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Confidence Interval for the Ratio of Bivariate Normal Means with a Known Coefficient of Variation

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Abstract: An approximate confidence interval for the ratio of bivariate normal means with a known coefficient of variation is proposed in this paper. This application has the area of bioassay and bioequivalence when a scientist knows the coefficient of variation of a control group. The proposed confidence interval is based on the approximated expectation and variance of the estimator by the Taylor series expansion. A Monte Carlo simulation study was conducted to compare the performance of the proposed confidence interval with the existing confidence interval. The results showed that the simulation is considered confidence interval and the estimated coverage probabilities close to the nominal confidence level for large sample sizes. The estimated coverage probabilities of the existing confidence interval are over estimated for all situations. In addition, the expected lengths of the proposed confidence interval are shorter than those of the existing confidence interval in all circumstances. When the sample size increases, the expected length become shorter. Therefore, our confidence interval presented in this paper performs well in terms of estimated coverage probability and the expected length in considering the simulation results. A comparison of the confidence intervals is also illustrated using an empirical application.

Keywords: Interval estimation, Central tendency, Standardized measure of dispersion, Coverage probability, Expected length.

1. Introduction

The ratio of normal means is widely used in the area of bioassay and bioequivalence (see, for example, Bliss, 1935a, 1935b; Irwin, 1937; Fieller, 1944, 1954; Finney, 1947, 1965; Cox, 1985; Srivastava, 1986; Vuorinen and Tuominen, 1994; Kelly, 2000; Lee and Lin, 2004; Lu, et al., 2014; Sun, et al., 2016). The ratio of normal means is defined by $\theta = \mu_x / \mu_y$, where μ_x and μ_y are the population means of X and Y, respectively. Several researchers have studied the confidence interval for the ratio of normal means. For example, Fieller's (1944, 1954) theorem constructed the confidence interval for the ratio means. Koschat (1987) demonstrated that the coverage probability of a confidence interval constructed using Fieller's theorem is exact for all parameters when a common variance assumption is assumed.

Niwitpong et al. (2011) proposed two confidence intervals for the ratio of normal means with a known coefficient of variation. Their confidence intervals can be applied in some situations, for instance, when the coefficient of variation of a control group is known. One of their confidence intervals was developed based on an exact method in which this confidence interval was constructed from the pivotal statistic Z, where Z follows the standard normal distribution. The other confidence interval was constructed based on the generalized confidence interval (Weerahandi, 1993). Simulation results in Niwitpong et al. (2011) showed that the coverage probabilities of the two confidence intervals were not significantly different. However, the confidence interval based on the exact method was shorter than the generalized confidence interval. The exact method used Taylor series expansion to find the expectation and variance of the estimator of θ and used these results for constructing the confidence interval for θ. The exact confidence intervals for θ proposed by Niwitpong et al. (2011) are difficult to compute since they depend on an infinite summation. Panichkitkosolkul (2015) considered an approximate confidence interval for θ with a known coefficient of variation. The computation of this confidence interval is easier than the exact confidence interval. Additionally, the proposed

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confidence interval performed as well as the exact confidence interval in terms of estimated coverage probability and expected length.

The existing confidence intervals for θ are constructed when two populations are independent. However, none of the confidence interval for the ratio normal means have been studied in the case of two dependent populations. Therefore, our main aim in this study is to propose an approximate confidence interval for the ratio of bivariate normal means with a known coefficient of variation. In addition, we also compare the estimated coverage probabilities and expected lengths of the new proposed confidence interval, and the confidence interval proposed by Panichkitkosolkul (2015) using a Monte Carlo simulation.

The manuscript is organized as follows. In Section 2, the theoretical background of the existing confidence interval for θ is discussed. We provide the theorem for constructing the approximate confidence interval for θ (Section 3). In Section 4, the performance of the confidence intervals for θ is investigated through a Monte Carlo simulation study. The proposed confidence interval is illustrated by using an example in Section 5. Conclusions are provided in Section 6.

2. Existing Confidence Interval

In this section, we review the theorem proposed by Panichkitkosolkul (2015) and use these to construct the approximate confidence interval for θ.

Theorem 1. Let $X_1,...,X_n$ be a random sample of size n from a normal distribution with mean μ_x and variance σ_x^2 and $Y_1,...,Y_m$ be a random sample of size m from a normal distribution with mean μ_y and variance σ_y^2. The estimator of θ is $\hat{\theta} = \bar{X}/\bar{Y}$ where $\bar{X} = n^{-1}\sum_{i=1}^{n} X_i$ and $\bar{Y} = m^{-1}\sum_{j=1}^{m} Y_j$. The approximate expectation and variance of $\hat{\theta}$ when a coefficient of variation, $\tau_y = \sigma_y/\mu_y$ is known, are respectively (Panichkitkosolkul, 2015)

$$E(\hat{\theta}) \approx \theta\left(1+\frac{\tau_y^2}{m}\right) \quad (1)$$

and

$$\text{var}(\hat{\theta}) \approx \frac{\sigma_x^2}{n\mu_y^2} + \frac{\theta^2}{m}\tau_y^2. \quad (2)$$

Proof of Theorem 1. See Panichkitkosolkul (2015).

It is clear from Equation (1) that $\hat{\theta}$ is asymptotically unbiased $\left(\lim_{m\to\infty} E(\hat{\theta}) = \theta\right)$ and $E\left[\hat{\theta}/v\right] = \theta,$ where $v = 1+\tau_y^2/m.$ Therefore, the unbiased estimator of θ is $\hat{\theta}/v = \bar{X}/v\bar{Y}.$ From Equation (2), $\hat{\theta}$ is consistent $\left(\lim_{n,m\to\infty} \text{var}(\hat{\theta}) = 0\right).$ Now we will use the fact that, from the central limit theorem,

$$Z = \frac{\hat{\theta}-\theta}{\sqrt{\text{var}(\hat{\theta})}} \sim N(0,1).$$

Based on Theorem 1, we get

$$Z = \frac{\hat{\theta}/v-\theta}{\sqrt{\dfrac{\sigma_x^2}{n\mu_y^2}+\dfrac{\theta^2}{m}\tau_y^2}} \sim N(0,1).$$

Therefore, the $(1-\alpha)100\%$ existing approximate confidence interval for θ is

$$CI_{existing} = \hat{\theta}/v \pm z_{1-\alpha/2}\sqrt{\frac{S_x^2}{n\bar{Y}^2}+\frac{\hat{\theta}^2}{m}\tau_y^2},$$

where $\hat{\theta} = \bar{X}/\bar{Y},$ $S_x^2 = (n-1)^{-1}\sum_{i=1}^{n}(X_i-\bar{X})^2,$ $v = 1+\tau_y^2/m$ and $z_{1-\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution.

3. Proposed Confidence Interval

To find a simple approximate expression for the expectation of $\hat{\theta},$ we use a Taylor series expansion of x/y around μ_x, μ_y :

$$\frac{x}{y} \approx$$

$$\left.\frac{x}{y}\right|_{\mu_x,\mu_y} + (x-\mu_x)\frac{\partial}{\partial x}\left.\left(\frac{x}{y}\right)\right|_{\mu_x,\mu_y} + (y-\mu_y)\frac{\partial}{\partial y}\left.\left(\frac{x}{y}\right)\right|_{\mu_x,\mu_y}$$

$$+\frac{1}{2}(x-\mu_x)^2\frac{\partial^2}{\partial x^2}\left.\left(\frac{x}{y}\right)\right|_{\mu_x,\mu_y} + \frac{1}{2}(y-\mu_y)^2\frac{\partial^2}{\partial y^2}\left.\left(\frac{x}{y}\right)\right|_{\mu_x,\mu_y}$$

$$+(x-\mu_x)(y-\mu_y)\frac{\partial^2}{\partial x\partial y}\left.\left(\frac{x}{y}\right)\right|_{\mu_x,\mu_y}$$

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$$+O\left(\left((x-\mu_x)\frac{\partial}{\partial x}+(y-\mu_y)\frac{\partial}{\partial y}\right)^3\left(\frac{x}{y}\right)\right). \qquad (3)$$

Theorem 2. Let $X_1,...,X_n$ and $Y_1,...,Y_n$ be a random samples of size n from a bivariate normal distribution; $N\left(\mu_x,\mu_y,\sigma_x^2,\sigma_y^2,\rho_{xy}\right)$. The estimator of θ is $\hat{\theta}=\bar{X}/\bar{Y}$ where $\bar{X}=n^{-1}\sum_{i=1}^{n}X_i$ and $\bar{Y}=n^{-1}\sum_{i=1}^{n}Y_i$. The approximate expectation and variance of $\hat{\theta}$ when a coefficient of variation, $\tau_y=\sigma_y/\mu_y$ is known, are respectively

$$E(\hat{\theta}) \approx \theta\left(1+\frac{\tau_y^2}{n}-\frac{\tau_y\rho_{xy}\sigma_x}{n\mu_x}\right)$$

and $\operatorname{var}(\hat{\theta}) \approx \dfrac{1}{n}\left(\dfrac{\sigma_x^2}{\mu_y^2}+\theta^2\tau_y^2-\dfrac{2\theta\tau_y\rho_{xy}\sigma_x}{\mu_y}\right).$

Proof of Theorem 2. Consider random variables $\bar{X}$ and $\bar{Y}$ where $\bar{Y}$ has support $(0,\infty)$. Let $\hat{\theta}=\bar{X}/\bar{Y}$. Find approximations for $E(\hat{\theta})$ and $\operatorname{var}(\hat{\theta})$ using Taylor series expansion of $\hat{\theta}$ around μ_x,μ_y as in Equation (3). The mean of $\hat{\theta}$ can be found by applying the expectation operator to the individual terms (ignoring all terms higher than two),

$$\begin{aligned}
E(\hat{\theta}) &= E\left(\frac{\bar{X}}{\bar{Y}}\right)\\
&= E\left(\frac{\bar{X}}{\bar{Y}}\right)\Bigg|_{\mu_x,\mu_y} + E\left[\frac{\partial}{\partial\bar{X}}\left(\frac{\bar{X}}{\bar{Y}}\right)(\bar{X}-E(\bar{X}))\right]\Bigg|_{\mu_x,\mu_y}\\
&\quad + E\left[\frac{\partial}{\partial\bar{Y}}\left(\frac{\bar{X}}{\bar{Y}}\right)(\bar{Y}-E(\bar{Y}))\right]\Bigg|_{\mu_x,\mu_y}\\
&\quad + \frac{1}{2}E\left[\frac{\partial^2}{\partial\bar{X}^2}\left(\frac{\bar{X}}{\bar{Y}}\right)(\bar{X}-E(\bar{X}))^2\right]\Bigg|_{\mu_x,\mu_y}\\
&\quad + \frac{1}{2}E\left[\frac{\partial^2}{\partial\bar{Y}^2}\left(\frac{\bar{X}}{\bar{Y}}\right)(\bar{Y}-E(\bar{Y}))^2\right]\Bigg|_{\mu_x,\mu_y}\\
&\quad + E\left[\frac{\partial^2}{\partial\bar{X}\partial\bar{Y}}\left(\frac{\bar{X}}{\bar{Y}}\right)(\bar{X}-E(\bar{X}))(\bar{Y}-E(\bar{Y}))\right]\Bigg|_{\mu_x,\mu_y}\\
&\quad + O(n^{-1})\\
&\approx \frac{\mu_x}{\mu_y}+0+0+0+\frac{1}{2}\left(\frac{2E(\bar{X})}{(E(\bar{Y}))^3}\operatorname{var}(\bar{Y})\right)-\frac{\operatorname{cov}(\bar{X},\bar{Y})}{(E(\bar{Y}))^2}\\
&\approx \frac{\mu_x}{\mu_y}+\operatorname{var}(\bar{Y})\frac{\mu_x}{\mu_y^3}-\frac{\operatorname{cov}(\bar{X},\bar{Y})}{\mu_y^2}\\
&= \frac{\mu_x}{\mu_y}+\frac{\sigma_y^2\mu_x}{n\mu_y^3}-\frac{\sigma_{xy}}{n\mu_y^2}\\
&= \frac{\mu_x}{\mu_y}+\frac{\mu_x\tau_y^2}{n\mu_y}-\frac{\tau_y\rho_{xy}\sigma_x}{n\mu_y}\\
&= \frac{\mu_x}{\mu_y}\left(1+\frac{\tau_y^2}{n}-\frac{\tau_y\rho_{xy}\sigma_x}{n\mu_x}\right)\\
&= \theta\left(1+\frac{\tau_y^2}{n}-\frac{\tau_y\rho_{xy}\sigma_x}{n\mu_x}\right). \qquad (4)
\end{aligned}$$

An approximation of the variance of $\hat{\theta}$ is obtained by using the first-order terms of the Taylor series expansion:

$$\begin{aligned}
\operatorname{var}(\hat{\theta}) &= \operatorname{var}\left(\frac{\bar{X}}{\bar{Y}}\right)\\
&= E\left[\left(\frac{\bar{X}}{\bar{Y}}-E\left(\frac{\bar{X}}{\bar{Y}}\right)\right)^2\right]\\
&\approx E\left[\left(\frac{\bar{X}}{\bar{Y}}-\frac{\mu_x}{\mu_y}\right)^2\right]\\
&\approx E\left[\left(\begin{array}{l}\dfrac{\mu_x}{\mu_y}+\dfrac{\partial}{\partial\bar{X}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)(\bar{X}-E(\bar{X}))\\ +\dfrac{\partial}{\partial\bar{Y}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)(\bar{Y}-E(\bar{Y}))-\dfrac{\mu_x}{\mu_y}\end{array}\right)^2\right]\Bigg|_{\mu_x,\mu_y}\\
&= \left.\begin{array}{l}\left(\dfrac{\partial}{\partial\bar{X}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)\right)^2\operatorname{var}(\bar{X})+\left(\dfrac{\partial}{\partial\bar{Y}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)\right)^2\operatorname{var}(\bar{Y})\\ +2\dfrac{\partial}{\partial\bar{X}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)\dfrac{\partial}{\partial\bar{Y}}\left(\dfrac{\bar{X}}{\bar{Y}}\right)\operatorname{cov}(\bar{X},\bar{Y})\end{array}\right|_{\mu_x,\mu_y}\\
&\approx \frac{\operatorname{var}(\bar{X})}{\mu_y^2}+\frac{\mu_x^2\operatorname{var}(\bar{Y})}{\mu_y^4}-\frac{2\mu_x\operatorname{cov}(\bar{X},\bar{Y})}{\mu_y^3}
\end{aligned}$$

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$$= \frac{\sigma_x^2}{n\mu_y^2} + \frac{\mu_x^2\sigma_y^2}{n\mu_y^4} - \frac{2\mu_x\sigma_{xy}}{n\mu_y^3}$$

$$= \frac{1}{n}\left(\frac{\sigma_x^2}{\mu_y^2} + \theta^2\tau_y^2 - \frac{2\theta\tau_y\rho_{xy}\sigma_x}{\mu_y}\right). \qquad (5)$$

It is clear from Equation (4) that $\hat{\theta}$ is asymptotically unbiased $\left(\lim_{n\to\infty} E(\hat{\theta}) = \theta\right)$ and $E\left[\hat{\theta}/\eta\right] = \theta,$ where $\eta = 1 + \frac{\tau_y^2}{n} - \frac{\tau_y\rho_{xy}\sigma_x}{n\mu_x}$. Therefore, the asymptotically unbiased estimator of the ratio of bivariate normal means is $\hat{\theta}/\hat{\eta} = \bar{X}/\hat{\eta}\bar{Y}$ where $\hat{\eta} = 1 + \frac{\tau_y^2}{n} - \frac{\tau_y r_{xy} S_x}{n}$ and r_{xy} is the sample Pearson's correlation coefficient. From Equation (5), $\hat{\theta}$ is consistent $\left(\lim_{n\to\infty} \mathrm{var}(\hat{\theta}) = 0\right)$. We then apply the central limit theorem and Theorem 2,

$$Z = \frac{\hat{\theta}/\eta - \theta}{\sqrt{\frac{1}{n}\left(\frac{\sigma_x^2}{\mu_y^2} + \theta^2\tau_y^2 - \frac{2\theta\tau_y\rho_{xy}\sigma_x}{\mu_y}\right)}} \sim N(0,1).$$

Therefore, it is easily seen that the $(1-\alpha)100\%$ approximate confidence interval for θ is

$$CI_{proposed} = \frac{\hat{\theta}}{\hat{\eta}} \pm z_{1-\alpha/2}\sqrt{\frac{1}{n}\left(\frac{S_x^2}{\bar{Y}^2} + \hat{\theta}^2\tau_y^2 - \frac{2\hat{\theta}\tau_y r_{xy} S_x}{\bar{Y}}\right)},$$

where $\hat{\theta} = \bar{X}/\bar{Y}$, $\hat{\eta} = 1 + \frac{\tau_y^2}{n} - \frac{\tau_y r_{xy} S_x}{n}$, $S_x^2 = (n-1)^{-1}\sum_{i=1}^{n}(X_i - \bar{X})^2$, r_{xy} is the sample Pearson's correlation coefficient and $z_{1-\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution.

4. Simulation Study

A Monte Carlo simulation was conducted using the R statistical software (Ihaka and Gentleman, 1996) version 3.2.2 to compare the estimated coverage probabilities and average lengths of the new proposed confidence interval and the existing confidence interval for the ratio of bivariate normal means. The data set was generated from a bivariate normal distribution with $\theta = 0.5, 1$ and 2 (They represent the case of $\mu_x < \mu_y, \mu_x = \mu_y$ and $\mu_x > \mu_y$), the correlation coefficients ρ_{xy} = 0.3, 0.5 and 0.7 (They represent the case of low, moderate and high correlations), and the ratio of variances σ_x^2/σ_y^2 = 0.25, 0.5, 0.8, 1, 2 and 3 (They represent the case of $\sigma_x^2 < \sigma_y^2, \sigma_x^2 = \sigma_y^2$ and $\sigma_x^2 > \sigma_y^2$). The sample sizes were set at n = 10, 20, 30 and 50. The number of simulation runs was 1,000 (The simulation results based on 1,000 runs were not different with those based on 10,000 runs) and the nominal confidence level $1-\alpha$ was fixed at 0.95. The simulation results are demonstrated in Tables 1-3 (Annex1). The proposed confidence interval has estimated coverage probabilities close to the nominal confidence level for large sample sizes. The estimated coverage probabilities of the existing confidence interval are over estimated for all situations. Additionally, the expected lengths of the proposed confidence interval are shorter than those of the existing confidence interval in all circumstances. When the sample sizes increase, the expected lengths become shorter (i.e., for the proposed confidence interval, ρ_{xy} = 0.3, σ_x^2/σ_y^2 = 0.25, 0.0721 for n =10; 0.0514 for n =20; 0.0327 for n =50). Therefore, the proposed confidence interval performs well in terms of estimated coverage probability and expected length in considering the simulation results.

5. An Illustrative Example

To illustrate an example of the two confidence interval for the ratio of bivariate normal means with a known coefficient of variation proposed in the previous section, we used the data taken from Fisher and Van Belle (1993, Example 9.3). The data represent *erythrocyte adenosine triphosphate* (ATP) levels in youngest and oldest sons in 17 families. The data are given in Table 4 (Annex1). The ATP level is important because it determines the ability of the blood to carry energy to the cells of the body (Krishnamoorthy and Xia, 2007). The histogram, density plot, Box-and-Whisker plot and normal quantile-quantile plot of each variable are displayed in Figures 1 and 2 (Annex1). Figure 3 shows the result of the Shapiro-Wilk multivariate normality test using package "mvnormtest" in the R statistical software.

As they appear in Figures 1 to 3, we find that the data are in excellent agreement with a bivariate normal distribution. From past research, we assume that the population coefficient of variation of ATP in the oldest sons is about 0.1. The 95% existing and proposal confidence intervals for the ratio of bivariate normal means with a known coefficient of variation are calculated and reported in Table 5

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(Annex1). The results confirm that the proposed confidence interval is more efficient than the existing confidence interval in terms of the length of the interval.

6. Conclusions

In this study, we proposed an approximate confidence interval for the ratio of bivariate normal means with a known coefficient of variation. Normally, this arises when a scientist knows the coefficient of variation of a control group. The approximate confidence interval proposed uses the approximation of the expectation and variance of the estimator. The new proposed confidence interval was compared with the existing approximate confidence interval constructed by Panichkitkosolkul (2015) through a Monte Carlo simulation study. The new proposed confidence interval performed well for all cases in terms of the estimated coverage probability and expected length.

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References

Bliss, C. I. (1935a). The calculation of the dose-mortality curve, *Annals of Applied Biology*, *22*(1), 134-167.

Bliss, C. I. (1935b).The comparison of dose-mortality data, *Annals of Applied Biology*, *22* (2), 309-333.

Cox, C. P. (1985). Interval estimates for the ratio of the means of two normal populations with variances related to the means, *Biometrics*, *41*(1), 261-265.

Fieller, E. C. (1944). A fundamental formula in the statistics of biological assay and some applications, *Quarterly Journal of Pharmacy and Pharmacology*, *17* (2), 117-123.

Fieller, E. C. (1954). Some problems in interval estimation, *Journal of the Royal Statistical Society: Series B*, *16* (2), 175-185.

Finney, D. J. (1947). The principles of the biological assay (with discussion), *Journal of the Royal Statistical Society: Series B*, *9* (1), 46-91.

Finney, D. J. (1965). The meaning of bioassay, *Biometrics*, 21 (4), 785-798.

Fisher, L. D. and Van Belle, G. (1993). *A Methodology for the Health Sciences*. New York: Wiley.

Ihaka, R. and Gentleman, R. (1996). R: A language for data analysis and graphics, *Journal of Computational and Graphical Statistics*, *5*, 299-314.

Irwin, J. O. (1937). Statistical method applied to biological assay, *Journal of the Royal Statistical Society: Series B*, *4* (1), 1-60.

Kelly, G. E. 2000. The median lethal dose-design and estimation, *Statistician*, *50*(1), 41-50.

Koschat, M. A. (1987). A characterization of the Fieller solution, *Annals of Statistics*, *15*(1), 462-468.

Krishnamoorthy, K. and Xia, Y. (2007). Inferences on correlation coefficients: One-sample, independent and correlated cases, *Journal of Statistical Planning and Inferences*, *137* (7), 2362-2379.

Lee, J. C. and Lin, S. H. (2004). Generalized confidence intervals for the ratio of means of two normal populations, *Journal of Statistical Planning and Inference*, *123* (6), 49-60.

Lu, Y., Chow, S.C. and Zhu, S. (2014). In vivo and in vitro bioequivalence testing, *Bioequivace & Bioavailability*, *6* (2), 67-74.

Niwitpong, S., Koonprasert, S. and Niwitpong, S. (2011). Confidence intervals for the ratio of normal means with a known coefficient of variation, *Advances and Applications in Statistics*, *25*(1), 47-61.

Panichkitkosolkul, W. (2015, October 13-17). Approximate confidence interval for the ratio of normal means with a known coefficient of variation, In V.N. Huynh, M. Inuiguchi, and T. Denoeux (Eds.), *Integrated Uncertainty in Knowledge Modelling and Decision Making*. Paper presented at The 4th symposium on Integrated Uncertainty in Knowledge Modelling and Decision Making, Nha Trang, Vietnam (pp.183-191). Switzerland: Springer

Srivastava, M. S. (1986). Multivariate bioassay, combination of bioassays and Fieller's theorem, *Biometrics*, *42*(1), 131-141.

Sun, W., Grosser, S. and Tsong, Y. (2016). Ratio of means vs. difference of means as measures of superiority, noninferiority, and average

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bioequivalence, *Journal of Biopharmaceutical Statistics,*doi:10.1080/10543406.2016.1265536.

Vuorinen, J. and Tuominen, J. (1994). Fieller's confidence intervals for the ratio of two means in the assessment of average bioequivalence from crossover data, *Statistics in Medicine*, *13* (23), 2531-2545.

Weerahandi, S. (1993). Generalized confidence intervals, *Journal of the American Statistical Association*, *88* (423), 899-905.

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Annex 1

Table 1. Estimated coverage probabilities and expected lengths of confidence intervals for the ratio of bivariate normal means with a known coefficient of variation when $\theta = 0.5$.

n	ρ_{xy}	σ_x^2/σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	Proposed	Existing	Proposed
10	0.3	0.25	0.976	0.932	0.0869	0.0715
		0.5	0.981	0.930	0.0755	0.0628
		0.8	0.966	0.922	0.0701	0.0603
		1	0.965	0.929	0.0682	0.0591
		2	0.952	0.926	0.0643	0.0579
		3	0.941	0.924	0.0627	0.0575
	0.5	0.25	0.995	0.919	0.0870	0.0610
		0.5	0.984	0.915	0.0752	0.0547
		0.8	0.974	0.914	0.0698	0.0530
		1	0.985	0.934	0.0680	0.0527
		2	0.966	0.912	0.0636	0.0525
		3	0.949	0.911	0.0634	0.0545
	0.7	0.25	0.998	0.932	0.0872	0.0482
		0.5	0.998	0.929	0.0750	0.0445
		0.8	0.997	0.924	0.0706	0.0456
		1	0.988	0.910	0.0679	0.0452
		2	0.982	0.934	0.0637	0.0476
		3	0.969	0.905	0.0623	0.0493
20	0.3	0.25	0.978	0.925	0.0618	0.0511
		0.5	0.980	0.951	0.0532	0.0449
		0.8	0.972	0.936	0.0503	0.0429
		1	0.970	0.924	0.0484	0.0422
		2	0.956	0.931	0.0462	0.0415
		3	0.959	0.935	0.0449	0.0411
	0.5	0.25	0.993	0.938	0.0617	0.0434
		0.5	0.994	0.941	0.0535	0.0391
		0.8	0.991	0.946	0.0498	0.0375
		1	0.975	0.932	0.0484	0.0375
		2	0.977	0.937	0.0465	0.0386
		3	0.975	0.939	0.0450	0.0386
	0.7	0.25	0.999	0.933	0.0617	0.0341
		0.5	0.999	0.951	0.0534	0.0313
		0.8	0.996	0.944	0.0496	0.0317
		1	0.990	0.926	0.0486	0.0322
		2	0.988	0.938	0.0462	0.0345
		3	0.981	0.945	0.0449	0.0356
30	0.3	0.25	0.987	0.954	0.0507	0.0422
		0.5	0.976	0.925	0.0436	0.0368
		0.8	0.969	0.939	0.0407	0.0350
		1	0.967	0.937	0.0397	0.0345
		2	0.961	0.934	0.0377	0.0338
		3	0.959	0.942	0.0372	0.0341
	0.5	0.25	1.000	0.949	0.0506	0.0357
		0.5	0.996	0.960	0.0437	0.0316
		0.8	0.985	0.946	0.0408	0.0310
		1	0.988	0.936	0.0396	0.0307
		2	0.982	0.945	0.0375	0.0311
		3	0.975	0.943	0.0370	0.0317
	0.7	0.25	1.000	0.959	0.0506	0.0279
		0.5	1.000	0.939	0.0437	0.0256
		0.8	0.996	0.947	0.0409	0.0260
		1	0.998	0.940	0.0398	0.0265
		2	0.987	0.938	0.0376	0.0281
		3	0.983	0.946	0.0371	0.0294

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Table 1. (Continued)

n	ρ_{xy}	σ_x^2 / σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	Proposed	Existing	Proposed
50	0.3	0.25	0.979	0.941	0.0392	0.0327
		0.5	0.975	0.938	0.0338	0.0284
		0.8	0.973	0.938	0.0319	0.0276
		1	0.968	0.937	0.0308	0.0267
		2	0.967	0.936	0.0293	0.0264
		3	0.968	0.946	0.0287	0.0263
	0.5	0.25	0.995	0.952	0.0392	0.0277
		0.5	0.992	0.937	0.0338	0.0245
		0.8	0.987	0.950	0.0318	0.0241
		1	0.982	0.937	0.0311	0.0240
		2	0.978	0.954	0.0293	0.0242
		3	0.974	0.948	0.0287	0.0247
	0.7	0.25	1.000	0.961	0.0391	0.0216
		0.5	0.998	0.946	0.0338	0.0197
		0.8	0.998	0.957	0.0316	0.0201
		1	0.997	0.943	0.0309	0.0205
		2	0.989	0.942	0.0293	0.0220
		3	0.986	0.958	0.0289	0.0229

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Table 2. Estimated coverage probabilities and expected lengths of confidence intervals for the ratio of bivariate normal means with a known coefficient of variation when $\theta = 1$.

n	ρ_{xy}	σ_x^2 / σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	Proposed	Existing	Proposed
10	0.3	0.25	0.980	0.946	0.2791	0.2421
		0.5	0.969	0.920	0.2150	0.1791
		0.8	0.976	0.911	0.1853	0.1529
		1	0.978	0.915	0.1745	0.1459
		2	0.968	0.902	0.1489	0.1259
		3	0.970	0.925	0.1403	0.1198
	0.5	0.25	0.986	0.933	0.2781	0.2146
		0.5	0.991	0.927	0.2145	0.1550
		0.8	0.993	0.914	0.1850	0.1292
		1	0.992	0.924	0.1751	0.1228
		2	0.986	0.923	0.1497	0.1089
		3	0.970	0.916	0.1423	0.1060
	0.7	0.25	0.997	0.928	0.2778	0.1843
		0.5	1.000	0.936	0.2149	0.1264
		0.8	0.998	0.921	0.1845	0.1028
		1	1.000	0.923	0.1729	0.0962
		2	0.999	0.930	0.1502	0.0882
		3	0.994	0.935	0.1407	0.0894
20	0.3	0.25	0.973	0.937	0.1959	0.1697
		0.5	0.966	0.925	0.1516	0.1277
		0.8	0.989	0.946	0.1312	0.1099
		1	0.973	0.934	0.1234	0.1023
		2	0.978	0.942	0.1062	0.0898
		3	0.972	0.944	0.1005	0.0864
	0.5	0.25	0.992	0.948	0.1963	0.1516
		0.5	0.989	0.945	0.1513	0.1104
		0.8	0.994	0.947	0.1312	0.0931
		1	0.989	0.926	0.1233	0.0873
		2	0.991	0.944	0.1066	0.0779
		3	0.985	0.939	0.1000	0.0752
	0.7	0.25	0.994	0.946	0.1965	0.1303
		0.5	0.999	0.916	0.1518	0.0886
		0.8	0.999	0.935	0.1312	0.0721
		1	1.000	0.936	0.1233	0.0684
		2	1.000	0.939	0.1071	0.0632
		3	0.997	0.955	0.1004	0.0632
30	0.3	0.25	0.974	0.938	0.1601	0.1389
		0.5	0.973	0.937	0.1243	0.1053
		0.8	0.980	0.955	0.1072	0.0893
		1	0.984	0.947	0.1009	0.0839
		2	0.977	0.949	0.0872	0.0734
		3	0.980	0.953	0.0823	0.0708
	0.5	0.25	0.987	0.937	0.1603	0.1238
		0.5	0.992	0.939	0.1234	0.0897
		0.8	0.993	0.942	0.1072	0.0758
		1	0.995	0.952	0.1012	0.0717
		2	0.992	0.945	0.0877	0.0636
		3	0.986	0.943	0.0823	0.0619
	0.7	0.25	0.998	0.941	0.1606	0.1058
		0.5	1.000	0.939	0.1240	0.0726
		0.8	0.999	0.937	0.1075	0.0593
		1	0.999	0.952	0.1012	0.0559
		2	1.000	0.943	0.0874	0.0511
		3	0.999	0.946	0.0821	0.0519

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Table 2. (Continued)

n	ρ_{xy}	σ_x^2/σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	**Proposed**	**Existing**	**Proposed**
50	0.3	0.25	0.976	0.945	0.1240	0.1079
		0.5	0.978	0.948	0.0960	0.0814
		0.8	0.978	0.946	0.0830	0.0693
		1	0.981	0.952	0.0783	0.0654
		2	0.979	0.945	0.0679	0.0573
		3	0.971	0.945	0.0637	0.0546
	0.5	0.25	0.993	0.953	0.1241	0.0960
		0.5	0.991	0.939	0.0961	0.0700
		0.8	0.996	0.951	0.0831	0.0586
		1	0.991	0.951	0.0783	0.0552
		2	0.995	0.957	0.0677	0.0491
		3	0.993	0.952	0.0639	0.0480
	0.7	0.25	0.994	0.944	0.1239	0.0827
		0.5	0.999	0.948	0.0963	0.0557
		0.8	1.000	0.947	0.0832	0.0459
		1	1.000	0.936	0.0784	0.0430
		2	0.997	0.951	0.0678	0.0397
		3	0.999	0.958	0.0638	0.0400

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Table 3. **Estimated coverage probabilities and expected lengths of confidence intervals for the ratio of bivariate normal means with a known coefficient of variation when $\theta = 2$.**

n	ρ_{xy}	σ_x^2/σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	Proposed	Existing	Proposed
10	0.3	0.25	0.964	0.948	0.5137	0.4757
		0.5	0.978	0.955	0.3725	0.3347
		0.8	0.976	0.945	0.3051	0.2675
		1	0.974	0.939	0.2779	0.2406
		2	0.981	0.924	0.2141	0.1792
		3	0.979	0.916	0.1879	0.1564
	0.5	0.25	0.969	0.942	0.5131	0.4488
		0.5	0.975	0.948	0.3727	0.3087
		0.8	0.988	0.924	0.3045	0.2376
		1	0.988	0.944	0.2775	0.2140
		2	0.995	0.932	0.2147	0.1533
		3	0.991	0.917	0.1889	0.1335
	0.7	0.25	0.976	0.945	0.5134	0.4228
		0.5	0.994	0.943	0.3729	0.2795
		0.8	0.991	0.939	0.3034	0.2088
		1	0.996	0.935	0.2769	0.1853
		2	1.000	0.915	0.2142	0.1252
		3	1.000	0.933	0.1891	0.1040
20	0.3	0.25	0.967	0.951	0.3619	0.3358
		0.5	0.977	0.953	0.2629	0.2364
		0.8	0.968	0.928	0.2148	0.1891
		1	0.982	0.950	0.1967	0.1694
		2	0.986	0.948	0.1512	0.1274
		3	0.984	0.961	0.1339	0.1112
	0.5	0.25	0.974	0.952	0.3632	0.3181
		0.5	0.987	0.959	0.2634	0.2181
		0.8	0.982	0.951	0.2145	0.1705
		1	0.990	0.940	0.1959	0.1512
		2	0.991	0.936	0.1517	0.1098
		3	0.994	0.928	0.1332	0.0944
	0.7	0.25	0.981	0.947	0.3620	0.2979
		0.5	0.991	0.941	0.2631	0.1977
		0.8	0.999	0.930	0.2149	0.1483
		1	0.993	0.930	0.1961	0.1302
		2	0.998	0.937	0.1512	0.0886
		3	1.000	0.939	0.1336	0.0744
30	0.3	0.25	0.964	0.950	0.2959	0.2748
		0.5	0.978	0.953	0.2147	0.1938
		0.8	0.975	0.950	0.1754	0.1536
		1	0.981	0.954	0.1598	0.1392
		2	0.976	0.946	0.1237	0.1051
		3	0.970	0.941	0.1090	0.0911
	0.5	0.25	0.977	0.960	0.2958	0.2584
		0.5	0.982	0.950	0.2147	0.1770
		0.8	0.986	0.955	0.1753	0.1383
		1	0.990	0.944	0.1598	0.1246
		2	0.996	0.943	0.1239	0.0898
		3	0.991	0.945	0.1093	0.0773
	0.7	0.25	0.978	0.940	0.2956	0.2419
		0.5	0.996	0.964	0.2146	0.1607
		0.8	0.997	0.936	0.1754	0.1210
		1	0.994	0.951	0.1601	0.1064
		2	1.000	0.949	0.1234	0.0725
		3	1.000	0.932	0.1091	0.0606

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Table 3. (Continued)

n	ρ_{xy}	σ_x^2/σ_y^2	Coverage Probabilities		Expected Lengths	
			Existing	**Proposed**	**Existing**	**Proposed**
50	0.3	0.25	0.978	0.960	0.2287	0.2118
		0.5	0.964	0.938	0.1664	0.1498
		0.8	0.973	0.946	0.1359	0.1196
		1	0.973	0.941	0.1238	0.1077
		2	0.973	0.948	0.0959	0.0810
		3	0.984	0.953	0.0844	0.0707
	0.5	0.25	0.976	0.959	0.2287	0.2000
		0.5	0.989	0.954	0.1664	0.1375
		0.8	0.988	0.960	0.1357	0.1079
		1	0.989	0.954	0.1240	0.0962
		2	0.993	0.952	0.0960	0.0698
		3	0.993	0.951	0.0846	0.0599
	0.7	0.25	0.984	0.951	0.2288	0.1877
		0.5	0.991	0.949	0.1662	0.1245
		0.8	0.995	0.945	0.1358	0.0938
		1	0.995	0.941	0.1237	0.0823
		2	1.000	0.938	0.0960	0.0565
		3	0.998	0.936	0.0846	0.0470

Table 4. ***Erythrocyte adenosine triphoshate*** **(ATP) levels in youngest and oldest sons.**

Family	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Youngest (x)	4.18	5.16	4.85	3.43	4.53	5.13	4.10	4.77	4.12	4.65	6.03	5.94	5.99	5.43	5.00	4.82	5.25
Oldest (y)	4.81	4.18	4.48	4.19	4.27	4.87	4.74	4.53	3.72	4.62	5.83	4.40	4.87	5.44	4.70	4.14	5.30

Table 5. The 95% confidence intervals for theratio of bivariate normal means with a known coefficient of variation of the ATP levels in youngest and oldest sons.

Methods	**Confidence intervals**		**Lengths**
	Lower limit	**Upper limit**	
Existing	0.9648	1.1424	0.1776
Proposed	0.9923	1.1159	0.1236

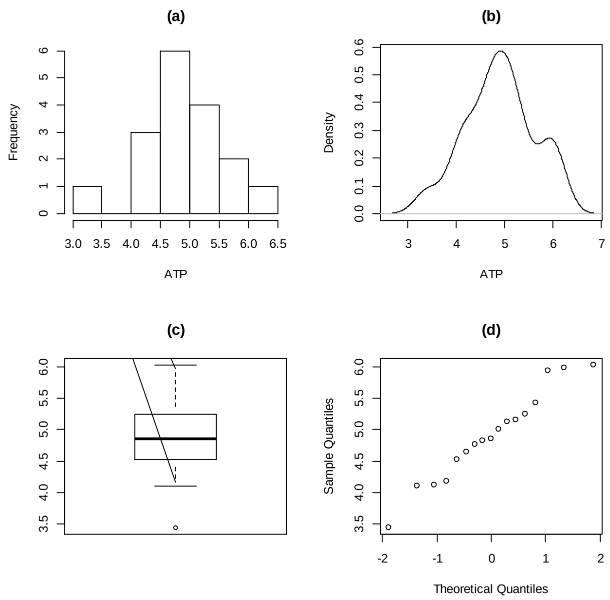

Figure 1. (a) histogram, (b) density plot, (c) Box-and-Whisker plot and (d) normal quantile-quantile plot of the ATP levels of youngest sons.

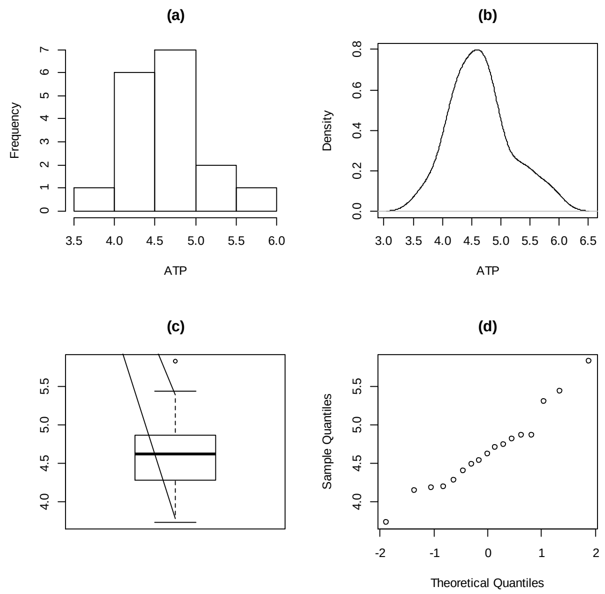

Figure 2. (a) histogram, (b) density plot, (c) Box-and-Whisker plot and (d) normal quantile-quantile plot of the ATP levels of oldest sons.

```
Shapiro-Wilk normality test

data:  Z

W = 0.9668, p-value = 0.7601
```

Figure 3. Shapiro-Wilk test for multivariate normality of the ATP of youngest and oldest sons.