffering from depression in the other case). In terms of statistical hypotheses, the qualitative theory implies that H_0: $p_1 = p_2 = p_3 \geq p_4 = p_5 = p_6$ while the quantitative theory implies that H_A: $p_1 \geq p_2 \geq \cdots \geq p_6$. Note that H_0 implies H_A so that an appealing way to decide between the two theories would be to use the data to test H_0 as a null hypothesis when the alternative is restricted by H_A (i.e., test H_0 vs. $H_A - H_0$ (H_A but not H_0)).

The data used by Cadoret et al. (1977) is contained in Table 1. In analyzing this data they use the techniques of order restricted inference contained in Barlow, Batholomew, Bremner and Brunk (1972). However, distribution theory was not available for testing H_0 against $H_A - H_0$ and Cadoret et al. tested separately the hypotheses

(a) H_0': $p_1 = p_2 = p_3$ vs. $H_A' - H_0'$ where H_A': $p_1 \geq p_2 \geq p_3$

and

(b) H_0'': $p_4 = p_5 = p_6$ vs. $H_A'' - H_0''$ where H_A'': $p_4 \geq p_5 \geq p_6$.

In each case the test statistic is of the form $-2 \ln \Lambda$, where Λ is the likelihood ratio and the asymptotic distribution is the chi-bar-square contained in Theorem 3.1 of Barlow et al. Thus for each set of data they computed two P-values. These P-values together with the results of our analysis (described later) are given in Table 2.

There are a number of techniques for combining P-values from independent tests. One of the more appealing techniques is based upon the facts that the null hypothesis distribution of a P-value is uniformly distributed over (0,1) and that $-2 \ln(U)$ (U is distributed uniformly on the interval (0,1)) has a chi-square distribution with two degrees of freedom. Thus in Table 2 we have combined the two P-values from the independent tests by computing $P[\chi_4^2 \geq -2(\ln p_1 + \ln p_2)]$, where p_1 and p_2 are the P-values obtained for the two separate tests.

TABLE 1. Proportions of alcoholic fathers and parents suffering from depression

A. FEMALES

Age at onset of illness	Sample Size	Proportion of alcoholic fathers	Proportion of depressive parents
< 20 yrs.	68	.16	.16
20-29	141	.11	.18
30-39	165	.15	.12
40-49	140	.09	.09
50-59	142	.04	.09
60-69	111	.02	.07

B. MALES

Age at onset of illness	Sample Size	Proportion of alcoholic fathers	Proportion of depressive parents
< 20 yrs.	33	.09	.21
20-29	82	.08	.10
30-39	67	.13	.15
40-49	83	.05	.15
50-59	58	.03	.09
60-69	70	.04	.10

LIKELIHOOD RATIO ANALYSIS. Consider the problem of testing H_0 against the alternative $H_A - H_0$. In order to be specific, we will talk about the fourth set of data, namely, the proportion of depressive parents in males suffering from u.a.d. (In some ways this is the most interesting data set.) Let $\hat{p}_i$; $i = 1,2,\cdots,6$ denote the unrestricted maximum likelihood estimates of the probabilities $p_1, p_2, \cdots, p_6$ (i.e., for our data $\hat{p}_1 = .21$, $\hat{p}_2 = .10, \cdots$). The maximum likelihood estimates subject to the restrictions H_0 and H_A can be found using any one of several algorithms in Barlow et al. (1972). Perhaps the easiest algorithm is the pool adjacent violators algorithm. Let p_i^*; $i = 1, 2,\cdots,6$ denote the maximum likelihood estimates subject to the restriction, H_A. Starting with the unsmoothed estimates .21, .10,.15,.15,.09,.10 the values of $\hat{p}_2$ and $\hat{p}_3$ constitute a violator since $\hat{p}_2 < \hat{p}_3$. They are both replaced by their weighted average, namely, $(n_2\hat{p}_2 + n_3\hat{p}_3)/(n_2 + n_3) = (9+10)/(87+67) = .12$ (n_i is the number of probands in the $i^{\underline{th}}$ group). Note that this value is obtained by "pooling" the samples from the $2^{\underline{nd}}$ and $3^{\underline{rd}}$ groups. We now consider the five numbers, .21,.12, .15,.09,.10. The violators, .12 and .15, are replaced by $(n_2\hat{p}_2 + n_3\hat{p}_3 + n_4\hat{p}_4)/(n_2+n_3+n_4) = .13$ and the violators .09 and .10 by $(n_5\hat{p}_5 + n_6\hat{p}_6)/(n_5+n_6) = .09$. The resulting three numbers are decreasing in i. Our estimates, restricted by H_A, are then .21,.13,.13,.13,.09,.09.

Let $\tilde{p}_i$; $i = 1,2,\cdots,6$ denote the maximum likelihood estimates subject to H_0. These estimates are obtained by pooling the data corresponding to ages less than 40, pooling the data corresponding to ages over 40 and then pooling the resulting values if we have a reversal. For the male-depression data, the estimates are $\tilde{p}_i = .14$; $i = 1,2,3$ and $\tilde{p}_i = .12$; $i = 4,5,6$. The likelihood ratio,

$$\Lambda = \frac{\prod_{i=1}^{6} (\tilde{p}_i)^{n_i \hat{p}_i} (1-\tilde{p}_i)^{n_i(1-\hat{p}_i)}}{\prod_{i=1}^{6} (p_i^*)^{n_i \hat{p}_i} (1-p_i^*)^{n_i(1-\hat{p}_i)}}$$

is then computed and the test rejects for large values of the statistic $T = -2 \ln \Lambda$. For this data the value of T is 8.51.

The authors have recently been able to derive the appropriate limiting, null hypothesis distribution of T. The test based upon T is not similar over the null hypothesis, H_0. However, one can show that if $n_i \longrightarrow \infty$; $i = 1,2,\cdots,6$ in such a way that the ratios n_i/n_j each converge to some strictly positive number, then

$$\sup_{p \in H_0} \lim_{n_i \to \infty} P_p[T \geq t] = \sum_{3 \leq \ell_1 + \ell_2 \leq 6} P_1[\ell_1, 3] P_2[\ell_2, 3] P[\chi^2_{\ell_1+\ell_2-2} \geq t]$$

where P_p is the probability computed under the hypothesis that p is the true vector of probabilities, χ^2_ℓ denotes a standard chi-square variable with ℓ degrees of freedom, and $P_1[\ell_1, 3]$ represents the probability that the estimates p_1^*, p_2^* and p_3^* assume ℓ_1 distinct values. These probabilities may be computed by the following formulas (see Barlow et al., 1972):

$$P_1(1,3) = \frac{1}{4} - \frac{1}{2\pi} \sin^{-1} \rho$$

$$P_1(2,3) = \frac{1}{2}$$

$$P_1(3,3) = \frac{1}{4} + \frac{1}{2\pi} \sin^{-1} \rho,$$

where

$$\rho = -\left[\frac{n_1 n_3}{(n_1+n_2)(n_2+n_3)}\right]^{\frac{1}{2}}.$$

The values for $P_2[\ell_2,3]$ are computed in like fashion. It is worth noting that even when one sample size is 3 or 4 times as large as another, the above probabilities remain close (i.e., to within .01) to the respective probabilities computed under the assumption of equal sample sizes, these being $P(1,3) = .3333$, $P(2,3) = .5$, and $P(3,3) = .1667$. The limiting distribution given above derives its form from the fact that it is the probability that the sum of two independent random variables exceeds the value t, each variable being distributed according to Bartholomew's chi-bar-square distribution (see Barlow et al., 1972).

Table 2 contains the value of the likelihood ratio statistic and the P-values for each of the four data sets. In addition, the P-values for separately testing H_0' vs. $H_A' - H_0'$ and H_0'' vs. $H_A'' - H_0''$ are given. A combined P-value has been computed using the facts given in the introduction.

The most interesting result produced by this analysis

TABLE 2. P-values for testing the two theories

	TEST			
	H_o vs. H_A	H_o' vs H_A'	H_o" vs H_A"	Combined p-value
Male Depression				
L-R Stat	8.51	3.54	3.10	
P-value	0.015	0.063	0.073	0.029
Male Alcoholism				
L-R Stat	0.11	0.0	0.11	
P-value	0.78	1.0	0.518	0.858
Female Depression				
L-R Stat	4.96	4.17	0.79	
P-value	0.082	0.043	0.303	0.069
Female Alcholism				
L-R Stat	7.94	0.36	7.60	
P-value	0.019	0.288	0.007	0.014

concerns male patients and depressed parents. Neither H_0' nor H_0'' can be rejected at the 5% level of significance. However, the P-value for the likelihood ratio statistic for testing H_0 against $H_A - H_0$ is .015. It is also interesting to note that this P-value is smaller than the "combined" P-value implying stronger evidence against H_0 than against $p_1 = p_2 = p_3$, $p_4 = p_5 = p_6$.

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REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER 6	2. GOVT ACCESSION NO. AD-A108 830	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) On testing two theories regarding the genetic makeup of patients suffering from unipolar affective disorder.		5. TYPE OF REPORT & PERIOD COVERED Technical Report
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Tim Robertson Giles Warrack		8. CONTRACT OR GRANT NUMBER(s) N00014-80-C-321
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Statistics The University of Iowa Iowa City, IA 52242		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Office of Naval Research Statistics and Probability Program - Code 436 Arlington, Virginia 22217		12. REPORT DATE 9-2-1981
		13. NUMBER OF PAGES 9
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Order restricted inference, hypothesis tests, χ-bar-squared distribution, unipolar affective disorder.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In an article in the Journal of Psychiatric Research, Cadoret, Woolson and Winokur (1977) consider two theories regarding the genetic makeup of patients suffering from unipolar affective disorder. Using likelihood ratio techniques from order restricted inference we analyze their data and compare the two analyses.

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