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RESEARCH ARTICLE

Asymptotic Relative Efficiencies of the Score and Robust Tests in Genetic Association Studies

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Abstract:

Introduction:

The score statistic $Z(\theta)$ and the maximin efficient robust test statistic Z_{MERT} are commonly used in genetic association study, but according to our knowledge there is no formal comparison of them.

Methods:

In this report, we compare the asymptotic behavior of $Z(\theta)$ and Z_{MERT}, by computing their Asymptotic Relative Efficiencies (AREs) relative to each other. Four commonly used ARE measures, the Pitman ARE, Chernoff ARE, Hodges-Lehmann ARE and the Bahadur ARE are considered. Some modifications of these methods are made to simplify the computations. We found that the Chernoff, Hodges-Lehmann and Bahadur AREs are suitable for our setting.

Results and Conclusion:

Based on our study, the efficiencies of the two test statistic varies for different criterion used, and for different parameter values under the same criterion, so each test has its advantages and dis-advantages according to the criterion used and the parameters involved, which are described in the context. Numerical examples are given to illustrate the use of the two statistics in genetic association study.

Keywords: Asymptotic relative efficiency, Genetic association study, Maximin efficiency robust test, Score test $Z(\theta)$, Test statistic Z_{mert}, Pitman ARE, Chernoff ARE.

1. INTRODUCTION

In genetic association studies, several test statistics are often used, including the score test $Z(\theta)$ and the maximin efficient robust test statistic Z_{MERT}. Although numerical behavior of the two tests are reported in various genetic association studies based on simulations, to our knowledge, a formal theoretical comparison of the two tests hasn't been seen in the literature. It is of meaning to compare their asymptotic performances. Although for likelihood ratio based test statistic for testing hypothesis of simple null versus simple alternative, there is a uniformly most powerful test under some regularity conditions. However, most test statistics are not constructed directly from likelihood ratio, the hypothesis are composite, and there is generally no such optimal test. Therefore, the classical method to compare any two test statistics is to evaluate the Asymptotic Relative Efficiency (ARE) between them.

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The ARE is a well studied area, with vast literatures and numerous different definitions. But often the computation of ARE is very difficult in the general case, some of the classical methods for ARE require that the test statistics have some standard forms, such as they have the same asymptotic distribution, or have the forms of i.i.d. summations. However, in practice, such as in genetic association studies, some test statistics do not have these forms. Sitlani and McKnight [1] studied AREs for the trend test under different models and stratifications. In this communication, wecompare the asymptotic behavior of two commonly used test statistics the score statistic $Z(\theta)$ and the maximin efficient robust test statistic Z_{MERT}, arise in case-control genetic association study, as given in Zheng, Li and Yuan [2], hereafter ZLY, by evaluate their AREs relative to each other. Four commonly used ARE measures, the Pitman ARE, Chernoff ARE, Hodges-Lehmann ARE and the Bahadur ARE are considered. Pitman's ARE does not apply directly. We found the Chernoff, Hodges-Lehmann and the Bahadur AREs are suitable for our setting. Some modifications of these methods are made to simplify the computations.

Existing studies on ARE are mainly focused on two categories. One is to compare efficiencies of estimators of the same parameter; the other is to compare test statistics of the same hypothesis, in which the test statistics may not estimate the same parameter. The latter study can be under the assumption that the test statistics in comparison are asymptotic normality. In this case, the ARE's can often be easily computed. There are also methods for compare ARE of different test statistics in general, in which different test statistics of the same hypothesis may have different asymptotic distributions. In this general case, Pitman, Bahadure and Hodges-Lehmann proposed different ways to compute the ARE, and it is often difficult. Although, when the test statistics have the same asymptotic distribution, the ARE can be computed easily. We also give a simple definition of ARE, so that it can be computed in the case of different asymptotic distributions, as long as the asymptotic distributions of the test statistics are known.

In Section 2, we describe the background of the genetic association study problem and a brief review of the classical definitions of ARE. In Section 3 we compare the ARE of the test statistics arose from our genetic association study. We found that he performances, or the efficiencies of the two test statistic varies for different criterion used, and for different parameter values under the same criterion, which described in the context. Section 4 gives brief numerical examples in simulation and application of the two tests in genetic association study, from our previous study, to illustration their usage.

2. BACKGROUND

Denote the log-likelihood function as, $l_n(\lambda_1, \lambda_2, \eta) = \sum_{i=1}^{n} \log f(Y_i|\lambda_1, \lambda_2, \eta^T X_i)$ where Y_i is the outcome, $(\lambda_1, \lambda_2) \in \Lambda \subset R^2$ are the parameters of interest, $\eta \in R^m$ is a vector of parameters ($m \geq 0$) for the covariate $X_i = (x_{1,\ldots,}x_{im})^T$, and n is the sample size. The goal is to test the null hypothesis $H_0: (\lambda_1, \lambda_2) = (1,1)$ against the alternative H_1 (λ_1, λ_2) $\Lambda \setminus \{(1, 1)\}$, where Λ has two edges with known slopes θ_0 and θ_1, and the null point (1, 1) is on the boundary of Λ. We assume $-\infty < \theta_0 < \theta_1 < \infty$ and the endpoints θ_0 and θ_1 satisfy some constraints as specified in ZLY. If $\theta_1 = \infty$ which corresponds to a vertical edge, we can switch λ_1 and λ_2 and define new (θ_1, θ_2) so $-\infty < \theta_0 < \theta_1 < \infty$ is satisfied by the new (θ_1, θ_2). For example, we can write $\lambda_1 = 1 + (\lambda_2 - 1)/\lambda_1^* (\lambda_2 - 1)$ and $\lambda_1 = 1 + (\lambda_2 - 1)/\theta_0 = 1 + \theta_0^* (\lambda_2 - 1)$ where $-\infty < \theta_0 < \theta_1 < \infty$.

Assume θ_0 and θ_1 are known from the problem of interest and/or scientific knowledge. Given $\lambda_1 = \lambda \geq 1$, λ_2 can be written as $\lambda_2 = 1 - \theta + \theta\lambda, \theta \in [\theta_0, \theta_1]$. We treat η as a nuisance parameter not estimable under H_0 $\lambda = 1$, but it is estimable under . Then the log-likelihood becomes. $l_n(\lambda, \eta, \theta)$ The score test statistic H_0 $\lambda = 1$ for is given by;

$$Z(\theta) = \frac{\frac{\partial}{\partial\lambda} l_n(\lambda, \eta, \theta)|_{H_0, \hat{\eta}_n}}{\left\{Var_{H_0, \hat{\eta}_n}\left(\frac{\partial}{\partial\lambda} l_n(\lambda, \eta, \theta)\right)\right\}^{1/2}}, \quad (1)$$

where $\hat{\eta}_n$ is the MLE of η under H_0. It would be difficult to deal with $l_n(\lambda, \eta, \theta)$ because θ in $Z(\theta)$ is implicitly expressed.

So we work with $l_n(\lambda, 1 - \theta + \theta\lambda, \eta)$, where θ is explicitly expressed. It is convenient to view $l_n(\lambda, \eta, \theta)$ as a tri-variate function with variables $x_1 = \lambda$, $x_2 = 1 - \theta + \theta\lambda$ and $x_3 = \eta$. Denote $l_{n,u} = \partial l_n / \partial x_u$ for, u = 1,2,3, $l_{n,uv} = \partial^2 l_n / \partial x_u \partial x_v$ for u = 1,2 and, v = 1.2.3, and $l_{n.33} = \partial^2 l_n / \partial x_3 \partial x_3^T$. Assume

$l_{n,uv} = l_{n,vu}$ for $u, v = 1{,}2$, $l_{n,uv} = l_{n,vu}^T$ for $u = 1{,}2$ and $v = 3$. Denote $L_{vu}(\eta) = E_{Hn} l_{lvu}(1.1, \eta)$.

Suppose we have a family of asymptotically normally distributed tests $T_0 = \{Z(\theta): \theta \in [a,b]\}$, where $Z(\theta) \xrightarrow{D} N(0,1)$ under H_1 $\lambda = 1$ for a given $\theta \in [a,b]$, which determines the data-generating model under H_0: $\lambda = 1$. When $\theta = \theta^{(0)} \in [a,b]$ is the true value $Z(\theta^{(0)})$, is asymptotically most powerful (optimal). In this case, $\theta^{(1)} \neq \theta^{(0)}$ when is used, the Pitman ARE of $Z(\theta^{(1)})$ relative to $Z(\theta^{(1)})$ is given by (Gastwirth [3, 4])

$$e\left(Z(\theta^{(1)}), Z(\theta^{(0)})\right) = \rho^2_{\theta^{(0)},\theta^{(1)}}, \tag{2}$$

where is the asymptotic null correlation coefficient between and. Let be a set of all convex linear combinations of. A simple robust test derived under efficiency robust theory (Gastwirth [3, 4]; Birnbaum and Laska [5],) is the maximin efficient robust test (MERT), denoted as. When, is given by;

$$Z_{\text{MERT}} = \left(Z(\theta_i) + Z(\theta_j)\right) / \left\{2(1 + \rho_{\theta_i,\theta_j})\right\}^{1/2}. \tag{3}$$

When T_0 has more than two members, generally exists and is unique (Gastwirth [3]), but its computation needs quadratic programming methods (Rosen [6]). However, when there is an extreme pair $(Z(\theta_i), Z(\theta_j))$ in T_0 *i.e.* $\rho_{\theta i, \theta i} = \inf_{\theta,\theta' \in [a,b]} \rho_{\theta,\theta'} > 0$, then $Z_{\text{MERT}} = \left(Z(\theta_i) + Z(\theta_j)\right) / \left\{2(1 + \rho_{\theta_i,\theta_j})\right\}^{1/2}$ is MERT for if and only if (Gastwirth [7]).

$$\rho_{\theta_i,\theta} + \rho_{\theta_j,\theta} \geq 1 + \rho_{\theta_i,\theta_j}, \quad \forall\, \theta \in [a,b].$$

and thus

$$e\left(Z_{\text{MERT}}, Z(\theta^{(0)})\right) = \sup_{Z \in T_1} \inf_{\theta \in [a,b]} e\left(Z, Z(\theta)\right). \tag{4}$$

That is, the MERT reaches the maximin ARE due to model uncertainty. The MERT was first derived for linear rank tests for the two-sample problem (Gastwirth [3]; Birnbaum and Laska [5],) and later extended to a family of asymptotically normally distributed tests (Gastwirth [4]).

The $Z(\theta)$ statistic has the following property (ZLY): Let. $\theta \in [\theta_i, \theta_j] \subseteq [\theta_0, \theta_1]$. Then where and

$$Z(\theta) = \sum_{l=i,j} W_l(\theta) Z(\theta_l),$$

where $W_i(\theta) = \{\sigma(\theta_i)/\sigma(\theta)\}\{(\theta_j - \theta)/(\theta_j - \theta_i)\}$ and $W_j(\theta) = \{\sigma(\theta_j)/\sigma(\theta)\}\{(\theta - \theta_i)/(\theta_j - \theta_i)\}$.

Let $\hat{\eta}_{0,n}$ be the MLE of η under H_0, and $(\hat{\eta}_{1,n}, \hat{\lambda}_n)$ be that of (η, λ) under H_1. For given θ, the X^2 likelihood ratio test statistic is $T(\theta) = 2[l_n(\hat{\lambda}_n, 1 - \theta + \theta\hat{\lambda}_n, \hat{\eta}_{1,n}) - l_n(1,1,\hat{\eta}_{0,n})]$. For fixed θ, the number of parameters under H_1 is just 1 more than that under H_0, so by Wilk's theorem, under H_0,

$$T(\theta) \xrightarrow{D} \chi^2_1,$$

the chi-squared distribution with one degree of freedom. The likelihood ratio test is also widely used in genetic association studies, its properties, including its ARE is well studied in the literature, so we will not investigate it here.

Let the MLE $(\partial l_n / \partial \eta)|_{H_0, \hat{\eta}_n} = l_{n,3}(1,1,\hat{\eta}_n) = \mathbf{0}$ here 0 presents a vector of 0's. Let η_0 be the true value (unknown) of η under either H_0 or H_1, we define the score function as;

$$U_n(1,1,\hat{\eta}_n) = \frac{\partial l_n}{\partial \lambda}|_{H_0,\hat{\eta}_n} = l_{n,1}(1,1,\hat{\eta}_n) + \theta l_{n,2}(1,1,\hat{\eta}_n)$$

and the test statistic for H_0 as;

$$z(\theta) = \frac{U_n(1,1,\hat{\eta}_n)}{\{Var_{H_0}(U_n(1,1,\hat{\eta}_n))\}^{1/2}} \sim \frac{n^{-1/2}U_n(1,1,\hat{\eta}_n)}{\{(1,\mathbf{0})I^{-1}(\eta_0)(1,\mathbf{0})^T\}^{-1/2}} \quad (5)$$

$$= \frac{n^{-1/2}\{l_{n,1}(1,1,\hat{\eta}_n)+\theta l_{n,2}(1,1,\hat{\eta}_n)\}}{\left(A_{\eta_0}\theta^2+2B_{\eta_0}\theta+C_{\eta_0}\right)^{1/2}},$$

where "~" means asymptotically equivalent, in the above $I^{-1}(\hat{\eta}_n)$ is replaced by $I^{-1}(\eta_0)$, $A_\eta = L_{23}(\eta)L_{33}^{-1}(\eta)L_{32} - L_{22}(\eta)$, $B_\eta = L_{13}(\eta)L_{33}^{-1}(\eta)L_{31}(\eta) - L_{12}(\eta)$ and $C_\eta = L_{13}(\eta)L_{33}^{-1}(\eta) L_{31}(\eta) - L_{11}(\eta)$. Recall that $L_{vu}(\eta) = E_{H_0}l_{1,vu}(1,1,\eta)$, and it is approximated by $n^{-1}l_{n,\ vu}$ (1.1, η).

Denote $W = \begin{pmatrix} 1 & 0 \\ W_0(\theta) & W_1(\theta) \\ 0 & 1 \end{pmatrix}$. For a vector v $(v_1, v_2, v_3)^T$, denote $||v|| = \sum_{i=1}^3 v_i$. Let $f(y|\lambda, 1-\theta+\theta\lambda, \eta)$. be the true density of the data y. The null model f(1, 1, η) is and the alternative model is $f(\cdot\ |\lambda, 1-\theta+\theta\lambda, \eta)$. The following notation is also used under H_1. For fixed, (λ, θ) let;

$$\eta_\theta \triangleq \alpha\,(\lambda,\theta) = \arg\sup_\eta \int f\,(x|\lambda, 1-\theta+\theta\lambda, \eta_0)\log f\,(x|1,1,\eta)dx. \quad (6)$$

Under H_1, the empirical version of η_0 is just $\hat{\eta}_n$. We denote the Fisher information and its inverse in the blocked forms as;

$$I(\eta_0) = \begin{pmatrix} I_{\lambda\lambda} & I_{\lambda\eta} \\ I_{\eta\lambda} & I_{\eta\eta} \end{pmatrix}, \text{ and } I^{-1}(\eta_0) = \begin{pmatrix} I^{\lambda\lambda} & I^{\lambda\eta} \\ I^{\eta\lambda} & I^{\eta\eta} \end{pmatrix}.$$

Let $\sigma^2(\theta) = \{(1,\mathbf{0})I^{-1}(\alpha_0)(1,\mathbf{0})^T\}^{-1} = (I^{\lambda\lambda})^{-1}$,

$$s(\theta,\eta) = l_{1,1}(1,1,\eta) + \theta l_{1,2}(1,1,\eta) - (L_{13}^T(\eta) + \theta L_{23}^T(\eta))L_{33}^{-1}(\eta)l_{1,3}(1,1,\eta),$$

$\mu(\lambda,\theta) = E_{H_1,\eta_0}(s(\theta,\eta_\theta))$, $u(\lambda,\theta) =^\Delta s\,(\theta,\eta_\theta) - \mu(\lambda,\theta)$, $\tau^2(\lambda,\theta) = E_{H_1,\eta_0}(u(\lambda,\theta))^2$, $\tilde{\sigma}^2(\lambda,\theta) = \tau^2(\lambda,\theta)/\sigma^2(\theta)$, and $\tilde{\Omega} = (\tilde{\omega}_{ij})_{2\times 2}$ with $\tilde{\omega}_{11} = \tilde{\sigma}^2(\lambda,\theta_0)$, $\tilde{\omega}_{22} = \tilde{\sigma}^2(\lambda,\theta_1)$, and $\tilde{\omega}_{12} = E_{H_1,\alpha_0}\{u(\lambda,\theta_0)u(\lambda,\theta_1)\}/\{\sigma(\theta_0)\sigma(\theta_1)\}$. Th e empiri cal vers ion of $\tilde{\Omega}$ is give n by $\tilde{\Omega}_n$, where η_θ in $\tilde{\Omega}$ is replacedby $\hat{\eta}_n$. Notetha twith $\eta_\theta = \alpha(\lambda,\theta)$ define d in theabove, $\mu(\lambda,\theta) = \int s\,(x|\theta,\eta_\theta)f(x|\lambda, 1-\theta+\theta\lambda,\eta_0)dx$.

Below we give a brief review of the notions of ARE for test statistics in the general case, more detailed account can be found in Serfling (1980) [8] and Nikitin (2011) [9].

The calculation of the existing of versions of ARE is generally not easy, as in the examples (Serfling, 1980 [8]; Nikitin, 1995 [10]; van der Varrt, 1998 [11]). We only point out that the Pitman ARE is based on the central limit theorem for test statistics, that the Bahadur ARE requires the large deviation asymptotics of test statistics under the null-hypothesis, while the Hodges-Lehmann ARE is connected with large deviation asymptotics under the alternative. Each type of ARE has its own advantage and dis-advantage, and the different notions of ARE are not always give consistent conclusion.

If the condition of asymptotic normality (or common asymptotic distribution) fails, considerable difficulties will arise in calculating the Pitman ARE as it may not at all exist or may depend on α and β. Usually one considers limiting Pitman ARE as α → 0 Wieand (1976) [12] established the correspondence between this kind of ARE and the limiting approximate Bahadur efficiency which is easy to compute.

The Bahadur (1960) [13] ARE is to fix the power of tests and compare the exponential rate of decrease of their sizes for the increasing number of observations and fixed alternative. Its computation is always non-trivial, and heavily depends on advancements in large deviation theory, as in Dembo and Zeitouni (1998) [14] and Deuschel and Strook (1989) [15].

It is proved that under some regularity conditions the likelihood ratio statistic is asymptotically optimal in Bahadur sense (Bahadur, 1967 [16]; Arcones, 2005 [17]). Often the Bahadur ARE is difficult to compute for any alternative but it is possible to calculate the limit of Bahadur ARE as θ approaches the null-hypothesis, to obtain the local Bahadur efficiency.

The Hodges-Lehmann ARE is, in contrast to Bahadur efficiency, it fixes the level of tests and compares the exponential rate of decrease of their type-II errors for the increasing number of observations and fixed alternative. The computation of Hodges-Lehmann ARE is also difficult as it requires large deviation asymptotics of test statistics under the alternative.

The drawback of Hodges-Lehmann efficiency is that most two-sided tests like Kolmogorov and Cramer-von Mises tests are all asymptotically optimal, and hence one cannot discriminate among them. On the other hand, under some regularity conditions the one-sided tests, such as linear rank tests can be compared, and their Hodges-Lehmann efficiency coincides locally with Bahadur efficiency (Nikitin, 1995 [10]).

The Chernoff ARE is to minimize, asymptotically, a linear combination of type I and type II errors, it does not depend on the nominal level nor the power. But it basically only applies to test statistics of the form of i.i.d. summation.

The local ARE is much easier to compute than the previous ones, but it only applies to test statistics which are asymptotical normal with rate $\sqrt{n}$. We will see that some test statistics used in genetic association studies do not satisfy this condition.

Besides the four commonly used AREs for hypothesis tests described above, there are some other interesting methods. Hoeffding's (1965) ARE [18], based on the work of Sanov (1957) [19], is theoretically appealing, but ony applies to multinomial data; Rubin and Sethurman ARE (1965) [20] is based on Bayes risk; others including Kallenberg ARE (1983) [21], and the Borovkov-Mogulskii ARE (1993) [22], *etc*.

3. ARE OF TWO TESTS IN GENETIC ASSOCIATION STUDIES

In this section, we investigate the uses of Pitman ARE, Chernoff ARE, Hodges-Lehmman ARE, and Bahadur ARE to the commonly used statistics in genetic association analysis. We focus on the statistics used in ZLY, $Z(\theta)$ and, $Z_{MERT}$and refer the notations there. Although some other commonly used test statistics in genetic association studies, such as the likelihood ratio statistic (chi-squared statistic), we will not discuss them here, as most of them are well studied in the literatures.

Pitman ARE. Consider testing $H_0: \lambda = \lambda_0$ vs $H_1: \lambda > \lambda_0$. Let S_n be a test statistic based on data of size n, with mean $\mu_n(\lambda)$ and standard deviation $\mu_n(\lambda)$. To use this method the following conditions are needed.

(P1). For some continuous strictly increasing distribution function *F* independent of λ, and some, δ > 0 as n → ∞,

$$\sup_{\lambda_0 \le \lambda \le \lambda_0 + \delta,} \sup_{-\infty < t < \infty} | P_\lambda (\frac{S_n - \mu_n(\lambda)}{\sigma_n(\lambda)}) - F(t) | \to 0.$$

(P2). For $\lambda \in [\lambda_0, \lambda_0 + \delta], \mu_n(\cdot)$, is k times differentiable, with $\mu_n^{(1)}(\lambda_0) = \cdots = \mu_n^{(k-1)}(\lambda_0) = 0 < \mu_n^{(k)}(\lambda_0)$

(P3). For d(n) → ∞ some and some constant $c > 0, \sigma_n(\lambda_0) \sim c\mu_n^{(k)}(\lambda_0)/d(n)$.

(P4). For $\lambda_n = \lambda_0 + O(d^{-1/k}(n)), \mu_n^{(k)}(\lambda_n) \sim \mu_n^{(k)}(\lambda_0)$ and $\sigma_n(\lambda_n) \sim \sigma_n(\lambda_0)$.

Pitman appears as the first to introduce the notion of ARE for tests in his unpublished lectures, and the following result was stated in Noether's works.

(Pitman, 1949 [23]; *Noether, 1950* [24]). *Assume* (*P1*)-(*P4*), that $\alpha_n = P_{\lambda 0}(S_n > u_{\alpha n}) \to \alpha$ $(0 < \alpha < 1)$, *that* $0 < \beta < 1 - \alpha$, *and that* $\lambda_n = \lambda_0 + O(d^{-1/k}(n))$, *then*
(i) $\beta_n(\lambda_n) = P_{\lambda_n}(S_n \le u_{\alpha n}) \to \beta$, *if and only if*

$$\frac{(\lambda_n - \lambda_0)^k}{k!} \frac{d(n)}{c} \to F^{-1}(1-\alpha) - F^{-1}(\beta). \tag{7}$$

(ii) Let $S_{1,n}$ and $S_{2,n}$ each satisfy (P1)-(P4) with the common F, K, n_1 and n_2 be the sample size required for $S_{1,n}$ and $S_{2,n}$ to have the same asymptotic power 1 - β, then

$$\frac{d(n_1)}{d(n_2)} \to \frac{c_1}{c_2}, \quad \text{with} \quad c_i = \lim_{n\to\infty} \frac{d(n)\sigma_{i,n}(\lambda_0)}{\mu_{i,n}^{(k)}(\lambda_0)} \quad (i = 1,2).$$

Thus, if d(n) = n^q (q > 0), then the Pitman ARE is given by; $e_P(\{S_{1,n}\},\{S_{2,n}\}) = (c_2/c_1)^{1/q}$. Typically, $k = 1$, $q = 1/2$, $\sigma_n(\lambda) = \sqrt{n}\sigma(\lambda)$, $\mu_n^{(1)} = n\mu(\lambda)$, then

$$c = \frac{\sigma(\lambda_0)}{\mu^{(1)}(\lambda_0)},$$

and Pitman ARE is then;

$$e_P(\{S_{1,n}\},\{S_{2,n}\}) = (\frac{c_2}{c_1})^2. \quad \textbf{(8)}$$

Let *I* (λ_0) be the Fisher information at λ_0. Under some additional conditions, Rao (1963) [25] proved that

$$(\frac{\sigma(\lambda_0)}{\mu^{(1)}(\lambda_0)})^2 \geq I^{-1}(\lambda_0).$$

Any test statistic S_n achieves the equality in the above is called *Pitman efficient*.

Under suitable conditions, Pitman ARE can be expressed in terms of correlation coefficient between the two test statistics in their standardized form, as given below.

(P5) $(S_{1,n} - \mu_{1,n}(\lambda))/\sigma_{1,n}(\lambda)$ and $(S_{2,n} - \mu_{2,n}(\lambda))/\sigma_{2,n}(\lambda)$ are asymptotic joint normal uniformly in a neighborhood of λ.

Denote p(λ)the asymptotic correlation coefficient between them under, and and be the distribution and density function of. The following result is true.

(van Eden, 1963 [26]). Assume that $S_{1,n}$ and $S_{2,n}$ satisfy (P1)-(P5) in their standardized form with $H = \Phi$, $k = 1$ *and* $d(n) = n^{1/2}$, *and that* p(λ_n) → p(λ λ_n): = p as $\lambda_n \to \lambda_0$ Then;

(i) For 0 ≤ λ ≤ 1, tests of the form $S_{\gamma,n} = (1-\gamma)S_{1,n} + \gamma S_{2,n}$ satisfy (P1)-(P5), and the "best" $S_{\gamma n}$ which maximizes $e_P(\{S_{\lambda,n}\},\{S_{1,n}\})$ is the one with;

$$\gamma = \frac{c_1 - \rho c_2}{(1-\rho)(c_1 + c_2)} = \frac{e_P^{1/2}(\{S_{2,n}\},\{S_{1,n}\}) - \rho}{(1-\rho)[1 + e_P^{1/2}(\{S_{2,n}\},\{S_{1,n}\})]}$$

and

$$e_P(\{S_{\gamma,n}\},\{S_{1,n}\}) = 1 + \frac{[e_P^{1/2}(\{S_{2,n}\},\{S_{1,n}\})]^2}{1-\rho^2}. \quad \textbf{(9)}$$

(ii) *If S_{1n} is the best test satisfying (P1)-(P5), then;*

$$e_P(\{S_{2,n}\},\{S_{1,n}\}) = \rho^2. \quad \textbf{(10)}$$

In the typical case, S_n is an i.i.d. summation (upto scale), then $\mu_n(\lambda)$ = $n\mu(\lambda)$ $\sigma_n(\lambda) = \sqrt{n}\sigma(\lambda)$, $d(n) = \sqrt{n}$, $k = 1$, $c = \sigma(\lambda_0)/\mu'$ (λ_0) and $\lambda_n = \lambda_0 + n^{-1/2}\sigma(\lambda_0)/\mu'$ $(\lambda_0)[F^{-1}(1-\alpha) - F^{-1}(\beta)]$.

Note $e_P(\{S_{1,n}\},\{S_{2,n}\})$ does not (α, β) depend on , thus if $e_P(\{S_{1,n}\},\{S_{2,n}\}) < 1$ or, $C_1 > C_2$ then $\{S_{1n}\}$ is better than $\{S_{2n}\}$ for all (α, β).

Pitman ARE given by (3) or (4) are easy to use. However, they require the two comparing test statistics have the same asymptotic distribution (after standardization), (4) require further that they are jointly asymptotic normal. In practice, these conditions some times cannot be satisfied. For example the chi-squared test $Z(\theta_0)$ and have different asymptotic distributions. Below we give a generalized version of (3) to the case the two comparing test statistics not necessarily have the same asymptotic distribution (after standardization). Similar generalizations may have already exist in the literature, we still state our version to see what form it has in this case. Let F_i be the asymptotic distribution of $(S_{i,n} - \mu_{i,n}(\lambda))/\sigma_{i,n}(\lambda)$ We have;

Assume *(P1)-(P4) for* S_{in} *with* μ_{in}, σ_{in} *and* F_i *separately, but with the same K and nominal level* α, n_1 *and* n_2 *be the sample sizes required for* S_{1n} *and* N_{2n} *to have the same asymptotic power* $1 - \beta(0 < \beta < 1 - \alpha)$, *then*

$$\frac{d(n_1)}{d(n_2)} \to \frac{\tilde{c}_1}{\tilde{c}_2}, \quad \text{with} \quad \tilde{c}_i = \lim_{n\to\infty} \frac{d(n)\sigma_{i,n}(\lambda_0)[F_i^{-1}(1-\alpha) - F_i^{-1}(\beta)]}{\mu_{i,n}^{(k)}(\lambda_0)} \quad (i = 1,2).$$

Thus for $d(n) = n^q$ $(q > 0)$, we define the generalized Pitman ARE as;

$$\tilde{e}_P(\{S_{1,n}\},\{S_{2,n}\}) = (\frac{\tilde{c}_2}{\tilde{c}_1})^{1/q}. \tag{11}$$

In the typical case $\mu_{i,n} = n\mu_i$, $\sigma_{i,n} = \sqrt{n}\sigma_i$, $k = 1$ and $d(n) = \sqrt{n}$ or $1/q = 2$, and;

$$\tilde{e}_P(\{S_{1,n}\},\{S_{2,n}\}) = (\frac{\tilde{c}_2}{\tilde{c}_1})^2, \quad \tilde{c}_i = \frac{\sigma_i(\lambda_0)[F_i^{-1}(1-\alpha) - F_i^{-1}(\beta)]}{\mu_i^{(1)}(\lambda_0)} \quad (i = 1,2).$$

Note, unlike the case of $F_1 = F_2$, in this case, Pitman's ARE depends on the values of level α and power β , and comparison of two tests may not have consistent result.

Can we have the corresponding form of (10) in the case S_{1n} and S_{2n} have different asymptotic distribution? For this we checked the proof for (4), and find in this case, although in principle there is a relationship among the asymptotic correlation coefficient p between S_{1n} and S_{2n} , the asymptotic distributions's, F_i*'s*, and the level α and power β , but its mathematically intractable. Below we give its actual value.

Proposition 1.

$$e_P(Z_{MERT}, Z(\theta^{(0)})) = \frac{(\rho_{\theta_i,\theta^{(0)}} + \rho_{\theta_j,\theta^{(0)}})^2}{2(1+\rho_{\theta_i,\theta_j})}.$$

Remark: When some of the conditions (P1)-(P5) are not satisfied, ARE may not be characterized by correlation coefficient. For example, $T_1 = Z$ is an estimate of $\theta = 0$ under H_0, and Z is symmetrically distributed around 0, so $E_{Ho}(Z) = 0$ and suppose $VAR_{Ho}(Z) = 1$. Let, $T_2 = |Z|$, T_2 is an estimate of $E_{H_0}(|Z|) \neq 0$. T_2 can also be used to test H_0. However $Cov_{H_0}(|Z|, Z) = E_{H_0}(|Z|Z) - E_{H_0}(|Z|)E_{H_0}(Z) = 0$, but we cannot say that T_2 is a 'bad' test statistic, and $e_P(T_1, T_2) \neq Cov^2_{H_0}/[Var_{H_0}(T_1)Var_{H_0}(T_2)]$.

Chernoff ARE. This notion only considers test statistic of the form $S_n = \sum_{i=1}^n Y_i$ with the s i.i.d. with $Y \sim F$. Let $M(z) = E_F(e^{zY})$ be the moment generating function of *Y*, and;

$$m(t) = \inf_z E\,(e^{z(Y-t)}) = \inf_z e^{-zt}\, M(z).$$

Let $\mu_0 = E(Y|H_0)$ and $\mu_1 = E(Y|H_1)$ (assume $\mu_0 \leq \mu_1$), $m_i(t) = \inf_z E\,(e^{z(Y-t)}|H_i) = \inf_z [e^{-zt} M_i(z)]$, $(i = 0,1)$, $\rho(t) = \max\{m_0(t), m_1(t)\}$ and $\rho = \inf_{\mu_0 \leq t \leq \mu_1} \rho(t)$ called the *Chernoff index* of $\{S_n\}$. For $0 \leq \gamma < \infty$, let $Q_n(t) = P(S_n \leq nt|H_1) + \gamma P(S_n > nt|H_0)$ be a linear combination of type I and type II errors evaluated at the critical value t, and $Q_n = \inf_{\mu_0 \leq t \leq \mu_1} Q_n(t)$ be the minimum of these errors for test statistic S_n. Chernoff (1952) [27] showed that Q_n tends to 0 at exponential rate, (so the faster the rate, or the larger absolute value of $\log Q_n$, the better the test statistic), and established.

$$\lim_n n^{-1} \log\, Q_n = \log\, \rho,$$

the result is independent of γ.

Let $\{S_{1,n}\}$ and $\{S_{2,n}\}$ both of the form of i.i.d. summation and have Chernoff indices p_1 and p_2 respectively, n_1 and n_2 be the corresponding sample sizes for which $Q_{1,n}$, ~ $Q_{2,n}$, the Chernoff ARE of $\{S_{1,n}\}$ relative to $\{S_{2,n}\}$ is defined and given by;

$$e_C(\{S_{1,n}\}, \{S_{2,n}\}) = \lim \frac{n_2}{n_1} = \frac{log\ \rho_1}{log\ \rho_2}. \quad \textbf{(12)}$$

For test statistic not in the form of i.i.d summation, its Chernoff index is difficult to compute. The following result sometimes is very helpful in this case, and give an upper bound of Chernoff index.

(Kallenberg, 1982 [28]*) Let for some* $t \in R^1$*, and* $\lambda \in \Lambda_1$

$$\lim_{n\to\infty} \log\, \sup\, \{ P_{\lambda_0}(S_n > nt) \colon \lambda_0 \in \Lambda_0\} = \lim_{n\to\infty} \inf\, \log\, P_\lambda\,(S_n \le nt) := u(\lambda)$$

Then $\rho(\lambda) = -u(\lambda)$.

In the case of simple null *vs* simple alternative, Kallenberg (1982) [28] also gives an upper bound of the Chernoff index, and any test statistic achieves this bound is said to be *Chernoff efficient*. As this bound itself is not easy to compute, we won't pursue it here, interested readers can check the mentioned paper or the book by Nikitin (1995) [10].

As another way to simplify the computation, we consider a modified version of this Chernoff index. Let S be the weak limit of S_n, be the distribution function of S, and H_n: $\lambda_n + \lambda_n = n^{-1/2}$be a sequence of local alternatives. As the sample size increases, the test statistic S_n is expected to be able to distinguish the local alternatives from the null. Let $\mu_0 = E(S|H_0), \mu_1 = \lim_n E\,(S|H_n)$ (assume $\mu_1 \ge \mu_0$), and $\tilde{Q}(t) = \lim_n G\,(S \le t|H_n) + G(S > t|H_0)$ be the asymptotic linear combination of type I and local type II errors evaluated at t, and $\tilde{Q} = \inf_{\mu_0 \le t \le \mu_1} \tilde{Q}\,(t)$. The smaller is $\tilde{Q}$, the better S_n as a test statistic for $H_0 vs. H_1$ For two test statistics S_{1n} and S_{2n} with $\tilde{Q}_1$ and $\tilde{Q}_2$, we define the modified Chernoff ARE as;

$$\tilde{e}_C(\{S_{1,n}\}, \{S_{2,n}\}) = \frac{\tilde{Q}_2}{\tilde{Q}_1}. \quad \textbf{(13)}$$

Let $\mu^{(1)}(\lambda,\theta) = \partial\mu(\lambda,\theta)/\partial\lambda$, and

$$\zeta^{(1)} = (\zeta_1^{(1)}, \ldots, \zeta_k^{(1)})^T = (\frac{\mu^{(1)}(\lambda_0, a_1)}{\sigma(a_1)}, \ldots, \frac{\mu^{(1)}(\lambda_0, a_k)}{\sigma(a_k)})^T.$$

Below we give values $p_{z(\theta(0))}$ and $p_{Z_{MERT}}$ and so that their Chernoff ARE can be obtained. We also give and, so their modified Chernoff ARE can be obtained. For the chi-squared test T, under T_1 its asymptotic distribution is a non-central chi-squared distribution, with a non-closed form, its modified Chernoff index is not directly computable. Let $b(g_i) = \log\,(1 - \theta + \theta\lambda)I_1(g_i) + \log\,(\lambda)I_2(g_i)$, where g_1 is the observed genotype of the i-th individual, x_1 is the corresponding covariates, and let;

$$a(\boldsymbol{x}_i, g_i, \lambda) = \frac{I_1(g_i)}{(1-\theta+\theta\lambda)\sigma^2} + \frac{I_2(g_i)}{\lambda\sigma^2} + \frac{(L_{13}^T(\eta_0) + \theta L_{23}^T(\eta_0))L_{33}^{-1}(\eta_0)\boldsymbol{x}_i}{\sigma^2}.$$

Let $b_1(g_r) = [\log\,(1 - \theta + \theta\lambda)I_1(g_r) + \log\,(\lambda)I_2(g_r)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$, and $a_1(\boldsymbol{x}_r, g_r) =$ $[a(\boldsymbol{x}_r, g_r, \theta_i, \lambda) + a(\boldsymbol{x}_r, g_r, \theta_j, \lambda)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$.

Proposition 2. *(i) Assume* $Y|(\boldsymbol{x}, g)$ *is normal with mean* $\eta^T\boldsymbol{x} + \sum_{j=1}^{2} \log\,(\lambda_j)I_j(g)$ *and variance* σ^2, $\lambda_1 = \lambda$, and $\lambda_2 = 1 - \theta + \theta\lambda$ *. Then, for E to denote expectation with respect to* (x_i, g_i)*, we have*;

$$\rho_{Z(\theta)} = E(\exp[-\frac{b^2(g_i)}{2(a(\boldsymbol{x}_i, g_i, 1) + a(\boldsymbol{x}_i, g_i, \lambda))^2}]),$$

$$\rho_{Z_{MERT}} = E(\exp[-\frac{b_1^2(g_i)}{2(a_1(\boldsymbol{x}_i, g_i, 1) + a_1(\boldsymbol{x}_i, g_i, \lambda))^2}]).$$

(ii)

$$\tilde{Q}_{Z(\theta^{(0)})} = 2(1 - \Phi(\frac{\mu^{(1)}(\lambda_0, \theta^{(0)})}{2\sigma(\theta^{(0)})})),$$

$$\tilde{Q}_{Z_{MERT}} = 2(1 - \Phi([\frac{\mu^{(1)}(\lambda_0, \theta_i)}{\sigma(\theta_i)} + \frac{\mu^{(1)}(\lambda_0, \theta_j)}{\sigma(\theta_j)}]/\sqrt{8(1 + \rho_{\theta_i,\theta_j})})).$$

Hodges-Lehmann ARE. Consider testing the null hypothesis be $H_0: \lambda \in \Lambda_0$ vs $H_1: \lambda \in \Lambda_1$, given a level α test statistic S_n with critical value $t_n(\alpha): \alpha_n := \sup_{\lambda \in \Lambda_0} P_\lambda(S_n \geq t_n(\alpha)) \to \alpha$. For $\lambda \in \Lambda_1$, the type II error at λ is $\beta_n(\lambda) = P_\lambda(S_n \leq t_n(\alpha))$. Typically, $\beta_n(\lambda)$ tends to zero at exponential rate, the faster the better S_n is. Hodges and Lehmann (1956) [29] proposed;

$$d(\lambda) = \lim_n -2n^{-1} \log \beta_n(\lambda)$$

as a measure of the performance of S_n and it called the Hodges-Lehmann index of the statistic S_n. For two test statistics S_{1n} and S_{2n} for the same $H_0 vs, H_1$ with d_1 (λ) and d_2 (λ), the Hodges-Lehmann ARE of $\{S_{1n}\}$ relative to $\{S_{2n}\}$ at $\lambda \in \Lambda_1$ is defined as;

$$e_{HL}(\{S_{1,n}\}, \{S_{2,n}\}) = \frac{d_1(\lambda)}{d_2(\lambda)}. \quad \textbf{(14)}$$

For probability density functions f and g, let $K(f,g) = \int f(x) \log[f(x)/g(x)]dx$ be the Kullback-Leibler divergence between f) and g). For any test statistic S_n $(X_1,.....,X_n)$ based on $(X_1,.....,X_n)$ i.i.d. density $f(\cdot|\lambda)$, the Hodges-Lehmann index has the following property;

$$\lim_n(1 - \beta_n(\lambda)) \geq -\inf\{K(f(\cdot|\lambda_0), f(\cdot|\lambda)): \lambda_0 \in \Lambda_0\},$$

and any test statistic achieve the equality in the above is said to be *Hodges-Lehmann efficient*.

Compared to the Pitman and Chernoff ARE, the Hodges-Lehmman ARE does not require the comparing test statistic have the same asymptotic distribution, nor they have the form of i.i.d. summations, so it has wilder application scope.

Proposition 3. Under conditions of Theorem 4 in Zheng *et al.* (2010) [30], with $\mu_{MERT}(\lambda) := [\mu(\lambda, \theta_i)/\sigma(\theta_i) + \mu(\lambda, \theta_j)/\sigma(\theta_j)]/\sqrt{2(1 + \rho_{\theta_i,\theta_j})}$, and $\tilde{\zeta}$, given in (2), for λ > 1, we have;

$$d_{Z(\theta)}(\lambda) = \frac{\mu^2(\lambda, \theta)}{\sigma^2(\theta)}, \quad d_{Z_{MERT}}(\lambda) = \mu_{MERT}^2(\lambda).$$

For the chi-squared test T, under H_1 its asymptotic distribution is a non-central chi-squared distribution, with no-closed form. So its Hodges-Lehmann ARE is not directly available.

Bahadur ARE. Consider testing the null hypothesis be $H_0: \lambda \in \Lambda_0$ vs $H_1: \lambda \in \Lambda_1$. Let $F_{n,\lambda}(.)$ be the distribution function of a test statistic S_n under p_λ, and for $\lambda \in \Lambda_1$, let;

$$L_n(\lambda) = \sup_{\xi \in \Lambda_0}[1 - F_{n,\xi}(S_n|\lambda)],$$

the p-value of the observed S_n under the distribution p_λ, and;

$$c(\lambda) = \lim_{n\to\infty}(-2n^{-1}\log L_n(\lambda))$$

if the limit exists. Typically, L_n tends to one and L_n tends to zero exponentially fast, and the faster, or the bigger c(.), the better S_n is. For two test statistics $S_{i,n}$ (l = 1,2) for the same hypothesis with L_n, $C_i(\lambda)$, and sample size n_i, to perform "equivalently" in the sense $\lim n_1^{-1}\log L_{2,n_2} = \lim n_1^{-1}\log L_{1,n_1}$, the Bahadur ARE of $S_{1,n}$ log L_{1n}, the Bahadur ARE of relative to $S_{2,n}$, at $\lambda \in \Lambda_1$, is defined as, and has the property

$$e_B(\{S_{1,n}\},\{S_{2,n}\}) = \lim \frac{n_2}{n_1} = \frac{c_1(\lambda)}{c_2(\lambda)}. \quad \textbf{(15)}$$

The limit C can be computed under the following conditions.

(B1). For $\lambda \in \Lambda_1$, $n^{-1/2}S_n \to b(\lambda)$ a.s. (P_λ), for some $-\infty < b(\lambda) < \infty$.

(B2). For the interval $I = \{b(\lambda): \lambda \in \Lambda_1\}$, there is a function g on l, such that;

$$\lim_n -2n^{-1}\log \sup_{\xi\in\Lambda_0}[1 - F_{n,\xi}(n^{1/2}t)] = g(t), \quad t \in I.$$

(Bahadur, 1960 [13]). *If S_n satisfies (B1)-(B2), then for* $\lambda \in \Lambda_1$,

$$c(\lambda) = g(b(\lambda)) \quad a.s.(P_\lambda).$$

For any test statistic S_n $(X_1,....,X_2)$ based on $X_1,....,X_n$ i.i.d. density $f(\cdot\,|\lambda)$, Bahadur (1967) [16] obtained the following;

$$\lim_n n^{-1}\log L_n(\lambda) \geq -\inf\{K(f(\cdot\,|\lambda), f(\cdot\,|\lambda_0)): \lambda_0 \in \Lambda_0\}.$$

Note although the above relationship is regarded as a dual to that of the Hodges-Lehmann index, the two are not equivalent as $K(f(\cdot\,|\lambda), f(\cdot\,|\lambda_0)) \neq K(f(\cdot\,|\lambda_0), f(\cdot\,|\lambda))$. A test statistic is said to be *Bahadur efficient* if for each $\lambda \in \Lambda_1$ $\lim_n$, log $L_n(\lambda) = -\inf\{K(f(\cdot\,|\lambda), f(\cdot\,|\lambda_0)): \lambda_0 \in \Lambda_0\}$.

Bahadur efficiency of likelihood ratio test has been studied by a number of researchers for some special distribution families. Arcones (2005 [17], Theorem 3.3) proved that, under some regularity conditions, the likelihood ratio statistic is Bahadur efficient. Let $f(\cdot\,|\lambda,\theta,\eta)$ be the density function of the data, under his conditions of Theorem 3.3, for each fixed λ > 1 and θ, we have;

$$c_T = -2\inf\inf\{K(f(\cdot\,|\lambda,\theta,\eta), f(\cdot\,|\eta,\lambda_0)): \eta\}.$$

Like the Hodges-Lehmman ARE, Bahadur ARE does not require the comparing test statistic have the same asymptotic distribution, nor they have the form of i.i.d. summations, so it has wide application scope.

For computation easiness, we consider a local version of Bahadur ARE. Consider testing H_0: $\lambda = \lambda_0$ *vs* the local alternative H_0: $\lambda = \lambda_0 + n^{-1/2}$. Let F_0 be the asymptotic distribution function of S_n under H_0, we define;

$$\tilde{c} = \lim_n[1 - F_0(S_n|H_n)].$$

Typically, $0 < \tilde{c} < 1$. The smaller $\tilde{c}$, the better S_n is. For two test statistics $S_{i,n}(i = 1,2)$ for the same hypothesis with $G_{i,n}$ and $\tilde{c}_i$, we define the local Bahadur ARE of $S_{1,n}$ relative to $S_{2,n}$as;

$$\tilde{e}_B(\{S_{1,n}\},\{S_{2,n}\}) = \frac{\tilde{c}_2}{\tilde{c}_1}. \quad \textbf{(16)}$$

Proposition 4. *(i) with $\mu_{MERT}(\lambda)$ given in Proposition 3, we have;*

$$c_{Z(\theta)}(\lambda) = \mu^2(\lambda,\theta)/\sigma^2(\theta), \qquad c_{Z_{MERT}}(\lambda) = \mu^2_{MERT}(\lambda).$$

(ii) *Under conditions of Theorem 4 in ZLY, $\mu_{MERT}(\lambda)$ with be the derivative of $\mu_{MERT}(\lambda)$, θ_0 be the value of θ H_0*

under, we have;

$$\tilde{c}_{Z(\theta)} = 1 - \Phi(\mu^{(1)}(1,\theta_0)/\sigma(\theta_0)),\quad \tilde{c}_{Z_{MERT}} = 1 - \Phi(\mu^{(1)}_{MERT}(1)).$$

4. SIMULATION AND APPLICATION TO GENETIC ASSOCIATION STUDIES

4.1. Simulation Study

Let P be the Minor Allele Frequency (MAF) of a marker of interest. We consider case-control data with r = 500 cases and s = 500 controls, $\lambda \in \{1.1,1.3,1.5\}$, $p \in \{0.15,0.30,0.45\}$, the true $\theta^{(0)} \in \{1/2,1\}$, and the disease prevalence K = 0.05. We generate 1000 datasets, and compute the means and standard deviations of $e_P(Z_{\text{MERT}}, Z_{\theta^{(0)}})$, $\tilde{e}_C(Z_{\text{MERT}}, Z_{\theta^{(0)}})$ and $\tilde{e}_B(Z_{\text{MERT}}, Z_{\theta^{(0)}})$. For Z_{MERT}, we choose $\theta_i = 0$ and $\theta_j = 1$.

Table **T1** shows the result, the means of AREs and the standard deviations of AREs are in brackets. First we can see the mean of all three AREs are less than 1, which show that Z_{θ^*} is consistent better than Z_{MERT}. Corresponding tothis fact when $\theta = \theta_{(0)}$ is the true value $Z_{\theta^{(0)}}$, is asymptotically most powerful. Then the three AREs are increased with the P or λ increased. Third, the e_p has the lowest variance among the three AREs, next is $\tilde{ldee}_C$, last is $\tilde{e}_B$.

Table 1. The AREs of Z_{MERT} and $Z_{\theta(0)}$.

-	-	λ - 1.1			λ - 1.1			λ - 1.1		
MAF$_0$	**θ (0)**	***ep***	$\tilde{e}_C$	$\tilde{e}_B$	***ep***	$\tilde{e}_C$	$\tilde{e}_B$	***ep***	$\tilde{e}_C$	$\tilde{e}_B$
0.15	1/2	0.874	0.876	0.827	0.887	0.904	0.856	0.895	0.917	0.869
-	-	(0.056)	(0.1)	(0.115)	(0.048)	(0.084)	(0.11)	(0.039)	(0.069)	(0.097)
-	1	0.654	0.814	0.723	0.654	0.837	0.746	0.652	0.85	0.761
-	-	(0.037)	(0.094)	(0.101)	(0.031)	(0.084)	(0.094)	(0.029)	(0.075)	(0.092)
0.3	1/2	0.963	0.94	0.912	0.97	0.954	0.929	0.973	0.961	0.937
-	-	(0.018)	(0.05)	(0.069)	(0.013)	(0.042)	(0.064)	(0.011)	(0.039)	(0.061)
-	1	0.73	0.841	0.751	0.729	0.853	0.763	0.728	0.863	0.775
-	-	(0.03)	(0.045)	(0.056)	(0.028)	(0.043)	(0.055)	(0.025)	(0.037)	(0.05)
0.45	1/2	0.991	0.985	0.978	0.993	0.986	0.978	0.995	0.989	0.983
-	-	(0.006)	(0.038)	(0.055)	(0.004)	(0.036)	(0.054)	(0.003)	(0.032)	(0.051)
-	1	0.76	0.85	0.766	0.758	0.856	0.771	0.76	0.861	0.775
-	-	(0.032)	(0.033)	(0.044)	(0.031)	(0.031)	(0.042)	(0.027)	(0.028)	(0.039)

4.2. Application

We use 6 reported SNPs associated with breast cancer 2 (Hunter *et al.* 2007 [31]; Li *et al.*, 2008 [32]) to illustrate the ARE of Z_{MERT}. These 6 SNPs are rs10510126, rs12505080, rs17157903, rs1219648, rs7696175, and rs2420946. The counts of subjects with three types of genotypes in cases and controls are shown in Table **2**, where (r, r_1, r_2) is the number of three genotypes in cases and (s, s_1, s_2) is the number of genotypes in controls. From the table, we find three AREs of E_p, E_c *and* E_b are higher than 75%, sometimes it can reach 97%. For example, for SNP rs17157903, the AREs of, and are 0.8255, 0.8453 and 0.7642, respectively. It shows that Z_{MERT} is a robust test.

Table 2. Three AREs of for 6 reported SNPs associated with breast cancer 2.

SNPid	*r*	r_1	r_2	*r*	r_1	r_2	E_p	E_c	*b*
rs10510126	955	180	10	854	272	14	0.8085	0.84	0.7594
rs12505080	608	477	50	628	408	99	0.8976	0.8725	0.8202
rs17157903	777	316	18	862	220	26	0.8255	0.8453	0.7642
rs1219648	352	543	250	433	538	170	0.9805	0.9719	0.9585
rs7696175	353	605	187	396	496	249	0.9686	0.9476	0.9285
rs2420946	357	546	242	440	537	165	0.9792	0.9673	0.9512

APPENDIX

Derivation of $\tilde{c}_i$: From (P3), we have $c_i = \lim_n d(n)\sigma_{i,n}(\lambda_0)/\mu_{i,n}(\lambda_0)$. Also, as in the proof in Serfling (1980 [8], p. 317-318), $P_{\lambda_0}(S_{i,n} > u_{\alpha,i,n}) \to \alpha$ and $\beta_{i,n}(\lambda_n) := P_{\lambda_n}(S_{i,n} \le u_{\alpha,i,n}) \to \beta$ if and only if

$$\frac{(\lambda_n-\lambda_0)^k}{k!}\frac{d(n)}{c_i}\to F_i^{-1}(1-\alpha)-F_i^{-1}(\beta) \text{ or } \frac{(\lambda_n-\lambda_0)^k}{k!}\frac{d(n)}{\tilde{c}_i}\to 1.$$

Thus, for $\beta_{i,n}$ (θ_n) → β, we must have;

$$\frac{(\lambda_n-\lambda_0)^k}{k!}\frac{d(n_1)}{\tilde{c}_1}\sim\frac{(\lambda_n-\lambda_0)^k}{k!}\frac{d(n_2)}{\tilde{c}_2}, \text{ or } \frac{d(n_1)}{d(n_2)}\to\frac{\tilde{c}_1}{\tilde{c}_2}.$$

Proof of Proposition 1: We use (4) to compute e_p ($Z_{MERT,}Z(\theta^{(0)})$). By definition of $Z(\theta^{(0)})$) and CLT we have $Z(\theta^{(0)})\xrightarrow{D}N(0,1)$, and by Theorem 3 in ZLY, $Z_{MERT}\xrightarrow{D}N(0,1)$. Also $Z(\theta^{(0)})$), and Z_{MERT})are jointly asymptotic normal with correlation $(\rho_{\theta_i,\theta^{(0)}}+\rho_{\theta_j,\theta^{(0)}})/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$. Thus the condition of (4) are satisfied, and it gives;

$$e_P(Z_{MERT},Z(\theta^{(0)}))=\frac{(\rho_{\theta_i,\theta^{(0)}}+\rho_{\theta_j,\theta^{(0)}})^2}{2(1+\rho_{\theta_i,\theta_j})}.$$

Proof of Proposition 2. (i) By assumption $Y|(\boldsymbol{x},g)\sim N(\eta^T\boldsymbol{x}+\sum_{j=1}^{2}\log(\lambda_j)I_j(g),\sigma^2)$, where $\lambda_1=\lambda$, $\lambda_2=1-\theta+\theta\lambda$. As in the proof of Theorem 4 in ZLY, we have that $\sqrt{n}Z(\theta)=\sum_{i=1}^{n}V_i+o_P(1)$ where the $V_i=V_i(\theta)$'s are i.i.d. with;

$$\begin{aligned} V_i &= \sigma^{-1}(l_{1,1}(Y_i,\boldsymbol{x}_i,g_i|1,1,\eta_0)+\theta l_{1,2}(Y_i,\boldsymbol{x}_i,g_i|1,1,\eta_0)\\ &\quad -(L_{13}^T(\eta_0)+\theta L_{23}^T(\eta_0))L_{33}^{-1}(\eta_0)l_{1,3}(Y_i,\boldsymbol{x}_i,g_i|1,1,\eta_0))\\ &= (\frac{I_1(g_i)}{(1-\theta+\theta\lambda)\sigma^2}+\frac{I_2(g_i)}{\lambda\sigma^2}+\frac{(L_{13}^T(\eta_0)+\theta L_{23}^T(\eta_0))L_{33}^{-1}(\eta_0)\boldsymbol{x}_i}{\sigma^2})\\ &\quad\times(Y_i-\eta^T\boldsymbol{x}_i-\log(1-\theta+\theta\lambda)I_1(g_i)+\log(\lambda)I_2(g_i))/\sigma\\ &:= a(\boldsymbol{x}_i,g_i,\lambda)(Y_i-\eta^T\boldsymbol{x}_i-\log(1-\theta+\theta\lambda)I_1(g_i)+\log(\lambda)I_2(g_i))/\sigma. \end{aligned}$$

Under $H_0:\lambda=1, V_i|(\boldsymbol{x}_i,g_i)\sim N(b_0(g_i),a_0{}^2(\boldsymbol{x}_i,G_i)$, with $b_0(g_i)=0$ and $a_0(\boldsymbol{x}_i,g_i)=a(\boldsymbol{x}_i,g_i,1)$. Under $H_1:\lambda\neq 1$, $V_i|(\boldsymbol{x}_i,g_i)\sim N(b_1(g_i),a_1^2(\boldsymbol{x}_i,g_i,\lambda))$, with $b_1(g_i)=b(g_i)=\log(1-\theta+\theta\lambda)I_1(g_i)+\log(\lambda)I_2(g_i)$ and $a_1(\boldsymbol{x}_i,g_i)=a(\boldsymbol{x}_i,g_i,\lambda)$. So we have

$$\mu_0=E(V_i|H_0)=E[E(V_i|(\boldsymbol{x}_i,g_i,H_0)]=0, \quad \text{and}$$

$$\mu_1=E(V_i|H_1)=E[E(V_i|(\boldsymbol{x}_i,g_i,H_1)]=E[\log(1-\theta+\theta\lambda)I_1(g_i)+\log(\lambda)I_2(g_i)].$$

By example A in Serfling (1980 [8], p. 330), we have;

$$e^{-ts}M_k(s)=E[e^{-ts}E(e^{sV_i}|\boldsymbol{x}_i,g_i,H_k)]=E[\exp((b_k(g_i)-t)s+\frac{1}{2}a_k^2(\boldsymbol{x}_i,g_i)s^2)],\quad (k=0,1)$$

$$m_k(t)=\inf_s[e^{-ts}M_k(s)]=E[\exp(-\frac{(b_k(g_i)-t)^2}{2a_k^2(\boldsymbol{x}_i,g_i)}],\quad (k=0,1),$$

and

$$\rho_{Z(\theta)}=E(\exp[-\frac{b_1^2(g_i)}{2(a_0(\boldsymbol{x}_i,g_i)+a_1(\boldsymbol{x}_i,g_i))^2}])=E(\exp[-\frac{b^2(g_i)}{2(a(\boldsymbol{x}_i,g_i,1)+a(\boldsymbol{x}_i,g_i,\lambda))^2}]).$$

Similarly, $\sqrt{n}Z_{MERT} = \sum^{n}{}_{k=1}(V_k(\theta_i) + V_k(\theta_j))/\sqrt{2(1+\rho_{\theta_i,\theta_j})} + o_P(1) := \sum_{k=1}^{n} V_k + o_P(1)$. We have, under H_0, $V_k|(\boldsymbol{x}_k, g_k) \sim N(b_0(g_k), a_0^2(\boldsymbol{x}_k, g_k))$, with $b_0(g_k) = 0$ and $a_0(\boldsymbol{x}_k, g_k) = [a(\boldsymbol{x}_k, g_k, \theta_i, 1) + a(\boldsymbol{x}_k, g_k, \theta_j, 1)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$; Under H_1, $V_k|(\boldsymbol{x}_k, g_k) \sim N(b_1(g_k), a_1^2(\boldsymbol{x}_k, g_k))$, where $b_1(g_k) = b(g_k) = E(V_k|H_1) = [\log(1-\theta+\theta\lambda)I_1(g_k) + \log(\lambda)I_2(g_k)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$, and $a_1(\boldsymbol{x}_k, g_k) = [a(\boldsymbol{x}_k, g_k, \theta_i, \lambda) + a(\boldsymbol{x}_k, g_k, \theta_j, \lambda)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$

similar to that for ($Z(\theta^{(0)})$).

(ii). We first compute $\tilde{Q}_{Z(\theta^{(0)})}$. In this case, let be the weak limit of ($Z(\theta^{(0)})$). Then, $S|H_0 \sim N(0,1)$, and $S|H_n \sim N(\sqrt{n}\mu(\lambda_n, \theta^{(0)})/\sigma(\theta^{(0)}), 1)$. So $\mu_0 = E(S|H_0) = 0$. Note $\mu(\lambda_n, \theta^{(0)}) = \mu(\lambda_0, \theta) + \mu^{(1)}(\lambda_0, \theta^{(0)})n^{-1/2} + O(n^{-1})$, we have $\mu_1 = \lim_n E(S|H_n) = \mu^{(1)}(\lambda_0, \theta^{(0)})/\sigma(\theta^{(0)})$. Thus

$$\tilde{Q}_{Z(\theta^{(0)})} = \inf_{0\le t\le\mu_1} \tilde{Q}_{Z(\theta^{(0)})}(t) = \inf_{0\le t\le\mu_1} (1 - \Phi(t) + \Phi(t-\mu_1)).$$

Proof of Proposition 3. Since under H_0, $Z(\theta) \xrightarrow{D} N(0,1)$, we have $t_n(\alpha) \to \Phi^{-1}(1-\alpha)$; and under H_1, $Z(\theta) - \sqrt{n}\mu(\lambda,\theta)/\sigma(\theta) \sim N(0,1)$. Since $\Phi(\cdot)$ is continuous on $(-\infty, \infty)$, the distribution function of $Z(\theta) - \sqrt{n}\mu(\lambda,\theta)/\sigma(\theta)$ converges to uniformly $\Phi(.)$. Note $\mu(\lambda, \theta) > 0$, so for $\lambda > 1$ we have;

$$\beta_{Z(\theta),n}(\lambda) = P_\lambda(Z(\theta) \le t_{Z(\theta),n}(\alpha)) = (1+o(1))P_\lambda(Z(\theta) \le \Phi^{-1}(1-\alpha))$$

$$= (1+o(1))\Phi(\Phi^{-1}(1-\alpha) - \sqrt{n}\frac{\mu(\lambda,\theta)}{\sigma(\theta)}).$$

Let $x = \sqrt{n}$, using L'hopital's rule twice, we get;

$$d_{Z(\theta)} = \lim_n -2n^{-1}\log\beta_{Z(\theta),n}(\lambda)$$

$$= \lim_{x\to\infty} -\frac{2(1+o(1))\,log\ \Phi\,(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}{x^2}$$

$$= \lim_{x\to\infty} -\frac{2\,log\ \Phi\,(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}{x^2}$$

$$= \lim_{x\to\infty} \frac{\frac{\mu(\lambda,\theta)}{\sigma(\theta)}\phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}{x\Phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}$$

$$= \lim_{x\to\infty} \frac{-x[\frac{\mu(\lambda,\theta)}{\sigma(\theta)}]^3\phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}{\Phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)}) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)}\phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}$$

$$= \lim_{x\to\infty} \frac{-x[\frac{\mu(\lambda,\theta)}{\sigma(\theta)}]^3\phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})}{-x\frac{\mu(\lambda,\theta)}{\sigma(\theta)}\phi(\Phi^{-1}(1-\alpha) - x\frac{\mu(\lambda,\theta)}{\sigma(\theta)})} = \frac{\mu^2(\lambda,\theta)}{\sigma^2(\theta)}.$$

Similarly, under H_0, $Z_{MERT} \xrightarrow{D} N(0,1)$, and under H_1, $Z_{MERT} - \sqrt{n}\mu_{MERT}(\lambda) \sim N(0,1)$ where $\mu_{MERT} = [\mu(\lambda,\theta_i)/\sigma(\theta_i) + \mu(\lambda,\theta_j)/\sigma(\theta_j)]/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$. The same way we get;

$$d_{Z_{MERT}}(\lambda) = \lim_n 2\,n^{-1}\log \beta_{Z_{MERT},n} = \mu^2_{MERT}(\lambda).$$

Proof of Proposition 4. i). In our case $\Lambda_0 = \{1\} = \{\lambda_0\}$, $\Lambda_1 = (1,\infty) = (\lambda_0,\infty)$, and when $\lambda = \lambda_0$, $Z(\theta) \xrightarrow{D} N(0,1)$, so $L_n(\lambda) = \sup_{\xi\in\Lambda_0}[1 - F_{n,\xi}(S_n|\lambda)] \sim 1 - \Phi(S_n|\lambda)$ uniformly in S_n. From proof of Theorem 4 in ZLY, we have that for $\lambda \in \Lambda_1$, $n^{-1/2}Z(\theta) \to \mu(\lambda,\theta)/\sigma(\theta)$ (a.s.). Now we compute, for $t \in (1,\infty)$,

$$g(t) := \lim_n -2n^{-1}L_n = \lim_n -2n^{-1}(1+o(1))\log(1-\Phi(n^{1/2}t)).$$

Let $x = \sqrt{n}$, and use L'Hopital's rule,

$$g(t) = \lim_{x\to\infty}\frac{-2(1+o(1))\,log\,(1-\Phi(xt))}{x^2} = \lim_{x\to\infty}\frac{-2\,log\,(1-\Phi(xt))}{x^2} = \lim_{x\to\infty}\frac{t\phi(xt)}{x(1-\Phi(xt))}.$$

Since $\phi(xt) \to 0$, and by L'hopital's rule, $x(1-\Phi(xt)) = (1-\Phi(xt))/(1/x) = tx^2\phi(xt) \to 0$, so use L'Hopital's rule on the above again,

$$g(t) = \lim_{x\to\infty}\frac{-t^3x\phi(xt)}{1-\Phi(xt)-xt\phi(xt)} = t^2.$$

Thus by Bahadur's (1960) [13] Theorem,

$$c_{Z(\theta)}(\lambda) = \mu^2(\lambda,\theta)/\sigma^2(\theta).$$

Since $Z_{MERT} = (Z(\theta_i) + Z(\theta_j))/\sqrt{2(1+\rho_{\theta_i,\theta_j})}$, for $\lambda \in \Lambda_0$, $Z_{MERT} \xrightarrow{D} N(0,1)$; for $\lambda \in \Lambda_1$, $n^{-1/2}Z_{MERT} \to \mu_{MERT}(\lambda)$ (a.s.), so $c_{Z_{MERT}}(\lambda)$ is similarly computed.

(ii. Note $\mu(1,\theta_0) = 0$, under H_0, $Z(\theta) \xrightarrow{D} N(0,1)$; under H_n, $Z(\theta) \sim \sqrt{n}\mu(\lambda_n,\theta_0)/\sigma(\theta_0) \sim \mu^{(1)}(1,\theta_0)/\sigma(\theta_0)$ (a.s.), so

$$e_{Z(\theta)} = \lim_n(1-\Phi(Z(\theta)|H_n)) = 1-\Phi(\mu^{(1)}(1,\theta_0)/\sigma(\theta_0)).$$

Similarly, under H_0, $Z_{MERT} \xrightarrow{D} N(0,1)$; under H_n, $Z_{MERT} \sim \mu_{MERT}(\lambda_n) \sim \mu^{(1)}_{MERT}(1)$, (a.s.), so

$$\tilde{e}_{Z_{MERT}} = \lim_n(1-\Phi(Z_{MERT}|H_n)) = 1-\Phi(\mu^{(1)}_{MERT}(1)).$$

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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