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Alternative Measure of Association in Diagnostic Screening Tests

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Abstract: *This paper proposes a measure of the strength of association between diagnostic screening test results and state of nature or condition in a population as a function of the sensitivity and specificity of the test. The proposed measure which always lies between -1 and 1 inclusively would be able to enable a researcher to determine not only whether or not an association exists but also when such an association exists, whether it is positive and direct or negative and indirect. An estimate of the standard error of the proposed measure is provided as well as a test statistic for the significance of the measure. The proposed method is shown to be simpler to use, easier to interpret and provides more information on the overall results of the screening test than the traditional odds ratio approach. The method is illustrated with some sample data and shown to compare favourably with the traditional odds ratio method.*

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I. Introduction

Ordinarily in measuring the strength of association between two variables of classification either in cross-sectional or longitudinal studies especially in medical research, the odds ratio, relative risk and other such measures rather than the phi-coefficient are preferably used because unlike the later, the former two measures are invariant under the three commonly used study methods (Fleis 1973, Akobeng 2007, Saeed 2001, Carolyn and Kenrad 2012). However, because odds ratio and relative risk are often relatively difficult to clearly interpret and understand, some researchers prefer to use Berkson's simple difference or Shep's relative difference between rates as measures of association in medical research (Fleis 1973). Unfortunately, these two last measures are not invariant under the various study designs.

When used in the analysis of data obtained from diagnostic screening tests, a probably more serious problem with the traditional odds ratio and relative risk as measures of association is that they often include in their specifications and formulations and those of their associated standard errors and test statistics the number of subjects testing positive among subjects in the population known or believed not to have the condition in nature and the number of subjects testing negative among subjects in the population known or believed to actually have the condition in nature. These are sample values that are in fact usually not readily known in diagnostic test results and ought not be used in such analysis without prior modification of the measure formulation before estimation.

When the prevalence rate of a condition in a population is known, then a measure of association between state of nature and test results in screening tests should ideally be based on true and false rates of the test that always factor in the prevalence rate (Linn 2004, Akobeng 2007). However the prevalence rates of many conditions are often not readily known, a problem that seriously limits the usefulness of measures of association based on them.

In this paper, we propose a measure of the strength of association between state of nature or condition and screening test results that does not require knowledge of the prevalence rate of a condition in the population. The proposed measure is based only on the sample data usually obtained in diagnostic screening tests, namely the total number of subjects studied consisting of the number of subjects known or believed to actually have the condition and the number of subjects known or believed not to actually have the condition in the population, the number testing positive among the subjects known or believed to actually have the condition, the number of subjects testing negative among subjects known or believed not to actually have the condition as well as the sensitivity and specificity of the test derived from these observations.

II. The Proposed Method

Suppose a clinician or research scientist collects a random sample of $n_{.1}$ subjects known or believed to have a certain condition in a population and also collects another random sample of $n_{.2}$, subjects from the same population known or believed not to have the condition in nature giving a total random sample of size $n = n_{..} = n_{.1} + n_{.2}$ subjects to be studied. Interest is to confirm through a diagnostic screening test whether each of the sampled subjects actually has or does not have the condition in nature.

Let B and $\bar{B}$ be respectively the events that a randomly selected subject from the population actually has or does not have the condition of interest. Let A and $\bar{A}$ be respectively the events that the randomly selected subject tests and does not test positive in the screening test.

The results from such a screening test may be presented as in Table 1

TABLE 1: FORMAT FOR PRESENTATION OF RESULTS IN DIAGNOSTIC SCREENING TESTS

	State of Nature or condition		
Test Result	Present (B)	Absent $(\bar{B})$	Total $(n_{i.})$
Positive (A)	$n_{11} = f^{+}$	n_{12}	$n_{1.}$
Negative $(\bar{A})$	n_{21}	$n_{22} = f^{-}$	$n_{2.}$
Total $(n_{.j})$	$n_{.1}$	$n_{.2}$	$n_{..}$

In Table 1, out of $n_{.1}$ subjects known or believed to have a condition in nature, n_{11} subjects test positive and n_{21} test negative. Similarly, out of $n_{.2}$ subjects known or believed not to have a condition in nature n_{12} test positive and n_{22} test negative. Of the $n = n_{..}$ subjects sampled, $n_{1.}$ subjects test positive while $n_{2.}$ subjects test negative.

In diagnostic screening test results however, only n_{11} and n_{22} subjects which are often of primary interest to the researcher are usually known. The values n_{12}, the number of subjects testing positive among those known or believed not to have the condition, and n_{21}, the number of subjects testing negative among those known or believed to have the condition usually are not known. Hence, the marginal totals $n_{1.}$ and $n_{2.}$ usually are not completely known and may not properly be directly used in calculations. In this paper; therefore, only $n_{.1}, n_{.2}, n_{11}, n_{22}$ and the sensitivity and specificity of the test derived from these known observations will be used in the calculations.

Furthermore, the present proposed method is based on the expectation that if a diagnostic screening test is a good one in the sense that it is able to accurately diagnose subjects who have a condition in nature as actually having the condition and subjects free of a condition as actually not having the condition, then the difference between the proportions testing positive among subjects having the condition and the subjects not having the condition in nature would be large and positive and similarly, the difference between the proportion of subjects testing negative among subjects having the condition and those testing negative among those not having the condition would be large and negative.

Now in terms of conditional probabilities, the proportion of subjects testing positive among subjects known or believed to have a condition in nature is

$$P(A/B) = \frac{P(AB)}{P(B)} = S_e \text{ ----------(1)}$$

Where S_e is the sensitivity of the test which is the proportion testing positive among the population of subjects known or believed to actually have the condition in nature.

Similarly, the proportion of subjects testing positive among subjects known or believed not to have the condition in nature is

$$P(A/\bar{B}) = \frac{P(A\bar{B})}{P(\bar{B})} = 1 - \frac{P(\bar{A}\bar{B})}{P(\bar{B})} = 1 - S_p \text{ ------(2)}$$

Where S_p is the specificity of the test which is the proportion testing negative among the population of subjects known or believed not to actually have the condition in nature.

$$\gamma = P(A/B) - P(A/\bar{B}) = S_e - (1 - S_p) \text{ ----(3)}$$

Now γ measures by how much the probability of positive test is higher (lower) if the subject tested is randomly drawn from among subjects known or believed to have a condition than if drawn from among subjects known or believed not to have the condition in nature; that is by how much the proportion testing positive among subjects with the condition exceeds (lags behind) the proportion of subjects testing positive among subjects without the condition in nature. When interpreted in percentage this would mean that the number of subjects testing positive among subjects in the population known or believed to have a condition is γ percent more (less) than the number of subjects testing positive among subjects in the population known or believed not have the condition in nature.

A positive value of γ would indicate that a randomly selected subject who tests positive is more likely to be drawn from among subjects known or believed to have the condition than from among subjects known or

believed not to have the condition in nature. Similarly, a negative value of γ would indicate that a randomly selected subject who tests positive is more likely to be drawn from among subjects that do not have the condition than from among subjects that have the condition in nature. If γ has a value of zero, this would indicate a probable lack of any association between screening test results and state of nature or condition.

Thus a positive and large value of γ would suggest a strong and positive or direct association between test results and state of nature or condition. A large and negative value of γ would suggest a strong and negative or inverse association between test results and state of nature. If γ is zero then there is likely to be no association between test results and state of nature or condition. In this case, knowing a subjects test result would be of no use in telling whether or not the subject actually has or does not have the condition. Thus γ assumes the value 0 if there is independence or no association between screening test result and state of nature or condition. As a difference between probabilities, γ always lies between -1 and 1 inclusively. γ assumes the value -1 if there is perfect and indirect association; the value 0 if there is no association, and the value 1 if there is perfect and direct association between test results and state of nature or condition in a population. As the absolute value of γ increases, the degree or level of association between screening test results and state of nature or condition also increases.

To obtain sample estimates of S_e,S_p and γ, we may proceed as follows:

Now to estimate S_e, the sensitivity of the test, we may let

$$\cup_{ij} = \begin{cases} 1, if\ the\ i^{th}\ sample\ subject\ has\ the\ condition\ and\ also\ tests\ positive. \\ 0, \qquad\qquad\qquad\qquad\qquad\qquad otherwise. \end{cases} --(4)$$

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

Let

$$\pi^+ = P(\cup_{i1} = 1) - - - - - - - - - - - - - - - - - - (5)$$

And

$$W_1 = \sum_{i=1}^{n} \cup_{i1} - (6)$$

Now

$$E(\cup_{i1}) = \pi^+; Var(\cup_{i1}) = \pi^+(1-\pi^+) - - - - - - - - (7)$$

Also,

$$E(W_1) = \sum_{i=1}^{n} E(\cup_{i1}) = n\pi^+ - - - - - - - - - - - (8)$$

And

$$Var(W_1) = \sum_{i=1}^{n} var(\cup_{i1}) = n\pi^+(1-\pi^+) - - - - - - - - (9)$$

Now π^+ is the probability that a randomly selected subject has the condition in nature and also tests positive in the screening test. Its sample estimate is

$$\hat{\pi}^+ = \frac{f^+}{n} = \frac{W_1}{n} - - - - - - - - - - - - - - (10)$$

where f^+ is the number of subjects, who actually have the condition in nature and test positive; that is, the total number of 1's in the frequency distribution of $\cup_{i1}$, for $i = 1, 2, \dots, n$.

The estimated variance of $\hat{\pi}^+$ is from equation 9;

$$Var(\hat{\pi}^+) = \frac{Var(W_1)}{n^2} = \frac{\hat{\pi}^+(1-\hat{\pi}^+)}{n} - - - - - - - - - (11)$$

Now the sample estimate of the sensitivity of the test is from equations 1 and 10;

$$\hat{\pi}_1 = \hat{S}_e = \frac{f^+}{n_{.1}} = \frac{n\left(f^+/n\right)}{n_{.1}} = \frac{n.\pi^+}{n_{.1}} \dots\dots\dots (12)$$

The estimated variance of $\hat{S}e$ is from equations 11 and 12

$$Var(\hat{\pi}_1) = Var\left(\hat{S}_e\right) = \left(\frac{n}{n_{.1}}\right)^2 Var(\hat{\pi}^+) = \frac{n\hat{\pi}^+(1-\hat{\pi}^+)}{{n_{.1}}^2} = \frac{\hat{S}_e\left(1 - \frac{n_{.1}\hat{S}_e}{n}\right)}{n_{.1}} - - - (13)$$

Similarly, to estimate S_p, the specificity of the test, we may let

$$U_{i2} = \begin{cases} 1, if\ the\ i^{th}\ sampled\ subject\ does\ not\ have\ the\ condition\ in\ nature\ and\ also\ tests\ negative \\ 0, otherwise \end{cases}$$

$$- - - - - (14)$$

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

Let

$$\pi^- = P(U_{i2} = 1) - - - - - - - - - - - (15)$$

Also define

$$W_2 = \sum_{i=1}^{n} U_{i2} - - - - - - - - - - (16)$$

Now

$$E(W_2) = \pi^-; Var(U_{i2}) = \pi^-(1-\pi^-) - - - - - - - - - - - - (17)$$

Also

$$E(W_2) = n\pi^- - - - - - - - - (18)$$

And

$$Var\ (W_2) = n\pi^-(1-\pi^-) - - - - - - - - - - (19)$$

Now π^- is the proportion of all the sampled subjects who are believed to be free of the condition in nature and also test negative in the screening test. Its sample estimate is

$$\hat{\pi}^- = \frac{f^-}{n} = \frac{W^2}{n} \dots\dots\dots\dots\dots (20)$$

Where $f^-$is the total number of sample subjects who are believed not to have the condition and also test negative; that is, the total number of 1's in the frequency distribution of the 'n' values of U_{i2}, for $i = 1, 2, \dots, n$. The sample variance of $\hat{\pi}^-$ is from equation 19

$$Var(\hat{\pi}^-) = \frac{Var(W_2)}{n^2} = \frac{\hat{\pi}^-(1-\hat{\pi}^-)}{n} - - - - - - - - - (21)$$

Now the sample estimate of Sp, the specificity of the test is from equation 2 and 20

$$\hat{\pi}_2 = \hat{S}_p = \frac{f^-}{n_{.2}} = \frac{n\left(f^-/n\right)}{n_{.2}} = \frac{n\hat{\pi}^-}{n_{.2}} - - - - - - - (22)$$

The corresponding estimated variance is from equations 19 and 20

$$Var(\hat{\pi}_2) = Var\left(\hat{S}_p\right) = \left(\frac{n}{n_{.2}}\right)^2 Var(\hat{\pi}^-) = \frac{n\hat{\pi}^-(1-\hat{\pi}^-)}{{n_{.2}}^2} = \hat{S}_p\frac{\left(1-\frac{n_{.2}}{n}\hat{S}p\right)}{n_{.2}} - - - (23)$$

Now using equations 12 and 22 in equation 3, we obtain the sample estimate of γ, the proposed measure of association between test results and state of nature or condition in a population as

$$\hat{\gamma} = \hat{\pi}_1 - (1-\hat{\pi}_2) = \hat{S}_e - \left(1-\hat{S}_p\right) - - - - - - - - - - - - (24)$$

To obtain the sample estimate of the variance of $\hat{\gamma}$ we have from equation 24 that

$$Var(\hat{\gamma}) = Var\left(\hat{S}_e\right) + Var\left(\hat{S}_p\right) + 2Cov\left(\hat{S}_e; \hat{S}_p\right) - - - - - - - - - - - - (25)$$

However, by their specifications in equations 4 and 14, U_{i1} and U_{i2} can easily be shown to be uncorrelated so that $Cov\left(\hat{S}_e; \hat{S}_p\right) = 0$. Hence from equations 25, 13 and 23 we have that

$$Var(\hat{\gamma}) = Var\left(\hat{S}_e\right) + Var\left(\hat{S}_p\right) = \frac{n_{.2}\hat{S}_e\left(1-\frac{n_{.1}\hat{S}_e}{n}\right) + n_{.1}\hat{S}_p\left(1-\frac{n_{.2}\hat{S}_p}{n}\right)}{n_{.1}n_{.2}} - - - - - (26)$$

Research interest is usually in determining whether there is significant association between screening test results and state of nature or condition in a population. That is, the null hypothesis that may be of interest is

$$H_0: \gamma = 0\ Versus\ H_1: \gamma \neq 0 - - - - - - - - - - - - - (27)$$

To test the null hypothesis of equation 27 we may use the test statistic

$$\chi^2 = \frac{\hat{\gamma}^2}{Var(\hat{\gamma})} = \frac{n_{.1}n_{.2}\left(\hat{\pi}_1 - (1-\hat{\pi}_2)\right)^2}{n_{.2}\hat{S}_e\left(1-\frac{n_{.1}\hat{S}_e}{n}\right) + n_{.1}\hat{S}_p\left(1-\frac{n_{.2}\hat{S}_p}{n}\right)}$$

$$= \frac{n_{.1}n_{.2}\left(1-\hat{S}_e-\hat{S}_p\right)^2}{n_{.2}\hat{S}_e\left(1-\frac{n_{.1}\hat{S}_e}{n}\right) + n_{.1}\hat{S}_p\left(1-\frac{n_{.2}\hat{S}_p}{n}\right)} - - - - - (28)$$

which under the null hypothesis, H_0, has approximately the chi-square distribution with 1 degree of freedom for sufficiently large $'n'$.

The null hypothesis of no association is rejected at the α-level of significance if

$$\chi^2 \geq {\chi^2}_{1-\alpha;1} - - - - - - - - - - - - - (29)$$

otherwise H_0 is accepted.

The proposed measure of association γ as a simple difference between rates is easier to explain, estimate, interpret and understand than the relatively more complex concepts of odds ratios and relative risks. Unlike some other measures of association used in diagnostic screening tests, the proposed measure does not require the

prior knowledge of the prevalence rate of a condition in a population and the estimation of the false rates of a test before it can be estimated.

The proposed method enables the researcher determine whether or not there is any association between test results and state of nature or condition; and when such association is found to exist, it readily enables the researcher determine whether the association is positive or negative, which are additional useful information for planning and management purposes.

III. Illustrative Example

We here use the following data on prostrate cancer screening results to illustrate the proposed method. A clinician collected a random sample of 98 subjects from a certain population, 12 of whom are believed to actually have prostrate cancer and 86 of whom are believed not to have the disease. The clinician's interest is to confirm through a diagnostic screening test whether or not each of the sampled subjects actually has prostrate cancer. The results of the screening test are presented in Table 2

TABLE 2: RESULT OF PROSTRATE CANCER SCREENING TEST

Clinical Diagnosis	Histolic Diagnosis		
	Present (B)	Absent $(\bar{B})$	Total $n_{i.}$
Positive for Prostrate Cancer (A)	$n_{11} = f^{+} = 4$	$n_{12} = 2$	$n_{1.} = 6$
Negative for Prostrate Cancer $(\bar{A})$	$n_{21} = 8$	$n_{22} = f^{-} = 84$	$n_{2.} = 92$
Total $n_{.j}$	$n_{.1} = 12$	$n_{.2} = 86$	$n_{..} = n = 98$

Now we have from Table 2 and equation 10 that the estimated proportion of the screened subjects who have prostrate cancer and also test positive is

$$\hat{\pi}^{+} = \frac{4}{98} = 0.041$$

with estimated variance (equation 11)

$$Var(\hat{\pi}^{+}) = \frac{0.041(1 - 0.041)}{98} = 0.0004$$

Hence from equation 12 we have that the estimated sensitivity of the test is

$$\hat{S}_e = \frac{98(0.041)}{12} = 0.335$$

with estimated variance (equation 13)

$$Var(\hat{S}_e) = \left(\frac{98}{12}\right)^2 (0.0004) = 0.027$$

Also from Table 2 and equation 20 we have that the estimated proportion of the screened subjects who do not have prostrate cancer and also test negative is

$$\hat{\pi}^{-} = \frac{84}{98} = 0.857$$

with estimated variance (equation 21) of

$$Var(\hat{\pi}^{-}) = \frac{0.857(1 - 0.857)}{98} = 0.001$$

Hence from equation 22 we have that the estimated specificity of the test is

$$\hat{S}_p = \left(\frac{98}{86}\right)(0.857) = 0.977$$

with estimated variance (equation 23)

$$Var(\hat{S}_p) = \left(\frac{98}{86}\right)^2 (0.001) = 0.001$$

Now from equation 24 we have that the sample estimate of the proposed measure of association γ is

$$\hat{\gamma} = 0.335 - (1 - 0.977) = 0.358$$

Now from equation 26 we have that the estimated variance of $\hat{\gamma}$ is

$$Var(\hat{\gamma}) = 0.027 + 0.001 = 0.028$$

To test the null hypothesis of equation 27, namely of the existence of no association between screening test results and presence of prostrate cancer in the population we have from equation 28

$$\chi^2 = \frac{0.358^2}{0.028} = 4.57 \;\; (P\ value = 0.0394)$$

which with 1 degree of freedom is statistically significant. Hence we may conclude that there is a significant association between screening test results and existence of prostrate cancer in the population. Also since $\hat{\gamma} = 0.358$ which is positive; we may further conclude that the association is positive and direct.

It would be instructive to compare the present results with what would have been obtained if we had used the traditional odds ratio method to analyse of the data of table 2 in spite of odds ratio's limitations as already noted above when used in the analysis of screening test results.
The sample estimate of the traditional odds ratio for the data of table 2 is

$$O = \frac{n_{11}n_{22}}{n_{12}n_{21}} = \frac{4(84)}{2(8)} = 21.00$$

This means that for every one subject who has prostrate cancer among those tested and erroneously informed that they are free of the disease 21 subjects among those tested and found to have prostrate cancer would be expected to be correctly so informed. This is probably more difficult to understand than the simple information conveyed by the $\hat{\gamma}$ statistic, namely that a randomly selected subject from the screened population who tests positive is about 35.8 percent more likely than not to be actually prostrate cancer positive or about 35.8 percent of all subjects tested and found to be prostrate cancer positive are more likely to actually have prostrate cancer than not have the disease in nature. In other words the number testing positive among the population of subjects known or believed to actually have the condition (prostrate cancer) in nature is estimated to be about 35.8 percent more than the number testing positive among the population of subjects known or believed not to have the condition (prostrate cancer) in nature.
The standard error of the estimated odds ratio is

$$Se\,(O) = O\sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}} = 21.00\sqrt{\frac{1}{4} + \frac{1}{2} + \frac{1}{8} + \frac{1}{84}}$$
$$= (21.00)(0.942) = 19.782$$

The measure of the error of O, namely 19.782 is clearly much larger than the error of only $Se(\hat{\gamma}) = 0.167$, for the estimated value of $\hat{\gamma}$ for our sample data. The chi-square test statistic for the significance of O is

$$\chi^2 = \frac{n(n_{11}n_{22} - n_{12}n_{21})^2}{n_{1.}n_{2.}n_{.1}n_{.2}} = \frac{98(4(84) - 2(8))^2}{(6)(92)(12)(86)} = 17.616$$
$$(Pvalue = 0.0000)$$

which is also statistically significant again leading to a rejection of the null hypothesis of no association.

IIII. Summary And Conclusion

We have in this paper proposed, presented and discussed a statistical measure of the strength of association between diagnostic screening test results and state of nature or condition in a population that is based on sensitivity and specificity of the test which are independent of the population being studied. The proposed measure always lies between -1 and 1 inclusively indicating the nature and degree of any existing association.

The proposed measure enables the researcher not only determine whether an association exists but if such association exists whether it is positive direct or negative and indirect.
A test statistic is developed for testing the significance of the proposed measure.
The method which is illustrated with some sample data is shown to be easier to use, conveys more information and is more easily interpreted than the traditional odds ratio.

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