Generalised Test For C- Matched Samples

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Abstract: This paper proposes a generalized statistical method for the analysis of multiple responses or outcome data in case control studies including situations in which the observations are either continuous or frequency data. Test statistics are proposed for assessing the statistical significance of differences between case-control response scores. The proposed methods are illustrated with some sample data. When there are only three possible response options in which the proposed method and the Stuart/Maxwell test can be equally used to analyze the data; the proposed test statistic is shown to be at least as powerful as the Stuart/Maxwell test statistic.

Keywords: Generalised Test, Multiple Responses, Standard and Control Drug, Staurt/ Maxwell Test, Test Statistic

1. Introduction

Often in controlled comparative prospective or retrospective studies involving matched samples of subjects or patients, the response of a subject to a predisposing factor in a retrospective study or to a condition or treatment in a prospective study, may be much finer than simply dichotomous. For example in a retrospective study where the predisposing factor maybe a subject's employment status, a subject maybe classified as unemployed, self employed, public servant, student, housewife etc. In a prospective study involving some conditions or tests, subjects or patients maybe classified as recovered, much improved, improved, no change, worse or dead. A treatment or drug may be graded as very effective, effective, ineffective etc. If there are only three possible response options or categories, then the Stuart-Maxwell test (Fleiss 1974, Robertson et al 1994, Schlesselman 1982, Zhao and Kolonel 1992, Box and Cox 1964, Maxwell 1970, Stuart 1955, Fleiss 1981, Everitt 1977) may be used to analyse the data. We however here present a more generalized approach to the problem.

2. The Proposed Method

In general, suppose we have a random sample of n - pairs of patients or subjects matched on a number of characteristics to be exposed to two experimental conditions, treatments, drugs or tests. Suppose further that the responses of these pairs of subjects are more than dichotomous but numbering c (c≥2) possible response options. Suppose further that i_{th} pair of patients is selected, for i = 1, 2, … ,n and one member of the pair is randomly assigned to one of the treatments T_1 (standard drug; control), say, and the remaining member of the pair is assigned to the second treatment T_2 (new drug; case) say, and the various c (c≥2) possible responses are recorded for each subject. That is the responses of each matched pair of subjects are classified into c mutually exclusive categories or classes. The appropriate data presentation format is as in

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Table 1

Table 1: Format for Presentation of Data on 'c' Outcomes in Matched Pairs

		Outcome Category for Control (Standard T_1)					
Outcome Category for Cases (Experimental Condition T_2)		1	2	.	.	. c	Total($n_{i.}$)
	1	n_{11}	n_{12}	.	.	$.n_{1c}$	$n_{1.}$
	2	n_{21}	n_{22}	.	.	$.n_{2c}$	$n_{2.}$
	.	.	.		.	.	
	.	.	.		.	.	
	.	.	.		.	.	
	C	n_{C1}	n_{C2}	.	.	. n_{CC}	$n_{C.}$
Total	$(n_{.j})$	$n_{.1}$	$n_{.2}$	.	.	. $n_{.c}$	$\mathrm{n}(=n_{..})$(Miettinen 1969, Box and Cox 1964))

Each entry in Table 1 consists of a matched pair of case and control subjects. For example n_{11} is the numbers of matched pairs of subjects in which both the case and control subjects are in category 1 response; n_{12} is the number of pairs in which the case is in category 1 response and the control subject is in category 2 response or in outcome category 2; and in general n_{1j} is the number of pairs in which the case is in category 'I' response while the corresponding control subject is in outcome or response category 'j'. Also $n_{1.}$ is the total number of pairs in which the case is in category 1 response, $n_{.2}$ is the total number of pairs in which the control subject is category 2 response. In general $n_{i.}\ and\ n_{.j}$ are respectively the total number of pairs in which the case is category 'I' response and the control is in category 'j' response for $i = 1, 2, \dots, c, j = 1, 2, \dots, c$.

In all, there are a total of

$$n = n.. = \sum_{i=1}^{c}\sum_{j=1}^{c} n_{ij} = \sum_{i=1}^{c} n_{i.} = \sum_{j=1}^{c} n_{.j}$$

subjects studied.

As in the Stuart/ Maxwell methods, let the difference between the number of pairs of respondents in the i_{th} category of responses for case and i_{th} category of responses for control be

$$d_i = n_{i.} - n_{.i}$$

(Miettinen, 1969, Maxwell 1970,

Everitt, 1977, Stuart, 1955) ……. 1

which is independent of n_{ii}, $i = 1, , \dots, c, the$ number of pairs in which both case and control subjects have the same response or outcome. Also let

$$d_{ij} = n_{ij} - n_{ji}$$

…… 2

which is the difference between the number of pairs in which the case is in the response category i and the control is in the response category j and the number of pairs in which the case is in response category j and the control is in the response category i; $i = 1, 2, \dots, c; j = 1, 2, \dots, c;\ i \neq j$.

Now having selected our random sample of n matched pairs, let x_{i1} be the response by a member of the randomly selected i_{th} pair of patients or subjects randomly assigned treatment T_1 (control standard drug) and x_{i2} be the response by the other member of the pair of patients or subjects assigned treatment $T_2(\,case, new\ drug)$ for $i = 1, 2, \dots, n$. We here assume for ease of presentation but without loss of generality, that the c mutually exclusive possible response categories have been ordered from the highest or most serious (lowest or least serious) level of response to the lowest or least serious (highest or most serious) level of response . for example, a patient's response to a treatment for an illness or disease may range from recovered , most improved, through no change to worse or death; a subject response to a screening test may range variously from definitely positive to definitely negative. For candidate's or student's performance in a job interview or examination may range from very poor to excellent etc.

$or\ subjects\ assigned\ treatmnt T_2\ (case)$is a higher or more serious (lower or less serious) level of response than x_{i1} , the

Now let

$u_i = \{1,$ *if* x_{i2}, *the response by the member in the* i_{th} *pair of patients* or subjects assigned treatment T_2 (case) is a higher or more serious () level of response than, the response by the other member of the pair assigned treatment T_1 (control) for all the c response categories.

0, if x_{i1} and x_{i2} are the same level of response for the two patients or subjects in the i_{th} pair for all the c response categories

-1, if x_{i2} the response by the member in the i_{th} pair of patients or subjects assigned treatment T_2 (case) is a lower or less serious (higher or more serious) level of response than x_{i1} the response by the other member of the pair assigned treatment T_1 (control) for all the c response categories ……3

For $i = 1, 2, \dots, n$

This means that u_i assumes the value 1, if the response of the member of the i_{th} pair of patients administered treatment T_2 (case) is a higher or more serious (lower or less serious) level of response than the response of the other member of the pair administered treatment T_1 (control); 0, if the response of the two members of the pair are the same; and -1 , if the response of the member of the i^{th} pair of patients administered treatment T_2 (case) is a lower or less serious(higher or more serious) level of response than the response of the other member of the pair administered treatment T_1 (control) for all the c response categories.

Now let

$\pi^+ = P(u_i = 1);\ \pi^0 = P(u_i = 0);\ \pi^- = P(u_i = -1)$ …….4

Where

$\pi^+ + \pi^0 + \pi^- = 1$ ……5

Let

$W = \sum_{i=1}^{n} u_i$ …….6

Now

$E(u_i) = \pi^+ - \pi^-$ ……..7

And

$Var(u_i) = \pi^+ + \pi^- - (\pi^+ - \pi^-)^2$ …….8

Also

$E(W) = \sum_{i=1}^{n} Eu_i = n(\pi^+ - \pi^-)$ ……9

Note that $\pi^+ - \pi^-$ is the differential response rate between the sub-populations administered treatments T_2 (case) and T_1(control) respectively in the paired population of patients or subjects for all the c response categories and is estimated by

$\pi^+ - \pi^- = \frac{W}{n}$ ……. 10

Note also that π^+, π^0 and π^- which are respectively the probabilities that a randomly selected case is at a higher (or more serious) level, the same or lower (or less serious) level of response than the corresponding control subject in the pair for all the c response categories are estimated using the notations in Table 1 and following the specifications in Equation 3 as

$$\hat{\pi}^+ = p^+ = \frac{f^+}{n} = \frac{\sum_{i=1}^{c-1}\sum_{j=2}^{c} n_{ij}}{\substack{n \\ i<j}} \quad \text{…..11}$$

$$\hat{\pi}^0 = p^0 = \frac{f^0}{n} = \frac{\sum_{i=1}^{c} n_{ii}}{n} \quad \text{….12}$$

And

$$\hat{\pi}^- = p^- = \frac{f^-}{n} = \frac{\sum_{i=2}^{c}\sum_{j=1}^{c-1} n_{ij}}{\substack{n \\ i>j}} \quad \text{…… 13}$$

Where f^+, f^0 *and* f^- are respectively the number of 1s, 0s and -1s in the frequency distribution of the n values of these numbers in u_i in accordance with Equation 3

Hence using these results in 10 we have

$$w = f^+ - f^- = \sum_{i=1}^{c-1}\sum_{j=2}^{c} n_{ij} - \sum_{i=2}^{c}\sum_{j=1}^{c-1} n_{ij}$$
$$i<ji>j \text{…..} \ 14$$

Furthermore the variance of W is obtained as

$$Var(w) = \sum_{i=1}^{n} Var(u_i) + \binom{n}{2} cov(u_i, u_j)$$
$$= nVar(u_i) + \binom{n}{2} cov(u_i, u_j)$$
$$i<ji<j$$

Where Var((u_i) is given by Equation 8 and

$cov(u_i, u_j) = Eu_iu_j - Eu_iu_j$

Now u_iu_j can assume only the values *1,0,−1*

$u_iu_j = 1$, if u_i *and* u_j are both equal to 1 or both equal to -1 with probabilities $(\pi^+)^2 + (\pi^-)^2$, the value 0, if u_i and u_j both assume the value 0, or u_i assume the value 0 no matter the values assumed by u_j, or u_j assumes the value '0' no matter the values assumed by u_i with probability

$2\pi^0(\pi^+ + \pi^-) + (\pi^0)^2$; and the value -1 if u_i assumes the value 1 and u_j assumes the value -1, or u_j assumes the value 1 and u_i assumes the value -1 with probability

$$\pi^+\pi^- + \pi^-\pi^+ = 2\pi^+\pi^-$$

Hence

$$Eu_iu_j = (1)(\pi^+)^2 + (\pi^-)^2 + (0)2\pi^0(\pi^+ + \pi^-) + (\pi^0)^2 + (-1) = (\pi^+)^2 + (\pi^-)^2 - 2\pi^+\pi^- = (\pi^+ - \pi^-)^2$$

So that using Equation 7, we have that

$$Cov(u_iu_j) = (\pi^+ - \pi^-)^2 - (\pi^+ - \pi^-)^2 = 0$$

Hence from Equation 8, we have that

$$Var(w) = n(\pi^+ + \pi^- - (\pi^+ - \pi^-)^2) \quad \ldots\ldots\ldots\ldots\ldots\ldots 15$$

Or equivalently using Equation 10, we have that

$$Var(w) = n(\pi^+ + \pi^-) - \frac{W^2}{n} \quad \ldots\ldots\ldots\ldots\ldots 16$$

As noted above π^+ is the proportion of pairs of case and control subjects in which on the average the response rate by the sub-population of patients or subjects administered treatment T_2 (new drug, case) is greater (less) than the response rate by the sub-population of patients or subjects administered treatment T_1 (standard drug, control); while π^- is the proportion of pairs in which on the average response rate by the sub- population of patients or subjects administered treatment T_1 (standard drug, control) is greater (less than the response rate by the sub-population of patients administered treatment T_2 (new drug, case) in the paired population of patients for all response categories. Hence the null hypothesis that there exists no difference between the response rates by the sub-population of patients administered treatment T_2 (new drug, case) and the sub-population of patients administered treatment T_1 (standard drug, control) in the paired population of patients for all response categories is equivalent to the null hypothesis

$$H_0: \pi^+ - \pi^- = 0 \; versus \; H_1: \pi^+ - \pi^- \neq 0 \quad \ldots\ldots\ldots\ldots\ldots 17$$

To test this null hypothesis, we may use the test statistic

$$\chi^2 = \frac{W^2}{Var(W)} = \frac{W^2}{n(\pi^+ - \pi^-) - \frac{W^2}{2}} \quad \ldots\ldots\ldots\ldots\ldots\ldots 18$$

which under H_0 has approximately a chi- square distribution with *1* degree of freedom for sufficiently large n. Although strictly speaking the test statistic in Equation 18 has a Chi-square distribution with 1 degree of freedom; however because its construction in equation 3 involves a combination of some c response categories, to help increase its power and reduce the chances of erroneously accepting a take null hypothesis (Type 1 error), it is here recommended that all comparisons should be made against critical Chi- Square values with c-1 degrees of freedom. Hence here H_0 is rejected at the α level of significance if $\chi^2 \geq \chi^2_{1-\alpha,\ c-1}$, otherwise H_0 is accepted.

In practical applications and use $\pi^+ and\ \pi^-$ in Equation 18 are replaced by their sample estimates given in Equations 11 and 13 respectively so that

$$n(\hat{\pi}^+ - \hat{\pi}^-) = \sum_{i=1}^{c-1}\sum_{j=2}^{c} n_{ij} + \sum_{i=2}^{c}\sum_{j=1}^{c-1} n_{ij} \quad \ldots\ldots\ldots 19$$

Hence the test statistic (Equation 18) becomes

$$\chi^2 = \frac{\left(\sum_{\substack{i=1\\ i<j}}^{c-1}\sum_{j=2}^{c} n_{ij} - \sum_{\substack{i=2\\ i>j}}^{c}\sum_{j=1}^{c-1} n_{ij}\right)^2}{\sum_{\substack{i=1\\ i<j}}^{c-1}\sum_{j=2}^{c} n_{ij} + \sum_{\substack{i=1\\ i>j}}^{c}\sum_{j=2}^{c-1} n_{ij} - \frac{\left(\sum_{\substack{i=1\\ i<j}}^{c-1}\sum_{j=2}^{c} n_{ij} - \sum_{\substack{i=1\\ i>j}}^{c}\sum_{j=2}^{c-1} n_{ij}\right)^2}{n}} \quad \ldots\ldots\ldots 20$$

Note that if $c = 2$, equation 20 under H_0 reduces to a modified version of the McNemar test statistic which is

$$\chi^2 = \frac{(n_{12} - n_{21})^2}{n_{12} + n_{21} - \frac{(n_{12} - n_{21})^2}{n}} \quad \ldots\ldots\ldots 21$$

which has a chi- square distribution with $c - 1 = 2 - 1 = 1$ degree of freedom. Note that equation 21 has smaller variance than the usual McNemar test because of its modification to provide for possible ties between case and control subject pairs in their responses.

If $c = 3$, equation 20 under H_0 reduces to

$$\chi^2 = \frac{\left((n_{12} - n_{21}) + (n_{13} - n_{31}) + (n_{23} - n_{32})\right)^2}{n_{12} + n_{13} + n_{21} + n_{23} + n_{31} + n_{32} - \frac{\left((n_{12} - n_{21}) + (n_{13} - n_{31}) + (n_{23} - n_{32})\right)^2}{n}} \quad \ldots\ldots\ldots 22$$

which has a chi-square distribution with $c - 1 = 3 - 1 = 2$ degrees of freedom. If $c = 4$, equation 20 becomes

$$\chi^2 = \frac{\left((n_{12} - n_{21}) + (n_{13} - n_{31}) + (n_{14} - n_{41}) + (n_{23} - n_{32}) + (n_{24} - n_{42}) + (n_{34} - n_{43})\right)^2}{n_{12} + n_{13} + n_{14} + n_{23} + n_{24} + n_{34} + n_{21} + n_{31} + n_{41} + n_{32} + n_{42} + n_{43} - \frac{\left((n_{12} - n_{21}) + (n_{13} - n_{31}) + (n_{14} - n_{41}) + (n_{23} - n_{32}) + (n_{24} - n_{42}) + (n_{34} - n_{43})\right)^2}{n}} \quad \ldots\ldots\ldots 23$$

which has a chi-square distribution with $c - 1 = 4 - 1 = 3$ degrees of freedom finally note that if we let

$$m = n_{ij} + n_{ji}, \; i \neq j \quad \ldots\ldots\ldots 24$$

Then the test statistic of equation 20 can be written in easier and more compact form using equations 2 and 24 as

$$\chi^2 = \frac{\left(\sum_{i=1}^{c-1}\sum_{j=2}^{c} d_{ij}\right)^2}{\sum_{\substack{i=1}}^{c-1}\sum_{\substack{j=2\\ i<j}}^{c} m_{ij} - \frac{\left(\sum_{i=1}^{c-1}\sum_{\substack{j=2\\ i<j}}^{c} d_{ij}\right)^2}{n}} \quad \ldots\ldots\ldots\ldots\ldots\ldots 25$$

If Equation 20 leads to a rejection of the null hypothesis of equal response rate, then one may wish to proceed to identifying the response categories or combination of categories that may have led to the rejection of H_0. This is done by appropriately pooling or combining the response options into (3) groups and applying the Stuart Maxwell test or into (2) groups and applying the McNemar test (McNemar 1983, Somes 1983, Sheskin 2000) to each of the groups. In all cases comparisons are made using critical chi- square values with $c-1$ degrees of freedom to again avoid erroneous conclusions.

3.1 Illustrative Example

We have use data on matched pairs of trial 230 patients from a controlled comparative clinical trial who manifest four possible responses to illustrate the proposed method. Suppose the data in Table 2 are obtained by assigning a standard treatment T_1 (control) and a new treatment T_2 (case) at random to members of each pair of a random sample of 230 pairs of malaria patients matched on age, gender and body weight used in a controlled clinical trial to compare the effectiveness of two malaria drugs.

Table 2: Data from Controlled Comparative Clinical Trial Using Matched Pairs with Four Responses

	Standard Treatment T_1 (Control)				
New Treatment T_2 (case)	Improved	No Change	Worse	Dead	Total
Improved	60	31	20	4	115 $(=n_{1.})$
No Change	16	24	16	6	62 $(=n_{2.})$
Worse	12	7	14	8	41 $(=n_{3.})$
Dead	3	4	2	3	12$(=n_{4.})$
Total	91	66	52	21	230$(=n_{..})$

To test the null hypothesis that case and control do not differ in their response to the treatments Equation 17, we have from equation 11 that

$$\hat{\pi}^+ = \frac{31+20+4+16+6+8}{230} = \frac{85}{230} = 0.370$$

And from Equation 13, we have that

$$\hat{\pi}^- = \frac{16+12+3+7+4+2}{230} = \frac{44}{230} = 0.191$$

Note that $\hat{\pi}^0 = 1 - (0.370 + 0.191) = 0.439$

Also from Equation 10, we have that

$$W = n(\hat{\pi}^+ - \hat{\pi}^-) = 230(0.370 - 0.191) = 230(0.179) = 41.17$$

From Equation 16, we have that

$$Var(W) = 230(0.370 + 0.191) - \frac{(41.17)^2}{230} = 129.03 - 7.369 = 121.661$$

Hence from Equation 23, we have that

$$\chi^2 = \frac{(41.17)^2}{121.661} = \frac{1694.969}{121.661} = 13.932 (Pvalue = 0.0014)$$

which with $c-1 = 4-1 = 3$ degrees of freedom is highly statistically significant.We may therefore conclude at the 1 percent significance level that the treatments have differential effects on the patients. To compare this method with the Stuart Maxwell test, we assume for this purpose that there were no reports on deaths. We therefore delete the 'dead' category giving a reduced sample size of $n = 200$. So that now $c = 3$ making the data appropriate for the Stuart -Maxwell test. With these reduced data, we have that

$$\hat{\pi}^+ = \frac{31+20+4+16}{200} = \frac{67}{200} = 0.335$$

$$\hat{\pi}^- = \frac{16+12+7}{200} = \frac{85}{200} = 0.175$$

Also

$$W = n(\hat{\pi}^+ - \hat{\pi}^-) = 200(0.335 - 0.175) = 200(0.160) = 32.00$$

And

$$Var(W) = 200(0.335 + 0.175) - \frac{(32.0)^2}{200} = 102.0 - 5.12 = 96.88$$

Hence from Equation 22, we have that

$\chi^2 = \frac{(32.00)^2}{96.88} = \frac{1024}{96.88} = 10.570 (Pvalue = 0.0051)$ which with $c-1 = 3-1 = 2$ degrees of freedom is statistically significant at $\alpha = 0.01\left(\chi^2_{0.99,\ 2} = 9.210\right)$. Hence the null hypothesis of equal response rates is rejected at the1 percent level of significance.

If we had used the Stuart Maxwell method to analyse the data we would have from Equation 1 that $d_1 = 111 - 88 = 23; d_2 = 56 - 62 = -6; d_3 = 33 - 50 = -17$

Also letting $\bar{n}_{ij} = \frac{n_{ij}+n_{ji}}{2}, i = 1,2,3; j = 1,2,3; i \neq j$, we have

$$\bar{n}_{12} = \frac{31+16}{2} = \frac{47}{2} = 23.5;\ \bar{n}_{13} = \frac{20+12}{2} = \frac{32}{2} = 16.0;\ \bar{n}_{23} = \frac{16+7}{2} = \frac{23}{2} = 11.5$$

Hence using the Stuart Maxwell test, we have

$$\chi^2 = \frac{115(23)^2 + 16.0(-6)^2 + 23.5(-17)^2}{2\big((23.5)(16.0) + (23.5)(11.5) + (16.0)(11.5)\big)} = \frac{6083.5 + 576 + 6791.5}{2(376 + 270.25 + 184)} = \frac{13451}{2(830.25)} = \frac{13451}{1660.5} = 8.101(Pvalue = 0.0237)$$

which with 2 degrees of freedom is statistically significant at the 2 percent but not statistically significant at the 1 percent significance level, the usually used norm in medical research. Thus the present (extended) method leads to a rejection of the null hypothesis H_0 while theStuart/ Maxwell test statistic leads to an acceptance of the null hypothesis at the 1 percent significance level. Hence the Stuart/ Maxwell test is likely to lead to an acceptance of a false null hypothesis (type 11 Error) more frequently than the present modifiedmethod. This means that the present test statistic is likely to be more efficient and powerful than the Stuart /Maxwell test statistic. The present generalized method may also be used to analyse quantitative data obtained in matched controlled studies. Often responses from controlled experiments are reported as numeric scores assuming all possible values on the real line. For example, these responses may be values on any real line such that scores in the interval (c_1, c_2) where $c_1$and c_2 are any real numbers $(c_1 < c_2), indicate$ that the responses by the subjects concerned are normal, negative, condition absent, no improved, etc ; values less than c_1 indicate that the subjects have abnormally low score ; and values above c_2 indicate that the subjects have abnormally high score. It is also possible to have situations in which subjects have scores that are either some c_3 units below $c_1$or some $c_4\ units\ above\ c_2$. These subjects may be considered to have non specific or non definitive manifestations. Subjects whose scores are below c_3 or above c_4 may be considered to have critically abnormal manifestations, one below the critical minimum and the other above the critical maximum normal scores. If these results are considered important manifestations, then the first set of subjects may be grouped into three response categories, while the second set of subjects may be grouped into five response categories for policy and management purposes. To illustrate the use of the present generalized method when case and control subjects in matched controlled studies have quantitative scores with three possible outcomes for instance, we would proceed as follows. Suppose as above, a random sample of n pairs of case and control subjects are used in a controlled experiment on two procedures $T_1(control\ standard)\ and\ T_2(case, new\ procedure)$.
Suppose as before, one member of each pair is randomly assigned treatment $T_1(control\ standard)$ and the remaining member assigned treatment $T_2(case)$ Let $y_{i1}\ and\ y_{i2}$ be respectively the responses or scores with real values quantitatively measured by the subjects assigned treatment $T_1(control)\ and\ T_2(case)$ for the i_{th} pair of subject for $i = 1, 2, \dots, n$. Then u_i of Equation 3 may now be defined as

$$\begin{cases} u_i = 1, & if\ either\ y_{i2} < c_1\ and\ c_1 \le y_{i1} \le c_2\ or\ y_{i2} < c_1\ and\ y_{i1} \ge c_2\ or\ c_1 \le y_{i2} \le c_2\ and\ y_{i1} \ge c_2 \\ 0, & if\ either\ y_{i2} < c_1\ and\ y_{i1} < c_1\ or\ c_1 \le y_{i2} \le c_2\ and c_1 \le y_{i1} \le c_2\ or\ y_{i2} > c_2\ and\ y_{i1} > c_2 \\ -1, & if\ either\ c_1 \le y_{i2} \le c_2\ and\ y_{i1} < c_1\ , or\ y_{i2} < c_2\ and\ y_{i1} < c_1\ , or\ y_{i1} > c_2\ and\ c_1 \le y_{i1} \le c_2 \end{cases} \quad \text{.....26}$$

For $i = 1, 2, \dots, n$

Note that this specification may be depicted in a 3x3 table if we let n_{ij} be the number of paired case and control subjects in the $(i,j)th$ case –control response classification for $i = 1,2,3\ and\ j = 1,2,3$. Specifications similar to Equation 26 can also be easily developed for more than three quantitative response categories. Now to use Equation20 to analyse these data, we would again simply define $\pi^+, \pi^0, \pi-\ and\ W\ as$ in Equations *4−6*. Then data analysis proceeds as usual

3.2 Illustrative Example 2

A medical researcher is interested in knowing the relationship between heart disease and low density lipo-protein levels (LDL). 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 patient with a heart disease patient matched in age, gender, body weight and occupation and then measured the LDL level of each subject in the pair . The results are presented in Table 3

Table 3: LDL levels of Paired Samples of Patients in a Clinical Trial

S/N	Paired LDL levels	Scores (u_i
1	$(1.97, 4.14)$	0
2	$(3.70, 1.57)$	-1
3	$(5.40, 5.60)$	0
4	$(2.60, 5.10)$	1
5	$(3.10, 1.50)$	-1
6	$(1.48, 4.56)$	1
7	$(1.69, 1.70)$	0
8	$(4.97, 1.21)$	-1
9	$(2.34, 2.51)$	0
10	$(3.95, 1.55)$	-1
11	$(4.84, 1.25)$	-1
12	$(4.65, 4.59)$	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	$(2.60, 5.10)$	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

LDL Normal range $(1.68, 4.53)$

Applying the specification of Equation 26 to the LDL levels of Table 3 with $c_1 = 1.68$, the lowest and 4.53 the highest normal values respectively, we obtain the corresponding scores u_i of $1_s, 0_s \; and \; -1_s$ shown in the $3rd$ column of this table

Thus we have $f^+ = 5, f^0 = 15 \; and \; f^- = 16$. Hence, we have from Equations *11 – 13* that

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

From Equation14, we have that the estimated variance of $W(Equation\ 16)$ 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 20 or 22, we have that

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

$$(P\ value = 0.0391)$$

which with $c - 1 = 3 - 1 = 2$ degrees of freedom is statistically significant at only the 5 percent level $\left(\chi^2_{0.95,2} = 5.991\right.$ we may therefore conclude that heart disease patients and non- heart disease patients do infact differ in their LDL levels. The data of Table 2 may infact be represented by a $3x3$ table and following the specifications of Equation 26 with $c_1 = 1.68 \; and \; c_2 = 4.53$ to aid in clearer analysis as in Table 3

Table 4: Distribution of Scores u_i of Matched pairs of case and control subjects of Table 3

	Control $(T_1)\ Scores$			
Case $(T_2)\ Scores$	Below Normal $y_{i1} < 1.68$	Normal $1.68 \leq y_{i1} \leq 4.53$	Above Normal $y_{i1} > 4.53$	Total
Below Normal $y_{i2} < 1.68$	4	0	2	6
Normal $1.68 \leq y_{i2} \leq 4.53$	5	6	3	14
Above Normal $y_{i2} > 4.53$	7	4	5	16
Total	16	10	10	36

To re-analyse these data consistent with the generalized method, we have from Equation 11 that

$$\hat{\pi}^+ = \frac{0 + 2 + 3}{36} = \frac{5}{36} = 0.139$$

From Equation 12, we have that

$$\hat{\pi}^0 = \frac{4 + 6 + 5}{36} = \frac{15}{36} = 0.417$$

And from Equation 13, we have that

$$\hat{\pi}^- = \frac{5 + 7 + 4}{36} = \frac{16}{36} = 0.444$$

These are the same results obtained earlier using the scores in Table 3. We would therefore obtain the same values of $W(-11)$and chi-square (*6.864*)and arrive at the same conclusions. Hence, the present example illustrates how to analyse matched quantitative test scores without first converting them into frequency data. The data of Example 2as presented in Table 4 may also be analysed using the Stuart/ Maxwell test. However as already pointed out, the Stuart/ Maxwell test statistic is atmost as powerful as the test statistic used in the proposed method presented here when the two methods are used with data of equal sample sizes

4. Summary and Conclusion

We have in this paper presented and discussed a generalized statistical method for the analysis of multiple responses $(at\ least\ three)$ or outcomes in case - control studies, including situations in which the data being analysed are either quantitative or qualitative frequency data. Test statistics are developed for testing the statistical significance of differences between responses. The proposed methods are illustrated with sample data and shown to be more powerful than the usual Stuart/ Maxwell test when the two methods are equally applicable to a set of data.

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