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LETTER TO THE EDITOR

Inconsistencies with formulas for the standard error of the standardized mean difference of repeated measures experiments

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Summary

There are inconsistencies between the formulas for the variance of standardized mean difference (SMD) in the Cochrane Handbook for Systematic Reviews and the variance reported in other sources. Instead of the variance appropriate for the SMD of a crossover experiment, the Cochrane Handbook uses the variance appropriate for a pre-test post-test experiment. This means that if there is a non-negligible time period effect, the formula reported by the Handbook will underestimate both the effect size and its variance.

In addition, the formula for the standard error of SMD reported in the Cochrane Handbook (in Section 23.2.7.2) is inconsistent with the variance derived from the variance of the related $t-$test. Even if the period effect is negligible, the Cochrane Handbook formula is biased towards underestimates. The difference between the estimates from the two formulas will be small if either the correlation between the repeated measures, or the magnitude of the SMD estimate, is small, or if the sample size is large. However, it can be can be quite substantial in other circumstances.

KEYWORDS:
cross-over trials, continuous data, effect sizes, effect size variances, formula inconsistencies

1 | INTRODUCTION

We explore the reasons for discrepancies between the formulas for estimates of the variance of standardized effect sizes, obtained from repeated measures experiments, between the one in the Cochrane Handbook for Systematic Reviews[1] and the one proposed by Becker[2], and later revised and validated by Morris[3].

2 | THE STANDARDIZED EFFECT SIZE AND ITS VARIANCE

The online Cochrane Handbook devotes Section 23.2 to crossover trials. In Section 23.2.7.2, the Handbook reports the following equation for the standardized mean difference SMD:

$$SMD = \frac{MD}{SD_{pooled}} \tag{1}$$

where $MD = M_E - M_C$, M_E is the mean of experimental intervention E, M_C is the mean of the comparator intervention C, and

$$SD_{pooled} = \sqrt{\frac{SD_E^2 + SD_C^2}{2}} \tag{2}$$

where SD_E is the standard deviation of the experimental intervention, SD_C is the standard deviation of the comparator intervention.

Thus, as the Handbook makes clear in Section 23.2.5, the formulas are based on the assumption that neither carry-over nor time period effects are important, and that the appropriate analysis is a paired $t-$test. This is the case discussed first by Becker[2], and later by Morris[3] who report equations for the exact variance and the approximate normal variance of the SMD as defined in Equation 1.

The equation for the standard error of the SMD which is presented in the Handbook is:

$$SE(SMD) = \sqrt{\frac{1}{N} + \frac{SMD^2}{2N}} \times \sqrt{2(1 - Corr)} \tag{3}$$

where $Corr$ is the correlation between the repeated measures and N is the number of participants.

However, the equation for the approximate normal variance of SMD reported by Becker, and validated by Morris, is:

$$var(SMD) = \frac{2(1-\rho)}{n} + \frac{\delta^2}{2f} \tag{4}$$

where δ^2 is the population parameter estimated by SMD, ρ is the population correlation between repeated measures estimated by $Corr$, and f was set either to n, the number of participants, or to $n-1$ which is the degrees of freedom of a pre-test post-test experiment.

Re-organizing Becker's equation to make it as similar as possible to the Handbook equation and converting to the standard error, we get:

$$SE(SMD) = \sqrt{\frac{2(1 - Corr)}{N} + \frac{SMD^2}{2f}} \tag{5}$$

Equation 3 and Equation 5 are clearly different. The reason for the difference is explained below.

3 | DERIVATION OF THE SMD VARIANCE

Becker[2] based her derivation of the standardized effect size variances on the variance of a t-variable. The normal approximation of the variance of a $t-$variable, was specified by Johnson and Welch[4] to be:

$$var(\theta) = 1 + \frac{\theta^2}{2f} \tag{6}$$

where θ is a $t-$variable and f is its degrees of freedom. In the case of a repeated measures experiment, the $t-$test is based on the standard deviation of the difference values (see the Cochrane Handbook, Section 23.2.7.1.):

$$t = \frac{MD}{\frac{SD_{diff}}{\sqrt{N}}} \tag{7}$$

where

$$SD_{diff} = \sqrt{SD_E^2 + SD_C^2 - 2 \times Corr \times SD_E \times SD_C} \tag{8}$$

Since $SD_E^2 = SD_C^2 = SD_{pooled}^2$, SD_{diff} simplifies to:

$$SD_{diff} = SD_{pooled}\sqrt{2(1 - Corr)} \tag{9}$$

giving the $t-$test value for a repeated measure design:

$$t = \frac{MD}{SD_{pooled}\sqrt{\frac{2(1-Corr)}{N}}} \tag{10}$$

Thus, from Equation 1, we have:

$$SMD = t \times \sqrt{\frac{2(1 - Corr)}{N}} \tag{11}$$

and, since if x and y are variables connected by the equation $x = cy$ and c is a constant, $var(x) = c^2 var(y)$, we have:

$$var(SMD) = var(t) \times \frac{2(1 - Corr)}{N} \tag{12}$$

Using Equation 6, the normal approximation for the variance of SMD is:

$$var(SMD) = \frac{2(1 - Corr)}{N}\left(1 + \frac{t^2}{2f}\right) \tag{13}$$

and since $t = SMD \times \sqrt{\frac{N}{2(1-Corr)}}$, leads to the equation proposed by Becker[2]:

$$var(SMD) = \frac{2(1 - Corr)}{N} + \frac{SMD^2}{2f} \tag{14}$$

where f is replaced either by N or $(N - 1)$. Theoretically, for consistency with Equation 6, the divisor should be $(N - 1)$. However, Morris performed simulation studies that found there was little impact on variance estimates by using N rather than $N - 1$.[3] Thus, if N is sufficiently large for the approximation to be appropriate, it would be reasonable to replace f with N.

There are four points to be noted concerning Equation 14:

- Morris[3] reports error rates for the approximate variance for different values of δ, N and ρ, e.g., for $N = 10$, if $\delta = 0$ and $\rho = 0$, the error is 22% and increases for larger values of δ and ρ. So for small samples sizes (where *small* depends on the variance error an analyst is willing to tolerate), the exact variance is preferable, where Becker's initial formula was later corrected by Morris to be:

$$\sigma^2(d) = [c(N - 1)]^2 \left(\frac{2(1 - \rho)}{N}\right)\left(\frac{N - 1}{N - 3}\right)\left(1 + \frac{N}{2(1 - \rho)}\delta^2\right) - \delta^2 \tag{15}$$

  where $c(N - 1)$ is defined in Equation 16.

- Rather than using the value of SMD defined in Equation 1, it is usual to apply a small sample bias correction[5] to SMD, defined by Morris[3] to be:

$$c(N - 1) \cong 1 - \frac{3}{(4(N - 1) - 1)} \tag{16}$$

  where $N - 1$ is the degrees of freedom of the related $t-$test and $c(N - 1)$ tends to 1 as N increases. However, for meta-analysis purposes, Lin[6] found, in a simulation study, that unadjusted SMD estimates gave *less* biased estimates of the overall mean than the adjusted estimates.

- The Cochrane Handbook presents a numerical example with $SMD = 0.218$, $N = 10$ and $Corr = 0.68$ which gives $SE(SMD) = 0.256$ using Equation 3. Using Equation 5 with the same parameters gives $SE(SMD) = 0.258$ for both $f = (N - 1)$ and $f = N$, which is an effectively negligible difference. However, if $SMD = 0.9$, $Corr = .9$ and $N = 10$ the variance obtained using the Handbook's equation is 0.168, while the variance using Becker's equation is 0.255 using $f = (N - 1)$ and 0.246 using $f = N$.

- Although the practical impact of the wrong equation may be limited, the derivation of the equation is important in order to allow researchers to derive the correct variance for effect sizes obtained from other experimental designs, as shown in Reference[7].

4 | CONCLUSIONS

The approach to crossover designs taken by the Cochrane Handbook assumes that both the period effect and the carry-over effect are negligible. If carry-over is negligible but there is a non-negligible period effect, the analysis recommended by the Handbook will underestimate the effect size, because the estimate of the pooled within-group variance will be inflated by the failure to remove the period effect (see Kitchenham and Madeyski[8] for the correct formula).

The formula for the normal approximation to the standard error of SMD reported in the Cochrane Handbook is inconsistent with the formula Becker derived from the variance of the paired $t-$test. Thus, theoretically, Becker's formula, with $f = (N - 1)$, is more appropriate, and her method can be extended to other experimental designs[7].

Unless $SME = 0$ or $Corr = 0$, Becker's formula will always produce estimates of the standard error larger than the Cochrane Handbook estimates. In practice, the difference will be negligible if the estimates of either $Corr$ or SMD are small, or N is large. The difference will be greater for large $Corr$ estimates, large SMD estimates and small N.

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