Determining the Relationship between Heart Disease and Low Density Lipoprotein levels (LDL) in Ebonyi State by a Method of Analyzing Matched Sample Data with three Possible Responses

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Abstract: Background -In controlled comparative study designs involving matched samples of subjects or patients often times, the response of a subject to a factor in a retrospective study or to a condition or treatment in a prospective study may be dichotomous with only two possible naturally exclusive outcomes and appropriate for analysis using the McNemar Test. This paper aims to analyze marched sample data with three possible responses.

Methods-We here propose a method of analyzing matched sample data in a clinical trial with three possible outcomes or responses. The responses may be qualitative or quantitative. In assessing the statistical significance of differences existing between case-control response scores, we proposed some test statistics.

Results-Given the three possible response categories, the proposed method is illustrated with some sample data. Here the results obtained shows that the proposed test statistic is rejected at the H_0 stated at 1 degree level of significance while the H_0 is accepted at 1 degree level of significance when the Stuart-Maxwell test statistic is applied to the sample data.

Conclusions-The proposed test statistic and the Stuart-Maxwell test statistic indicates that the later test is likely to accept a false null hypothesis (Commit Type II Error) more frequently than the proposed test. The proposed test is likely to be more efficient and powerful than the Stuart-Maxwell test statistic.

Keywords: Stuart-Maxwell test, case, control, clinical trial, matched sample, McNemar Test

INTRODUCTION

In a clinical trial assessing the efficacy of two treatments or drugs or the results of diagnostic tests, subjects or patients are often matched on characteristics associated with the condition of interest [1,2,3]. A member of each pair of the matched subject is randomly assigned to one treatment T_1,the case say and the other member is assigned the other treatment T_2 ,the control say.

Suppose we have n such pairs of case and control subjects. The responses of these pairs to the two treatments or procedures are to be compared. Two situations may arise; the responses may be either numeric with values on the real line or nominal as dichotomized information. First suppose they are numeric such that values in the interval (c_1, c_2) where c_1 and c_2 are real number indicate that the responses by the subjects concerned are normal, negative, condition absent, no, improved, etc and values outside this interval indicate the converse, that is, that the responses by the subjects are abnormal, positive, condition present, yes, not improved etc. If responses are on the nominal scale of measurement, then they may be dichotomous responses of the paired form such as (case positive, control positive); (case positive, control negative); (case negative, control positive) and (case negative, control negative).

Dichotomized data of the later form are usually appropriate for analysis using the McNemar test [4,5,6,1,7]. However, the problem with this dichotomized data is that they are too coarse and do not allow for intermediate values, such as no difference, no effect, indefinite, undecided, no response, etc [8,9,10,11].

In this paper, we propose a method of analyzing data from a clinical trial that allows for three possible responses whether or not the data are measured on a nominal or ratio scale of measurement.

THE PROPOSED METHOD

Suppose a Clinician draws a random sample of n pairs of subjects matched on some characteristics to be used in a clinical trial of two drugs or procedures T_1 *and* T_2 where here T_1 is considered the case and T_2 the control.

Suppose a member of the ith pair of subjects is randomly assigned to treatment T_1 and the remaining member assigned to treatment T_2 for i=1,2,…,n. Let y_{i1} *and* y_{i2} be respectively the responses or scores by the subject assigned treatments T_1 *and* T_2 respectively for the ith pair of subjects for i=1,2,…,n.

Let

$$u_i = \begin{cases} 1, if\ either\ y_{i1} < c_1\ and\ c_1 \le y_{i2} \le c_2, or\ y_{i1} < c_1 \\ and\ y_{i2} > c_2, or\ c_1 \le y_{i1} \le c_2\ and\ y_{i2} > c_2 \\ 0, if\ either\ y_{i1} < c_1\ and\ y_{i2} < c_1, or\ c_1 \le y_{i1} \le c_2 \\ and\ c_1 \le y_{i2} \le c_2, or\ y_{i1} > c_2\ and\ y_{i2} > c_2 \\ -1, if\ either\ c_1 \le y_{i1} \le c_2\ and\ y_{i2} \le c_1, or\ y_{i1} > c_2 \\ and\ y_{i2} < c_1, or\ y_{i1} > c_2\ and\ c_1 \le y_{i2} \le c_2. \end{cases} \quad 1$$

Note that u_i assumes the values 1 if the case in the ith pair of subjects either does not manifest definitive symptoms or responses(has a low score) and the control subject either responds negative (has a normal score) or responds positive (has a high score),or the case responds negative and the control subject responds positive; u_i assumes the value 0 if the case and the control subjects in the ith pair of subjects both manifest the same responses; u_i assumes the value -1 if the case responds either negative or responds positive and the control in the ith pair does not manifest any definitive responses, or the case responds positive and the control responds negative.

Let

$$\pi^+ = P(u_i = 1), \pi^0 = P(u_i = 0), \pi^- = P(u_i = -1) \quad 2$$

$$where\ \pi^+ + \pi^0 + \pi^- = 1 \quad 3$$

$$Define W = \sum_{i=1}^{n} u_i \quad 4$$

Now

$$E(u_i) = \pi^+ - \pi^-\ and\ \mathrm{var}(u_i) = E(u_i^2) - E(u_i)^2 \quad 5$$

That is

$$\mathrm{var}(u_i) = \pi^+ + \pi^- - (\pi^+ - \pi^-)^2 \quad 6$$

Also

$$E(W) = E\left(\sum_{i=1}^{n} u_i\right) = \sum_{i=1}^{n} E(u_i)$$

Or

$$E(W) = n(\pi^+ - \pi^-) \quad 7$$

Note that the sample estimates of π^+, π^0 *and* π^- are respectively P^+, P^0 *and* P^- given as

$$P^+ = \hat{\pi}^+ = \frac{f^+}{n}; P^0 = \hat{\pi}^0 = \frac{f^0}{n} and\ P^- = \hat{\pi}^- = \frac{f^-}{n} \quad 8$$

Where f^+, f^0 *and* f^- are respectively the number of 1s, 0s and -1's in the frequency distribution of the n values of numbers in u_i .Note also that the difference between π^+ *and* π^- namely $\pi^+ - \pi^-$ is estimated as

$$\hat{\pi}^+ - \hat{\pi}^- = \frac{W}{n} = \frac{f^+ - f^-}{n} \quad 9$$

Now

$$Var(W) = E(W^2) - E(W)^2 = E\left(\sum_{i=1}^{n} u_i^2\right) - E\left(\sum_{i=1}^{n} u_i\right)^2$$

which on simplification and evaluation yields

$$Var(W) = n\left(\pi^+ + \pi^- - (\pi^+ - \pi^-)^2\right) \quad 10$$

Alternatively

Var(W) may be written using Equ 9 as

$$Var(W) = n\left(\pi^+ + \pi^-\right) - \frac{W^2}{n} \quad 11$$

The null hypothesis that the case and control subjects do not differ in their responses to the treatments or drugs is equivalent to testing the null hypothesis.

$$H_0: \pi^+ = \pi^- \ or\ H_0: \pi^+ - \pi^- = 0\ versus\ H_1: \pi^+ - \pi^- \neq 0 \quad 12$$

H_0 may be tested using the test statistic

$$\chi^2 = \frac{W^2}{n\left(\hat{\pi}^+ + \hat{\pi}^-\right)} - \frac{W^2}{n} \quad 13$$

Which under H_0 has the chi-square distribution with 1 degree of freedom for sufficiently large n. H_0 is rejected at the α level of significance if $\chi^2 \geq \chi^2_{1-\alpha;1}$. Otherwise H_0 is accepted. Where $\chi^2 \geq \chi^2_{1-\alpha;1}$, is the critical chi-square value obtained from an appropriate table of the chi-square distribution with 1 degree of freedom for a specified α level.

ILLUSTRATIVE EXAMPLE

A medical researcher is interested in knowing the relationship between heart disease and low density lipoprotein levels (LOL). Using a random sample of 36 non-heart disease patients and another random sample of 36 heart disease patients she paired each non-heart disease with a heart disease patient matched on age, gender, body weight and occupation and then measured the LOL level of each subject in the pair. The results are presented in Table 1

S/n	LOL Paired	Scored number (u_i)
1	(1.97,4.14)	0
2	(3.70,1.57)	-1
3	(5.4,5.6)	0
4	(2.6,5.1)	1
5	(3.1,1.50)	-1
6	(1.48,4.56)	1
7	(1.69,1.70)	0
8	(4.99,1.21)	-1
9	(2.34,2.51)	0
10	(3.95,1.55)	-1
11	(4.84,1.25)	-1
12	(4.68,4.59)	0
13	(1.29,1.37)	0
14	(1.15,6.24)	1
15	(5.41,1.20)	-1
16	(4.62,1.25)	-1
17	(2.02,1.53)	-1
18	(1.45,1.30)	0
19	(5.31,1.07)	-1
20	(5.18,4.37)	-1
21	(4.52,5.38)	1
22	(5.03,3.34)	-1
23	(5.21,4.55)	0
24	(4.74,5.59)	0
25	(3.76,3.96)	0
26	(5.21,3.50)	-1
27	(5.09,4.66)	0
28	(1.97,4.14)	0
29	(2.6,5.1)	1
30	(1.69,1.70)	0
31	(3.95,1.55)	-1
32	(1.29,1.37)	0
33	(4.62,1.25)	-1
34	(5.31,1.07)	-1
35	(5.03,3.34)	-1
36	(3.76,3.96)	0

LOL Normal range (1.68,4.53).

Applying the specifications of Equation 1 to the LDL levels in table 1 with $c_1 = 1.68$ the lowest LDL normal level and $c_2 = 4.53$ the highest LDL normal level, we obtain the corresponding scores of 1s,0s and -1s levels shown in the 3rd column of the table.

Thus we have $f^+ = 5, f^0 = 15 \; and \; f^- = 16$

Hence we have from Equation 8 that

$$p^+ = \hat{\pi}^+ = \frac{5}{36} = 0.139, p^0 = \hat{\pi}^0 = \frac{15}{36} = 0.417 \; and \; p^- = \hat{\pi}^- = \frac{16}{36} = 0.444$$

And from Equation 9 we have that

$$W = 5 - 16 = -11$$

The estimated variance of W (Equation 11) is

$$Var(W) = 36(0.139 + 0.444) - \frac{(-11)^2}{36} = 20.988 - 3.361 = 17.627.$$

The null hypothesis to be tested is that heart disease patients and non-heart disease patients do not differ in their LDL levels which is equivalent to testing

$$H_0 : \pi^+ - \pi^- = 0 \; versus \; H_1 : \pi^+ - \pi^- \neq 0.$$

Using the test statistic of Equation 13 we have that

$$\chi^2 = \frac{(-11)^2}{17.627} = \frac{121}{17.627} = 6.864(P - value = 0.0091)$$

which has 1 degree of freedom.

Therefore, since P-value=0.0091, the null hypothesis H_0 would be rejected at the percent significant level enabling the conclusion that heart disease patients and non-heart disease patients do in fact differ in their LDL levels. We now use the Stuart-Maxwell test [12,13,14,2,15,16] to re-analyze the above data which are represented in table 2 for comparative purposes.

Table 2: Matched Sample Data on LDL levels of Patients Analysis using Stuart-Maxwell Method.

	Control Score			
	1	0	-1	Total
Case Score	$(y_1 < c_1)$	$(c_1 \leq y_2 \leq c_2)$	$(y_2 > c_2)$	
1	4	0	2	6
$(y_1 < c_1)$				
0	5	6	3	14
$(c_1 \leq y_2 \leq c_2)$				
-1	7	4	5	16
$(y_2 > c_2)$				
Total	16	10	10	36

The Stawart-Maxwell test statistic is

$$\chi^2 = \frac{\bar{n}_{23} d_1^2 + \bar{n}_{13} d_2^2 + \leq \bar{n}_{12} d_3^2}{2\left(\bar{n}_{12}\bar{n}_{13} + \bar{n}_{12}\bar{n}_{23} + \bar{n}_{13}\bar{n}_{23}\right)} \qquad 14$$

$where$

$$d_i = n_{i.} + n_{.i}, i = 1, 2, 3 \qquad 15$$

and

$$\bar{n}_{ij} = \frac{n_{ij} + n_{ji}}{2} \qquad 16$$

$for \; i = 1, 2, 3; \; j = 1, 2, 3; i \neq j$

$Hence \; from \; Table \; 2 \; we \; have \; that$

$$d_1 = 6-16 = -10; d_2 = 14-10 = 4; d_3 = 16-10 = 6 \textit{ and}$$

$$\bar{n}_{12} = \frac{0+5}{2} = 2.5; \bar{n}_{13} = \frac{2+7}{2} = 4.5; \textit{and } \bar{n}_{23} = \frac{3+4}{2} = 3.5$$

Thus from Equation 4 we have that

$$\chi^2 = \frac{(3.5)(-10)^2 + (4.5)(4)^2 + (2.5)(6)^2}{2(2.5)(4.5) + (2.5)(3.5) + (4.5)(3.5)} = \frac{512}{2(35.75)} = 7.161(P-value = 0.0354)$$

which is a Chi-Square distribution with 2 degrees of freedom. With P-value of 0.0354; the calculated Stuart-Maxwell test statistic, $\chi^2 = 7.161$ with 2 degrees of freedom is now statistically significant. At the 1 percent level and hence the null hypothesis of equal LDL levels for patients with and without heart disease is now no longer rejected. Furthermore, the results so far obtained on the basis of the proposed test statistic and the Stuart-Maxwell test statistic indicates that the later test is likely to accept a false null hypothesis (Commit Type II Error) more frequently than the proposed test. This suggests that the proposed test is likely to be more efficient and powerful than the Stuart-Maxwell test statistic.

SUMMARY AND CONCLUSIONS

We have in this paper presented a method of analyzing matched sample data in a clinical trial with three possible outcomes or responses. The responses may be qualitative or quantitative. The proposed method is illustrated with some data. In particular, the results obtained shows that the proposed test statistic is rejected at the H_0 stated at 1 degree level of significance while the H_0 is accepted at 1 degree level of significance when the Stuart-Maxwell test statistic is applied to the sample data. Therefore, the proposed test statistic and the Stuart-Maxwell test statistic indicates that the later test is likely to accept a false null hypothesis (Commit Type II Error) more frequently than the proposed test. This suggests that the proposed test is likely to be more efficient and powerful than the Stuart-Maxwell test statistic.

Ethical approval

No ethical approval.

Author contribution statement

Dr. Okeh, U.M.: Conceived and proposed the method, Analyzed and interpreted the data, wrote the paper. He provided materials that assisted in writing the paper, proofread the manuscript and made useful inputs. Emeji E.O.: Collected the data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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